## EXERCISE

Seventh Edition


William D. McArdle I Frank I. Katch I Victor L. Katch
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# EXERCISE PHYSIOLOGY 

Nutrition, Energy, and Human Performance

Seventh Edition

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# Nutrition, Energy, and Human Performance 

Seventh Edition

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To my wife Kathleen, my best friend and biggest supporter, and to the rest of the A team: my children, Theresa, Amy, Kevin, and Jennifer; their spouses, Christian, Jeff, Nicole, and Andy; and my grandchildren, Liam, Aidan, Quinn, Dylan, Kelly Rose, Owen, Henry, Kathleen (Kate), Grace, Elizabeth, Claire, and Elise.

Bill McArdle

To my wife and life partner, Kerry, for four decades of love and support; to my two sons, David and Kevin, for achieving the honorable in their business and personal lives; to my daughter, Ellen, for current and future years of dedicated service as a pediatrician; and to her new husband, Sean.

Frank Katch

To those most important in my life: Heather, Erika, Leslie, and the J-man.
Im a lucky man.
Victor Katch


## PREFACE

As in the publication of the first edition of Exercise Physiology: Nutrition, Energy, and Human Performance in 1981, this seventh edition reflects our continued commitment to integrate the concepts and science of the different disciplines that contribute to a more comprehensive understanding and appreciation of modern-day exercise physiology. Consistent with previous editions, we believe firmly that the content domain of exercise physiology must be predicated on the logical and natural flow of basic knowledge concerning nutrient-energy intake, nutrient-energy metabolism, and systems physiology as related to submaximal and maximal human movement. Current concepts of energy balance intimately link the role of physical inactivity to the creeping obesity epidemic that continues to afflict the world's population. We are encouraged that the medical establishment and governmental agencies have finally acknowledged regular physical activity as an important weapon in the armamentarium for prevention and rehabilitation of diverse disease states, including obesity.

We are gratified with the small part we have played in the education of more than 350,000 undergraduate and graduate students who have used this text since the publication of the first edition in 1981. A source of great pride for us is that some of the first students enrolled in our own classes that used this text have gone on to earn advanced degrees in the same or similar fields. This tradition of textbook adoption has now been passed down to their students, many of whom comprise the next generation of aspiring teachers, exercise specialists, and researchers. In fact, one of us (VK) has had the opportunity on three different occasions to teach students whose parents were former students. We are forever grateful to our former teachers and mentors for igniting a spark that has not diminished. We hope you will become as excited as we first were (and continue to be) in the science of exercise physiology and human performance.

## ORGANIZATION

This seventh edition maintains the same seven-section structure as previous editions, including an introductory section about the origins of exercise physiology and a concluding On the Horizons section that deals with a maturing effort in exercise physiology to incorporate molecular biology to human performance and the many interrelated aspects of health and disease.

## FEATURES

Many features throughout the text are included to engage the student and facilitate learning. These include the following:

Introduction: A View of the Past. The text's introduction, Exercise Physiology: Roots and Historical Perspectives, reflects our interest and respect for the earliest underpinnings of the field, and the direct and indirect contributions of the men and women physicians/scientists who contributed to the field.

In a Practical Sense. This element in every chapter highlights practical applications that include:

> Lowering high blood pressure with dietary intervention: the DASH diet
> Leveraging nutrition to prevent chronic athletic fatigue
> Predicting $\mathrm{VO}_{2 \text { max }}$ during pregnancy from
> submaximal exercise heart rate and oxygen consumption
> Predicting energy expenditure during treadmill
> walking and running
> Determining anaerobic power and capacity: the
> Wingate cycle ergometer test
> Predicting pulmonary function variables in males and females
> Measuring lactate threshold
> Blood pressure measurement, classifications, and recommended follow-up
> Placing electrodes of bipolar and 12-lead ECG recordings
> Diabetes, hypoglycemia, and exercise
> Protecting the lower back
> Assessing heat quality of the environment: how hot is too hot?

Focus on Research. Each chapter's Focus on Research features a key research article from a renowned scientist. These well-designed studies illustrate how theory comes to life through research.

Integrative Questions. Another element in each chapter, Integrative Questions, poses open-ended questions to encourage students to consider complex concepts without a single correct answer.

Expanded Art Program. The full-color art program continues to be an important feature of the textbook. New figures have been added to enhance the new and updated content.

Up-Close and Personal Interviews. The text features nine contemporary scientists whose important research contributions and visionary leadership continue the tradition of the scientists of prior generations-Steven Blair, Frank Booth, Claude Bouchard, David Costill, Barbara Drinkwater, John Holloszy, Loring Rowell, Bengt Saltin, and Charles Tipton.

These individuals clearly merit recognition, not only for expanding knowledge through their many scientific contributions, but also for elucidating mechanisms that underlie responses and adaptations to exercise and health enhancement. Each person has been placed within a section linked to his or her main scholarship interests, yet all of them span one or more sections in terms of scientific contributions. Appendix E, which is available online at http://thepoint.lww. com/mkk7e, lists individual honors and awards for each of these distinguished and meritorious scientist researchers. The intimate insights from the superstars should inspire current exercise physiology students to actualize their potential, whether through accomplishments in graduate school, teaching, research, or numerous other exciting opportunities to achieve excellence.

References and Appendices Available Online. All references and appendices are available online at http://thepoint. lww.com/mkk7e. Appendices feature valuable information about nutritive values, energy expenditures, metabolic computations in open-circuit spirometry, and more.

## NEW TO THE SEVENTH EDITION

The flow of information in this edition remains similar to prior editions. Where applicable, figures, tables, and Web sites have been updated and/or expanded to include the most relevant current information, including new tabular material and illustrations to clarify important concepts and information.

## Significant Additions and Modifications to the Text

Section 1 summarizes the current (2009) energy, nutrient, and fluid recommendations from the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine for active adults and competitive athletes. It also provides an expanded discussion of the efficacy and health benefits of routinely consuming vitamin and mineral supplements versus obtaining these micronutrients in the foods of a well-balanced diet.
In Section 2, we have included the latest information regarding the energy yield from the catabolism of the different macronutrients and we have rewritten several of the sections to increase clarity and specificity. We have expanded our discussion of the increasing incidence of hypertension with age in Section 3, along with lifestyle choices to lower blood pressure. In Section 4, we present a research-based alternative method to estimate maximal heart rate from chronological age for adults. Additionally, we present the latest information regarding sling exercise training as a means of muscle activation and overload that is gaining in popularity based on new research about how muscles are activated and contribute to improved movement. We have also expanded our review of the effects of carbohydrate protein supplement timing
and resistance training on muscle fiber hypertrophy, muscular strength, and body composition.
Section 5 includes a discussion of the secret First Lady Astronaut Trainees (FLATS) program intended to include highly experienced female aviators for future space missions, and how that program was unceremoniously scuttled because of bureaucratic cronyism at the highest levels of the early space agency. Also included is an explanation of the longterm United States human and robotic program to explore the solar system, starting with a return to the moon to ultimately enable future exploration of Mars and other destinations, including the new manned exploration, the Crew Exploration Vehicle (CEV). Section 6 presents the 2009 summary statement of the American College of Sports Medicine as to the appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Also included is a discussion of an apparent anomaly in body proportions in champion swimmer Michael Phelps, winner of 8 gold medals in the 2008 Beijing Olympics, related to his use of a controversial swim suit and swimming speed. This section also analyzes body size (BMI) differences among 1124 Division 1 Big Ten Collegiate offensive and defensive linemen and their teams related to team standings in league play. We provide the first presentation on the height and weight, and BMI of professional male tour Professional golfers $(n=33)$ and Champions Tour players $(n=18)$ compared to 257 golfers, stratified by proficiency levels based on handicap index, and 300,818 Swedish golfers (203,778 men and 97,040 women) with stratification for age, sex, and socioeconomic status. We also include the latest information about brown adipose tissue in humans, and its role in metabolism and link to health and disease.
Section 7 presents an updated section on coronary heart disease. Our final chapter discusses the new molecular exercise physiology program at the University of Aberdeen in Scotland, where the MSc program, including Diploma and Certificate programs, offers courses in a new subfield in sports science that focuses on genetics and signal transduction related to exercise. Current statistics reveal the impact of molecular biology-related research on different fields of science. For example, searching on the terms muscle and genes increased from 502 in 2001 to over 58,000 at the start of 2009 ! We also highlight Darwin's monumental contributions in evolutionary theory. A new feature of this final chapter links to the LWW website and includes (1) readings related to molecular biology and genetics, twins, and human performance; (2) reference to excellent texts that devote hundreds of pages to the intricacies of the molecular biology of gene transcription and protein synthesis; (3) articles from Scientific American that concern molecular biology; (4) useful molecular
biology Internet sites; (5) microscope technologies germane to molecular biology (light microscope, fluorescence microscope, electron microscope, and positron emission tomography or PET); (6) reprint of Watson and Crick's one-page classic paper in Nature about their deduction of DNA's structure, which nearly six decades later unraveled the pieces to the primordial jigsaw puzzle of the Human Genome Project; and (7) a timeline of events about genetics before Mendel, followed by notable events in genetics and molecular biology to 2005.

Our current reference list includes the latest research gleaned from national and international journals related to specific topic areas. We hope you profit from and enjoy this continuation of our journey through the ever-expanding and relevant field of exercise physiology.

## ANCILLARIES: THE TOTAL TEACHING PACKAGE

Exercise Physiology: Nutrition, Energy, and Human Performance, Seventh Edition, includes additional resources for both instructors and students that are available on the book's companion website at http://thepoint.lww.com/mkk7e.

Instructors and students will have access to animations illustrating the most important concepts in human physiology. Both instructors and students will also be able to access the searchable Full Text Online.

## Instructors

Approved adopting instructors will be given access to the following additional resources:

Brownstone test generator
PowerPoint presentations: one set with lecture out-
lines; one set with images only
Image bank
WebCT, Blackboard, and Angel-Ready Cartridge

## Students

Students who have purchased Exercise Physiology: Nutrition, Energy, and Human Performance, Seventh Edition, have access to the following additional resources:

Online quiz bank with study and test options Animations
References
Appendices
Featured information on microscope technologies, notable events in genetics, Nobel prizes, and outstanding female scientists.

Ancillaries were prepared by the authors as well as by Jeff Woods (University of Illinois at Urbana-Champaign) and Lamia Scherzinger (Indiana University Purdue University Indianapolis).

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We are collectively indebted to the nine researchers scholars who took time from their busy schedules to answer our interview questions and provide personal photos. Each of those individuals, in his or her own unique way, inspired the three of us in our careers by their work ethic, scientific excellence, and generosity of time and advice with colleagues and students. Over the years, we have had the good fortune to
come to know these individuals both socially and in the academic arena. We must admit, however, that the interviews provided insights previously unknown to us. We hope you too are as impressed as we are by all they have accomplished and given back to the profession. Frank Katch also wishes to thank Dr. Drinkwater, who served on his MS thesis committee at UC Santa Barbara. He now 'fesses up after 45 years that she provided much needed statistical and grammatical assistance beyond the call of duty with that project!

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William D. McArdle<br>Sound Beach, NY

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## USERS GUIDE

Exercise Physiology, Seventh Edition, offers comprehensive coverage of exercise physiology uniting the topics of physical conditioning, sports nutrition, body composition, weight control, and more. To help your comprehension of the material, the authors have included numerous features that reinforce concepts and enhance your learning experience. Look for these features


## INTRODUCTION: A VIEW OF THE PAST

## EXERCISE PHYSIOLOGY: ROOTS AND HISTORICAL PERSPECTIVES

Since the first edition of our textbook 28 years ago in 1981, knowledge has exploded concerning the physiologic effects of exercise in general, and the body s unique and specific responses to training in particular. Tipton s search of the 1946 English literature for the terms exercise and exertion yielded 12 citations in 5 journals. ${ }^{66}$ Tipton also cited a 1984 analysis by Booth, who reported that in 1962, the number of yearly citations of the term exertion increased to 128 in 51 journals, and by 1981, there were 655 citations for the word exertion in 224 journals. The accompanying figure reveals the number of entries for the words exercise or exertion from an Internet search of Index Medicus (Medline) for the years 2000 to December 18, 2008, using the National Center for Biotechnology Information (NCBI) database (www.ncbi.nlm.nih.gov/ sites/entrez). In just a 4-year period since publication of the sixth edition, the number of citations increased tremendously to $224,421(312 \%)$ ! For the fourth edition published in 1996,


Exercise or exertion as a topic (top bars) and frequency of the word exercise appearing in a scientific journal (bottom bars) for the years 1966 to 1996 (from Index Medicus). The last three columns used PubMed via an Internet search for citations with the terms exercise or exertion.
we noted that the greatest increases occurred between 1976 and 1986, and that citation frequency appeared to level off from 1986 and 1996. From that time, the rate of increase has been even greater. Obviously, we misjudged how greatly exercise-related topics would affect scholarly productivity in biologic sciences research. The number of citations has increased beyond our wildest expectations, and with expanding interest in the role of exercise and physical activity, the rate of citations devoted to these topics undoubtedly will continue to accelerate.

As graduate students in the late 1960s, we never believed that interest in exercise physiology would increase so dramatically. A new generation of scholars committed to studying the scientific basis of exercise had set to work. Some studied the physiologic mechanisms involved in adaptations to regular exercise; others evaluated individual differences in exercise and sports performance. Collectively, both approaches contributed knowledge to the growing field of exercise physiology. At our first scientific conference (American College of Sports Medicine [ACSM] in Las Vegas, 1967), still as graduate students, we rubbed elbows with the giants of the field, many of whom were themselves students of the leaders of their era. Sitting under an open tent in the Nevada desert with one of the world s leading physiologists, Dr. David Bruce Dill (then age 74; see page xlvii), we listened to his researcher-a high school student-lecture about temperature regulation in the desert burro. Later, one of us (FK) sat next to a whitehaired gentleman and chatted about a Master s thesis project. Only later did an embarrassed FK learn that this gentleman was Captain Albert R. Behnke, MD (1898 1993; ACSM Honor Award, 1976), the modern-day father of human body composition assessment whose crucial experiment in diving physiology established standards for decompression and use of mixed gases. His pioneering studies of hydrostatic weighing in 1942, the development of a reference man and reference woman model, and creation of the somatogram based on anthropometric measurements underlie much current work in body composition assessment (see Chapter 28 and its Focus on Research ). That fortuitous meeting began a lasting personal and fulfilling professional friendship until Dr. Behnke s death in 1993. Several hundred ACSM members listened attentively as the superstars of exercise physiology and physical


Albert R. Behnke
fitness (Per-Olof strand, Erling Asmussen, Bruno Balke, Elsworth Buskirk, Thomas Cureton, Lars Hermansen, Steven Horvath, Henry Montoye, Bengt Saltin, Charles Tipton) presented their research and fielded penetrating questions from an audience of young graduate students eager to devour the latest scientific information.

Over the years, the three of us have been fortunate to work with the very best in our field. William McArdle studied for the PhD at the University of Michigan with Dr. Henry Montoye (charter member of ACSM; President of ACSM, 1962 1963; Citation Award, 1973) and Dr. John Faulkner (President of ACSM, 1971 1972; Citation Award, 1973; and ACSM Honor Award, 1992). At the University of California, Berkeley, Victor Katch completed the MS thesis in physical education under the supervision of Dr. Jack Wilmore (ACSM President, 1978 1979; Citation Award, 1984; and first editor of Exercise and Sport Science Reviews, 1973 1974) and was a doctoral student of Dr. Franklin Henry (ACSM Honor Award, 1975; originator of the Memory-Drum Concept about the specificity of exercise; and author of the seminal paper Physical Education-an Academic Discipline, JOHPER 1964;35:32). Frank Katch completed the MS degree at the University of California, Santa Barbara, under the supervision of thesis advisors Dr. Ernest Michael, Jr., (former PhD student of pioneer exercise physiologist physical fitness scientist Dr. Thomas Kirk Cureton, ACSM Honor Award, 1969) and Dr. Barbara Drinkwater (President of ACSM, 1988 1989; ACSM Honor Award, 1996), and then also completed doctoral studies at the University of California, Berkeley, with Professor Henry. Professor Roberta Park, also at the University of California, Berkeley, was inspirational over the years in sparking interest in the history of physical education as an academic discipline. She encouraged each of us (and our future students) to honor the past accomplishments of those in the profession who helped to pave the way.

As the three of us examine those earlier times, we realize, like many of our colleagues, that our academic good fortunes prospered because our professors and mentors shared an unwavering commitment to study sport and exercise from a strong scientific and physiologic perspective. These scholars demonstrated why it was crucial that physical educators be well grounded in both the scientific basics and underlying concepts and principles of exercise physiology.

We are so pleased to acknowledge the pioneers who created exercise physiology, realizing full well the difficult task in an introduction to adequately chronicle the history of exercise physiology from its origins in ancient Asia to the present. Instead, our brief review presents a historical tour regarding topics not adequately developed in exercise physiology or history textbooks. Our discussion begins with an acknowledgment of the ancient but tremendously influential Indian, Arabic, and prominent Greek physicians; along the way, we highlight some milestones (and ingenious experiments), including the many contributions from Sweden, Denmark,

Norway, and Finland that fostered the study of sport and exercise as a respectable field of scientific inquiry.

A treasure of information about the early beginnings of exercise physiology in America was uncovered in the archives of Amherst College, Massachusetts, in an anatomy and physiology textbook (incorporating a student study guide) written by the first American father-and-son writing team. The father, Edward Hitchcock, was President of Amherst College; the son, Edward Hitchcock, Jr., an Amherst graduate and Harvard-trained physician, made detailed anthropometric and strength measurements of almost every student enrolled at Amherst College from 1861 to 1889. A few years later in 1891, much of what forms current college curricula in exercise physiology, including evaluation of body composition by anthropometry and muscular strength by dynamic measurements, began in the first physical education scientific laboratory at Harvard University s Lawrence Scientific School. Even before the creation of this laboratory, another less formal but still tremendously influential factor affected the development of exercise physiology: the publication during the 19th century of American textbooks on anatomy and physiology, physiology, physiology and hygiene, and anthropometry. Table 1 lists a sampling of textbooks published between 1801 and 1899 containing information about the muscular, circulatory, respiratory, nervous, and digestive systems-including the influence of exercise and its effectsthat eventually shaped the content area of exercise physiology during the next century. Roberta Park, distinguished UC Berkeley physical education historian, chronicles the early contributions of many physicians and science-oriented physical educators who steadfastly believed that physical education (and medicine) should be grounded on a sound scientific foundation fueled by cutting-edge research. ${ }^{50,52,54,56}$ These well-documented historical chronologies and other contributions ${ }^{51,53,55}$ provide context and foster appreciation for the scholars and educators who paved the way for the new generation of researchers; the early innovators developed new techniques and methodologies in the fields of health, fitness, performance, and physical activity that became essential components of the exercise physiology core curriculum. Textbooks from 1900 to 1947 dealing with exercise, training, and exercise physiology also were influential. ${ }^{a}$

## IN THE BEGINNING: ORIGINS OF EXERCISE PHYSIOLOGY FROM ANCIENT GREECE TO AMERICA IN THE EARLY 1800s

Exercise physiology arose mainly in early Greece and Asia Minor, although the topics of exercise, sports, games, and health concerned even earlier civilizations. These included the Minoan and Mycenaean cultures, the great biblical empires of David and Solomon, Assyria, Babylonia, Media,

[^1]TABLE 1 - Sampling of Textbooks on Anatomy and Physiology, Anthropometry, Exercise and Training, and Exercise Physiology (1801 1947)

| Year | Author and Text |
| :---: | :---: |
| 1801 | Willich AFM. Lectures on Diet and Regimen: Being a |
|  | Systematic Inquiry into the Most Rational Means of |
|  | Preserving Health and Prolonging Life: Together with |
| Physiological and Chemical Explanations, Calculated |  |
|  | Chiefly for the Use of Families, in Order to Banish the |
| Prevailing Abuses and Prejudices in Medicine. New |  |
| York: T and J Sworos, 1801. |  |

1831 Hitchcock E. Dyspepsy Forestalled and Resisted, or, Lectures on Diet, Regimen, and Employment. 2nd ed. Northampton: J.S. \& C. Adams, 1831.
1833 Beaumont W. Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Pittsburgh: F.P. Allen, 1883.
1839 Carpenter WB. Principles of Physiology, General and Comparative. London: John Churchill, 1839. 4th ed. 1854.
1842 Carpenter WB. Principles of Human Physiology. London: Churchill, 1842.
1843 Carpenter WB. Principles of Human Physiology, with Their Chief Applications to Pathology, Hygiene, and Forensic Medicine. Especially Designed for the Use of Students. Philadelphia: Lea \& Blanchard, 1843, Numerous reprints and editions; 9th ed, 1881 (London): 4th American ed., 1890.
1843 Combe A. The Principles of Physiology Applied to the Preservation of Health, and to the Improvement of Physical and Mental Education. New York: Harper \& Brothers, 1843.
1844 Dunglison R. Human Health: The Influence of Atmosphere and Locality; Change of Air and Climate; Seasons; Food; Clothing: Bathing and Mineral Springs; Exercise; Sleep; Corporeal and Intellectual Pursuits, on Healthy Man; Constituting Elements of Hygiene. Philadelphia: Lea \& Blanchard, 1844.
1846 Warren JC. Physical Education and the Preservation of Health. Boston: William D. Ticknor, 1846.
1848 Cuder C. Anatomy and Physiology Designed for Academies and Families. Boston: Benjamin B. Mussey and Co., 1848.
1852 Ehickwell E. The Laws of Life, with Special Reference to the Physical Education of Girls. New York: George P. Putnam, 1852.
Stokes W. Diseases of the Heart and Aorta. Philadelphia: Lindsay, 1854.
1855 Combe A. The Physiology of Digestion, Considered with the Relation to the Principles of Dietetics. Philadelphia: Harper and Brothers, 1855.
1856 Beecher C, Physiology and Calisthenics for Schools and Families. New York: Harper and Brothers, 1856.
1859 Flint A. The Clinical Study of the Heart Sounds in Health and Disease. Philadelphia: Collins, 1859.
1860 Hitchcock E, Hitchcock E Jr. Elementary Anatomy and Physiology for Colleges, Academies, and Other Schools. New York: Ivison, Phinney \& Co., 1860.
1863 Ordronaux J. Manual of Instruction for Military Surgeons, on the Examination of Recruits and Discharge of Soldiers. New York: D. Van Nostrand, 1863.
1866 Flint A. A Treatise on the Principles and Practice of Medicine; Designed for the Use of Practitioners and Students of Medicine. Philadelphia: H.C. Les, 1866; 5th edition, 1884.

## Year

Flint A. The Physiology of Man; Designed to Represent the Existing State of Physiological Science as Applied to the functions of the Human Body. Vol. 1. Introduction; The Blood; Circulation; Respiration. 1866. Vol II. Digestion; Absorption; Lymph and Chyle (1867). Vol. III. Secretion; Excretion; Ductless Glands; Nutrition; Animal Heat; Movement; Voice and Speech (1870). Vol. IV. Nervous System (1873). Vol. V. Special Senses; Generation (1874). New York: D. Appleton and Company.
1866 Huxley TH. Lessons in Elementary Physiology. London: Macmillan and Co., 1866.
1866 Lewis D. Weak Lungs and How to Make them Strong. Boston: Ticknor and Fields, 1866.
Dalton JC. A Treatise on Physiology and Hygiene; for Schools, Families, and Colleges. New York: Harper \& Brothers, 1869.
Gould BA. Investigations in the Military and Anthropological Statistics of American Soldiers. Published for the U.S. Sanitary Commission. New York: Hurd and Houghton, 1869.
1871 Flint A. On the Physiological Effects of Severe and Protracted Muscular Exercise; with Special Reference to Its Influence Upon the Excretion of Nitrogen. New York: D. Appleton \& Co., 1871.

1878 Flint A. On the Sources of Muscular Power, Arguments and Conclusions Drawn from Observations Upon the Human Subject, Under Conditions of Rest and of Muscular Exercise. New York: D. Appleton and Company, 1878.
Huxley TH, Youmans WJ. The Elements of Physiology and Hygiene for Educational Institutions. New York: D. Appleton \& Co., 1873.
Morgan JE. University Oars. London: MacMillan, 1873.
Baxter JH. Statistics, Medical and Anthropological, of the Provost-Marshal-Generals Bureau, Derived from Records of the Examination for Military Service in the Armies of the United States During the Late War of the Rebellion, of Over a Million Recruits, Drafted Men, Substitutes, and Enrolled Men. Vol. 1. Washington, DC: U.S. Government Printing Office, 1875.

Hitchcock E. A part of the course of instruction given in the Department of Physical Education and Hygiene in Amherst College. First issued by the class of 1877 while juniors. Amherst, MA, 1876.
Flint A. A Text-Book of Human Physiology; Designed for the Use of Practitioners and Students of Medicine. New York: D. Appleton, 1877. (2nd ed., rev. and cor. 1879; 3rd ed., rev. and cor. 1881, 1882, 1884, 1888; 4th ed., entirely rewritten 1888 and published 1889, 1891, 1892, 1893, 1895, 1896, 1897, 1901.) lint A. The Source of Muscular Power, as Deduced from Observations Upon the Human Subject Under Conditions of Rest, and of Muscular Exercise. London: 1877.
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Huxley TH, Youmans WJ. The Elements of Physiology and Hygiene: A Text-Book for Educational Institutions. New York: Appleton and Co., 1881.

## TABLE 1 - Continued

Year

Howell WH, ed. An American Text-Book of Physiology. Vol. 2. Muscle and Nerve; Central Nervous System; The Special Senses; Special Muscular Mechanisms; Reproduction. 2nd. rev. Philadelphia: W.B. Saunders \& Company, 1901.
Martin HN, Martin HC. The Human Body. A Beginners Text-book of Anatomy, Physiology and Hygiene. New York: H. Holt and Company, 1884 (261 p); revised, 1885.

Martin HN, Martin HC. The Human Body. A Beginners Text-book of Anatomy, Physiology and Hygiene, with Directions for Illustrating Important Facts of Mans Anatomy from That of the Lower Animals, and with Special References to the Effects of Alcoholic and Other Stimulants, and of Narcotics. New York: Henry Holt and Son, 1885.
Huxley TH, Martin HN. A Course of Elementary Instruction in Practical Biology. Rev. ed. London: Macmillan and Co., 1888.
Lagrange F. Physiology of Bodily Exercise. New York: D. Appleton and Company, 1890.

Hitchcock E, Seelye HH. An Anthropometric Manual, Giving the Average and Mean Physical Measurements and Tests of Male College Students and Method of Securing Them. 2nd ed. Amherst, MA: Williams, 1889.
Kolb G. Physiology of Sport. London: Krohne and Sesemann, 1893.
Galbraith AM. Hygiene and Physical Culture for Women. New York: Dodd, Mead and Company, 1895.
Atkinson E. The Science of Nutrition. 7th edition. Boston: Damrell \& Upham, 1896.
Martin H.N. The Human Body. An Account of Its Structure and Activities and the Conditions of Its Healthy Working. New York: Holt \& Co., 1881; 3rd ed. rev., 1864; $4^{\text {th }}$ ed. rev. 1885; 5th ed. rev., 1888, 1889 (621 p); 6th ed. rev., 1890, 1894 ( 621 p); 7th ed., 1896 ( 685 p); 8th ed. rev., 1896 (685 p).
Seaver, JW. Anthropometry and Physical Examination. A Book for Practical Use in Connection with Gymnastic Work and Physical Education. New Haven, CN: Press of the O.A. Dorman Co., 1896.
Martin H.N. The Human Body. A Text-book of Anatomy, Physiology and Hygiene; with Practical Exercises. 5th ed., rev. by George Wells Fitz. New York: H. Holt and Company. 1898 (408 p), 1899 (408 p); 5 editions 1900, 1902, 1911, 1912, 1930.
Atwater WO, Bryant AP. Dietary Studies of University Boat Crews. U.S. Department of Agriculture, Office of Experiment Stations, Bulletin no. 25. Washington, DC: U.S. Government Printing Office, 1900.

Howell WH, ed. An American Text-Book of Physiology. Vol. 1. Blood Lymph, and Circulation; Secretion, Digestion, and Nutrition; Respiration and Animal Heat; Chemistry of the Body. 2nd. rev. Philadelphia: W.B. Saunders \& Company, 1900.

Hastings WW. A Manual for Physical Measurements for

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 Use in Normal Schools, Public and Preparatory Schools, Boys Clubs, Girls Clubs, and Young Mens Christian Associations. Springfield: Young Men s Christian Association Training School, 1902.Year

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Hippocrates (460 377 вс)
and Persia, including the Empires of Alexander. Other early references to sports, games, and health practices (personal hygiene, exercise, and training) were recorded in the ancient civilizations of Syria, Egypt, Macedonia, Arabia, Mesopotamia and Persia, India, and China. Tipton chronicles the doctrines and teachings of Susruta (Sushruta, an Indian physician) regarding the influence of different modes of exercise on human health and disease. ${ }^{67}$ As an example, Tipton points out that Susruta considered obesity a disease caused by an increase in the humor vayu (from increases in lymph chyle) and thought that a sedentary lifestyle contributed to obesity. The greatest influence on Western civilization, however, came from the Greek physicians of antiquityHerodicus (5th century BC), Hippocrates (460 377 BC), and Claudius Galenus, or Galen (AD $131201^{b}$ ).

Herodicus, a physician and athlete, strongly advocated proper diet in physical training. His early writings and devoted followers influenced the famous physician Hippocrates ( father of preventive medicine ), credited with producing 87 treatises on medicine-several on health and hygieneduring the influential Golden Age of Greece. ${ }^{7,43}$ Hippocrates espoused a profound understanding of human suffering, emphasizing a doctor s place at the patient s bedside. Today, physicians take either the classical or modern Hippocratic Oath (www.pbs.org/wgbh/nova/doctors/oath_classical.html) based on Hippocrates Corpus Hippocraticum.


The World According to Galen. The white dots refer to the 14 major cities of that time period.

[^2]Five centuries after Hippocrates, during the early decline of the Roman Empire, Galen emerged as perhaps the most well-known and influential physician that ever lived. The son of a wealthy architect, Galen was born in the city of Pergamos ${ }^{c}$ and educated by scholars of the time. He began studying medicine at approximately age 16 . During the next 50 years, he implemented and enhanced current thinking about health and scientific hygiene, an area that some might consider applied exercise physiology. Throughout his life, Galen taught and practiced the laws of health : breathe fresh air, eat proper foods, drink the right beverages, exercise, get adequate sleep, have a daily bowel movement, and control one s emotions. ${ }^{7}$ A prolific writer, Galen produced at least 80 sophisticated treatises (and perhaps 500 essays) on numerous topics, many of which addressed human anatomy and physiology, nutrition, growth and development, the beneficial effects of exercise, the deleterious consequences of sedentary living, and a variety of diseases, including obesity, and their treatment. Susruta s notions about obesity were undoubtedly influenced by Galen, who introduced the concept polisarkia, now known as morbid obesity. ${ }^{64}$ Galen proposed treatments commonly in use today-diet, exercise, and medications.

One of the first bench physiologists, Galen conducted original experiments in physiology, comparative anatomy, and medicine, including dissections of humans, goats, pigs, cows, horses, and elephants. Also, as physician to the gladiators of Pergamos, Galen treated torn tendons and muscles ripped apart in combat with various surgical procedures he invented, including the procedure depicted in the 1544 woodcut of shoulder surgery shown at the top right, with commentaries from his Greek text De Fascius. Galen formulated rehabilitation therapies and exercise regimens, including treatment for a dislocated shoulder. He followed the Hippocratic school of medicine that believed in logical science grounded in experimentation and observation.

Galen wrote detailed descriptions about the forms, kinds, and varieties of swift and vigorous exercises, including their proper quantity and duration. The following definition of exercise is from the first complete English translation by Green ${ }^{23}$ of Hygiene (De Sanitate Tuenda, pp. 53 54; see Table 2), Galen s insightful and detailed treatise on healthful living:

To me it does not seem that all movement is exercise, but only when it is vigorous. But since vigor is relative, the same movement might be exercise for one and not for another. The criterion of vigorousness is change of respiration; those movements that do not alter the respiration are not called exercise. But if anyone is compelled by any movement to breathe more or less or faster, that movement becomes exercise from him. This therefore is what is commonly called exercise or gymnastics, from the gymnasium or public-place to which the inhabitants of a city come to anoint and rub themselves, to wrestle, throw


Woodcut by Renaissance artist Francesco Salviati (1510 1563) based on Galens De Fascius from the first century вс. The woodcut showing shoulder surgery provides a direct link with Hippocratic surgical practice that continued through the Byzantine period.
the discus, or engage in some other sport. . . . The uses of exercise, I think are twofold, one for the evacuation of the excrements, the other for the production of good condition of the firm parts of the body. For since vigorous motion is exercise, it must needs be that only these three things result from it in the exercising body-hardness of the organs from mutual attrition, increase of the intrinsic warmth, and accelerated movement of respiration. These are followed by all the other individual benefits which accrue to the body from exercise; from hardness of the organs, both insensitivity and strength for function; from warmth, both strong attraction for things to be eliminated, readier metabolism, and better nutrition and diffusion of all substances, whereby it results that solids are softened, liquids diluted, and ducts dilated. And from the vigorous movement of respiration the ducts must be purged and the excrements evacuated.

During the early Greek period, the Hippocratic school of physicians devised ingenious methods to treat common maladies; these methods included procedures to reduce pain from dislocated lower lumbar vertebrae. The illustration from the 11th-century Commentairies of Apollonius of Chitiron on the Periarthron of Hippocrates (top left) provided details about

[^3]

Ancient treatment for low-back pain.
early Greek surgical sports medicine interventions to treat athletes as well as the common citizen.

While most of the credit for modern day medicine has been attributed to the early Greek physicians, other influential physicians also contributed to knowledge about physiology, particularly the pulmonary circulation. West, in an insightful review of the contribution of Arab physician Ibn al-Nafis (1213 1288), ${ }^{68}$ points out that he challanged the long-standing beliefs of Galen about how blood moved from the right to left sides of the heart, and also predicted the existence of capillaries that predated Malpighi s discovery of the pulmonary capillaries by 400 years. The time line shows the period of the Islamic Golden Age. During this interval, interspaced between the Galenic era in 200 ad to the late 1400s and early 1500s, many physicians, including Persian physician Ibn Sina (Avicenna [ca. 980 1037]): www.muslimphilosophy.com/ sina/), contributed new knowledge in 200 books, including the influential Shifa (The Book of Healing) and Al Qanun fi Tibb (The Canon of Medicine) about bodily functions, ${ }^{68}$ as well as contributions from da Vinci ( 1452 1519; p. xxvii), Michael Servetus (1511 1564; discovered that blood passed through the pulmonary circulation without moving directly


| TABLE 2 - Table of Contents for Books 1 and $2^{a}$ of Galens De Sanitate Tuenda (Hygiene) |  |
| :---: | :---: |
|  | Book 1 The Art of Preserving Health |
| Chapter | Title |
| I | Introduction |
| II | The Nature and Sources of Growth and of Disease |
| III | Production and Elimination of Excrements |
| IV | Objectives and Hypothesis of Hygiene |
| V | Conditions and Constitutions |
| VI | Good Constitution: A Mean Between Extremes |
| VII | Hygiene of the Newborn |
| VIII | The Use and Value of Exercise |
| IX | Hygiene of Breast-Feeding |
| X | Hygiene of Bathing and Massage |
| XI | Hygiene of Beverages and Fresh Air |
| XII | Hygiene of the Second Seven Years |
| XIII | Causes and Prevention of Excrementary Retardation |
| XIV | Evacuation of Retained Excrements |
| XV | Summary of Book 1 |


|  | Book 2 |
| :--- | :--- |
|  | Exercise and Massage |

${ }^{a}$ Book III. Apotherapy, Bathing, and Fatigue. Book IV. Forms and
Treatment of Fatigue. Book V. Diagnosis, Treatment, and Prevention of Various Diseases. Book VI. Prophylaxis of Pathological Conditions.
from the right to left ventricle), Realdus Columbus (1516 1559; student of Vesalius who developed concepts concerning pulmonary circulation and that the heart has two ventricles, not three as postulated by the Galenic School), Andreas Vesalius (1514 1564; p. xxviii), Santorio (1514 1564; p. xxix), and William Harvey (1578 1657; p. xxix).

The era of more modern-day exercise physiology includes the periods of Renaissance, Enlightenment, and Scientific Discovery in Europe. It was then that Galen s ideas affected the writings of the early physiologists, anatomists, doctors, and teachers of hygiene and health. ${ }^{48,57,58}$ For example, in Venice in 1539, the Italian physician Hieronymus Mercurialis (1530 1606) published De Arte Gymnastica Apud Ancientes (The Art of Gymnastics Among the Ancients). This


Figure 1 - The early Greek influence of Galens famous essay Exercise with the Small Ball and specific strengthening exercises (throwing the discus and rope climbing) appeared in Mercurialiss De Arte Gymnastica, a treatise about the many uses of exercise for preventive and therapeutic medical and health benefits. Mercurialis favored discus throwing to aid patients suffering from arthritis and to improve the strength of the trunk and arm muscles. He advocated rope climbing because it did not pose health problems, and he was a firm believer in walking (a mild pace was good for stimulating conversation, and a faster pace would stimulate appetite and help with digestion). He also believed that climbing mountains was good for those with leg problems, long jumping was desirable (but not for pregnant women), but tumbling and handsprings were not recommended because they would produce adverse effects from the intestines pushing against the diaphragm! The three panels above represent the exercises as they might have been performed during the time of Galen.
text, heavily influenced by Galen and other early Greek and Latin authors, profoundly affected subsequent writings about physical training and exercise (then called gymnastics) and health (hygiene), not only in Europe (influencing the Swedish and Danish gymnastic systems), but also in early America (the 19th-century gymnastic hygiene movement). The panel in Figure 1, redrawn from De Arte Gymnastica, acknowledges the early Greek influence of one of Galen s famous essays, Exercise with the Small Ball, and his technical regimen of specific strengthening exercises (discus throwing and rope climbing).

## RENAISSANCE PERIOD TO THE 19TH CENTURY

New ideas formulated during the Renaissance exploded almost every idea inherited from antiquity. Johannes Gutenberg s (ca. 14001468 AD ) printing press disseminated both classic and newly acquired knowledge. The commoner could learn about local and world events. Education became more available because universities sprang up in Oxford, Cambridge, Cologne, Heidelberg, Prague, Paris, Angiers, Orleans, Vienna, Padua, Bologna, Siena, Naples, Pisa, Montpellier,

Toulouse, Valencia, Lisbon, and Salamanca. Art broke with past forms, emphasizing spatial perspective and realistic depictions of the human body.

Although the supernatural still influenced discussions of physical phenomena, many persons turned from dogma to experimentation as a source of knowledge. For example, medicine had to confront the new diseases spread by commerce with distant lands. Plagues and epidemics decimated at least 25 million people throughout Europe in just 2 years (1348 1350; www.pegasplanet.com/articles/EuropeanBlack Plaque.htm). New towns and expanding populations in confined cities led to environmental pollution and pestilence, forcing authorities to cope with new problems of community sanitation and care for the sick and dying. Science had not yet solved the medical problems from disease carriers such as insects and rats.

As populations expanded throughout Europe and elsewhere, medical care became more important for all levels of society. Unfortunately, medical knowledge failed to keep pace with need. For roughly 12 centuries, few advances had been made since the advances in Greek and Roman medicine. The writings of the early physicians had either been lost or preserved only in the Arab world. Thanks to the prestige of classical authors, Hippocrates and Galen still dominated medical education until the end of the 15 th century. Renaissance discoveries greatly modified these men s theories, however. New anatomists went beyond simplistic notions of four humors (fire, earth, water, air) and their qualities of hot, dry, cold, and wet when they discovered the complexities of circulatory, respiratory, and excretory mechanisms. ${ }^{7,9}$

Once rediscovered, these new ideas caused turmoil. The Vatican seemed to ban human dissections, but a number of progressive medical schools continued to conduct them, usually sanctioning one or two cadavers a year, or with official permission to perform an anatomy (the old name for a dissection) every 3 years. Performing autopsies helped physicians solve legal questions about a person s death or determine the cause of a disease. In the mid-1200s at the University of Bologna (founded in 1088 as a law school), every medical student had to attend one dissection each year, with 20 students assigned to a male cadaver and 30 students to a female cadaver. The first sanctioned dissection in Paris took place in 1407. In Rembrandt s first major portrait commission, the 1632 The Anatomy Lesson of Dr. Nicholas Tulp, shown top right, medical students listen intensely to the renowned Dr. Tulp as he dissects the arm of a recently executed criminal. The pioneering efforts of Vesalius (p. xxviii) and Harvey (p. xxix) made anatomic study a central focus of medical education, yet conflicted with the Church s strictures against violation of the individual rights of the dead because of the doctrine concerning the eventual resurrection of each person s body. In fact, the Church considered anatomic dissections a disfiguring violation of bodily integrity, despite the dismemberment of criminals as an extension of punishment. Nevertheless, the art of the period reflected close collaboration between artists and medical school physicians to portray anatomic dissections, essential for medical educa-


Rembrandts 1632 The Anatomy Lesson of Dr. Nicholas Tulp.
tion, and to satisfy a public thirst for new information in the emerging fields of physiology and medicine.

In 1316, Mondino de Luzzio (ca. 1275 1326), professor of anatomy at Bologna, published Anathomia, the first book of human anatomy. He based his teaching on human cadavers, not Greek and Latin authorities or studies of animals. The 1513 edition of Anathomia presented the same drawing as the original edition of the heart with three ventricles, a tribute to his accuracy in translation of the original inaccuracies! Certainly by the turn of the 15 th century, anatomic dissections for postmortems were common in the medical schools of France and Italy; they paved the way for the Golden Age of the Renaissance anatomists whose careful observations accelerated understanding of human form and function. Two women from the University of Bologna achieved distinction in the field of anatomy. Laura Bassi (1711 1778), the first woman to earn a doctor of philosophy degree, and the university s first female professor, specialized in experimental physics and basic sciences but had to conduct her experiments at home. Soon after, female scholars were allowed to


Professor Laura Bassi teach in university classrooms. At the time, Bassi gave her yearly public lectures on topics related to physics (including electricity and hydraulics, correction distortion in telescopes, hydrometry, and relation between a flame and stable air ). Anna Morandi Manzolini (1717 1774), also a professor and chair of the Department of Anatomy at the University of


Professor Anna Manzolini
Bologna, was an expert at creating wax models of internal organs and became the anatomy department s chief model maker. She produced an ear model that students took apart and reassembled to gain a better understanding of the ear s internal structures. Her wax and wood models of the abdomen and uterus were used didactically in the medical school for several hundred years. The wax self-portrait (top left) in the Museum of Human Anatomy of the University of Bologna (http://pacs.unica.it/cere/mono02_en.htm) shows Manzolini performing an anatomical dissection, clad in the traditional white lab coat, but also dressed in silks with diamonds and pearl jewelry-the manner expected of a woman of her high social and economic status.

Progress in understanding human anatomic form paved the way for specialists in physical culture and hygiene to


Anatomical sketch of stomach, intestines, kidney, and pancreas by Da Vinci.
design specific exercises to improve overall body strength, and training regimens to prepare for rowing, boxing, wrestling, competitive walking, and track and field activities and competitions.

## Notable Achievements by European Scientists

An explosion of new knowledge in the physical and biologic sciences helped prepare the way for future discoveries about human physiology during rest and exercise. ${ }^{1}$

Leonardo da Vinci (1452 1519)
Da Vinci dissected cadavers at the hospital of Santa Maria Nuova in Florence and made detailed anatomic drawings. Accurate as the sketches were, they still preserved Galenic ideas. Although he never saw the pores in the septum of the heart, he included them, believing they existed because Galen had seen them. Da Vinci first accurately drew the heart s inner
 structures and constructed models of valvular function that showed how the blood flowed in only one direction. This observation contradicted Galen s notion about the ebb and flow of blood between the heart s chambers. Because many of Da Vinci s drawings were lost for nearly two centuries, they did not influence later anatomic research.


Da Vincis Vitruvian Man.

Da Vinci s work built on and led to discoveries by two fellow artists. Leon Battista Alberti (1404 1472), an architect who perfected 3-dimensional perspectives, which influenced Da Vinci s concepts of internal relationships. Da Vinci s drawings (while not published during his lifetime) no doubt inspired the incomparable Flemish anatomist Andreas Vesalius (1514 1564). These three exemplary Renaissance anatomists empowered physiologists to understand the systems of the body with technical accuracy, not theoretical bias.

## Albrecht D rer (1471 1528)

D rer, a German contemporary of Da Vinci, extended the Italian s concern for ideal dimensions as depicted in Da Vinci s famous 1513 Vitruvian Man by illustrating age-related differences in body segment ratios formulated by 1st century BC Roman architect Marcus Vitruvius Pollio (c. 9020 bce; De architectura libri decem [Ten books on architecture]). D rer created a canon of proportion, considering total height as unity. For example, in his schema, the length of the foot was one-sixth of this total, the head one-seventh, and the hand onetenth. Relying on his artistic and printmaking skills rather than objective comparison, D rer made the ratio of height between men and women as 17 to 18 (soon thereafter proved incorrect). Nonetheless, D rer s work inspired Behnke ${ }^{69}$ in the 1950s to quantify body proportions into reference standards to evaluate body composition in men and women (see Chapter 28).

## Michelangelo Buonarroti (1475 1564)

Michelangelo, like Da Vinci, was a superb anatomist. Body segments appear in proper proportion in his accurate drawings. The famous David (right) clearly shows the veins, tendons, and muscles enclosing a realistic skeleton. Although his frescos on the Sistine ceiling often exaggerate musculature, they still convey a scientist s vision of the human body.


## Andreas Vesalius (1514 1564)

Belgian anatomist and physician Vesalius learned Galenic medicine in Paris, but after making careful human dissections, he rejected the Greek s ideas about bodily functions. At the start of his career, Vesalius authored books on anatomy, originally relying on Arabic texts, but then incorporating observations from his own dissections, including a self-portrait (right) from



Vesaliuss anatomic drawings. Left, Major nerves. Right, Muscular system in action. Note the graveyard crypts.

Fabrica, published at age 29, showing the anatomic details of an upper and lower right arm. His research culminated in the exquisitely illustrated text first published in Basel, Switzerland, in 1543, De Humani Corporis Fabrica (On the Fabric of the Human Body). Many consider Vesalius s drawings with 200 accompanying woodcuts the best anatomical renderings ever made, ushering in the age of modern medicine (www.metmuseum.org/TOAH/HD/anat/ho_53.682.htm\#). The same year, he published Epitome, a popular version of De Fabrica without Latin text.

Some physicians and clergymen became outraged, fearful that the new science was overturning Galen s time-honored speculations. Vesalius s treatise accurately rendered bones, muscles, nerves, internal organs, blood vessels (including veins for blood-letting), and the brain, but he differed from Galenic tradition by ignoring what he could not see. His remarkably detailed record of the muscular and skeletal architecture of the human body pared away one muscle layer at a time to reveal the hidden structures underneath.

Despite his attempt at accuracy, some of Vesalius s drawings contain curious inaccuracies. For example, he drew the inferior vena cava as a continuous vessel; he inserted an extra muscle to move the eyeball; and added an extra neck muscle present only in apes. Despite these minor discrepancies, Vesalius attempted to connect form with function. He showed that a muscle contracted when a longitudinal slice was made along the muscle s belly, but a transverse cut prevented contraction. Vesalius substantiated that nerves controlled muscles and stimulated movement. His two texts profoundly influenced medical education. They demolished traditional theories about human anatomy and emboldened later researchers to explore circulation and metabolism unburdened by past misconceptions. The illuminating work of Vesalius hastened the subsequent important discoveries in physiology and the beginning of modern science.

## Santorio Santorio (1561 1636)

A friend of Galileo and professor of medicine at Padua, Italy, Santorio used innovative tools for his research (www.sportsci.org/ news/history/santorio.html). He recorded changes in daily body temperature with the first air thermometer as a temperature-measuring device he crafted in 1612. Accuracy was poor because scientists had not yet discovered the effects of differential air pressures on temperature. Santorio also measured pulse rates with Galileo s pulsilogium (pul-
 siometer; www.skyscript.co. uk/galileo.html). Ever inventive, Santorio, a pioneer physician in the science of physical measurement, studied digestion and changes in metabolism by constructing a wooden frame that supported a chair, bed, and worktable (see illustration above). Suspended from the ceiling with scales, the frame recorded changes in body weight.

For 30 years, Santorio slept, ate, worked, and made love in the weighing contraption to record how much his weight changed as he ate, fasted, or excreted. He invented the term insensible perspiration to account for differences in body weight, because he believed that weight was gained or lost through the pores during respiration. Often depriving himself of food and drink, Santorio determined that the daily change in body mass approached 1.25 kg . Santorio s book of medical aphorisms, De Medicina Statica Aphorismi (1614), drew worldwide attention. Although this scientifically trained Italian instrument inventor did not explain the role of nutrition in weight gain or loss, Santorio nevertheless inspired later 18th century researchers in metabolism by quantifying metabolic effects.

## William Harvey (1578 1657)

Harvey discovered that blood circulates continuously in one direction and, just as Vesalius had done, overthrew 2000 years of medical dogma. Animal vivisection disproved the ancient supposition that blood moved from the right to left side of the heart through pores in the septum-pores that even Da Vinci and Vesalius acknowledged. Harvey announced his discovery during a 3-day

dissection lecture on April 16, 1616, at the oldest medical institution in England-the Royal College of Physicians in London, originally founded in 1518 by a small group of distinguished physicians. Twelve years later, Harvey published the details in a 72-page monograph, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (An Anatomical Treatise on the Movement of the Heart and Blood in Animals; www.bartleby.com/38/3/1.html). Harvey was aware of the uniqueness of his contributions, and he penned these prescient thoughts in the introduction to his masterpiece:

> At length, yielding to the requests of my friends, that all might be made participators in my labors, and partly moved by the envy of others, who, receiving my views with uncandid minds and understanding them indifferently, have essayed to traduce me publicly, I have moved to commit these things to the press, in order that all may be enabled to form an opinion both of me and my labours. This step I take all the more willingly, seeing that Hieronymus Fabricius of Aquapendente, although he has accurately and learnedly delineated almost every one of the several parts of animals in a special work, has left the heart alone untouched. Finally, if any use or benefit to this department of the republic of letters should accrue from my labours, it will, perhaps, be allowed that I have not lived idly. . . So will it, perchance, be found with reference to the heart at this time; or others, at least, starting hence, with the way pointed out to them, advancing under the guidance of a happier genius, may make occasion to proceed more fortunately, and to inquire more accurately.

By combining the new technique of experimentation on living creatures with mathematical logic, Harvey deduced that contrary to conventional wisdom, blood flowed in only one direction-from the heart to the arteries and from the veins back to the heart. It then traversed to the lungs before completing a circuit and reentering the heart. Harvey publicly demonstrated the one-way flow of blood by placing a tourniquet around a man s upper arm that constricted arterial blood flow to the forearm and stopped the pulse (see illustration left top, p. xxx). By loosening the tourniquet, Harvey allowed some blood into the veins. Applying pressure to specific veins forced blood from a peripheral segment where there was little pressure into the previously empty veins. Thus, Harvey proved that the heart pumped blood through a closed, unidirectional (circular) system, from arteries to veins and back to the heart. As he put it:

It is proved by the structure of the heart that the blood is continuously transferred through the lungs into the aorta as by two clacks of a water bellows to raise water. It is proved by a ligature that there is a passage of blood from the arteries to the veins. It is therefore demonstrated that the continuous movement of the blood in a circle is brought about by the beat of the heart. ${ }^{21}$

Harvey s experiments with sheep proved mathematically that the mass of blood passing through the sheep s heart in a


Harveys famous illustration demonstrating the one-way flow of the circulation.
fixed time was greater than the body could produce-a conclusion identical to that concerning the human heart. Harvey reasoned that if a constant mass of blood exists, then the large circulation volumes would require a one-way, closed circulatory system. Harvey did not explain why the blood circulated, only that it did. However, he correctly postulated that circulation might distribute heat and nourishment throughout the body. Despite the validity of Harvey s observations, distinguished scientists criticized them. Jean Riolan, an ardent Galenist who chaired the anatomy and botany departments at the University of Paris in the 1640s, maintained that if anatomic findings differed from Galen s, then the body in question must be abnormal and the results faulty. Nevertheless, Harvey s epic discovery governed subsequent research on circulation and demolished 1500 years of dogma.

## Giovanni Alfonso Borelli (1608 1679)

Borelli, a prot $g$ of Galileo and Benedetto Castelli (1578 1643) and a mathematician at the University of Pisa, Italy, used mathematical models to explain how muscles enabled animals to walk, fish to swim, and birds to fly. His ideas explaining how air entered and exited the lungs, though equally important, were less well-known. Borelli s accomplished student, Marcello
 Malpighi (1628 1694), described blood flowing through
microscopic structures (capillaries) around the lung sterminal air sacs (alveoli). Borelli observed that lungs filled with air because chest volume increased as the diaphragm moved downward. He concluded that air passed through the alveoli and into the blood, a sharp contrast to Galen s notion that air in the lungs cooled the heart, and an advance on Harvey s general observation concerning blood flow.

## Robert Boyle (1627 1691)

Working at Gresham College, London with his student Robert Hooke (1635 1703), Boyle devised experiments with a vacuum pump and bell jar to show that combustion and respiration required air. Boyle partially evacuated air from the jar containing a lit candle. The flame soon died. When he removed air from a jar containing a rodent or bird, it be-
 came unconscious; recirculating air back into the jar often revived the animal. Compressing the air produced the same results: Animals and flames survived longer.

Boyle removed the diaphragm and ribs from a living dog and forced air into its lungs with a bellows. Although the experiment did not prove that air was essential for life, it demonstrated that air pressure (and volumes) alternately contracted and expanded the lungs. He repeated the experiment, this time pricking the lungs so air could escape. Boyle kept the animal alive by forcing air into its lungs, proving that chest movement maintained airflow and disproving the earlier assertion that the lungs affected circulation.

Scientific societies and journals broadcasted these discoveries. Boyle belonged to the Royal Society of London, chartered in 1662 by Charles II. Four years later in France, Louis XIV sponsored the Acad mie Royale des Sciences so its salaried members could conduct a variety of studies. Both societies established journals (Philosophical Transactions of the Royal Society and Journal des Scavans, respectively) to disseminate information in chemistry, physics, medicine, nutrition, and metabolism to scientists and an increasingly educated lay public.

## Stephen Hales (1677 1761)

A renowned English plant physiologist and Fellow of the Royal Society, Hales amassed facts from his experiments with animals about blood pressure, the heart s capacity, and velocity of blood flow in Vegetable Statics: Or, an Account of Some Statical Experiments on the Sap in Vegeta-
 bles (1727). In this venerable text, Hales tells how water absorbed air when phosphorus and melted brimstone (sulfur)
burned in a closed glass vessel (see illustration [right] that shows the transfer of air released from substances burned in a closed vessel). Hales measured the volume of air either released or absorbed, and he demonstrated that air was a constituent of many common substances. His experiments proved that chemical changes occurred in solids and liquids during calcination (oxidation during combustion). Hales developed an idea suggested by Newton in 1713 that provided the first
 experimental evidence that the nervous system played a role in muscular contraction.

## James Lind (1716 1794)

Trained in Edinburgh, Lind entered the British Navy as a Surgeon s Mate in 1739 (www.sportsci.org/news/ history/lind/lind_sp.html). During an extended trip in the English Channel in 1747 on the 50-gun, 960-ton H.M.S. Salisbury, Lind carried out a decisive experiment (the first planned, controlled clinical trial) that changed the course of naval medicine. He knew
 that scurvy ( the great sea plague ) often killed two-thirds of a ship s crew. Their diet included 1 lb 4 oz of cheese biscuits daily, 2 lb of salt beef twice weekly, 2 oz of dried fish and butter thrice weekly, 8 oz of peas 4 days per week, and 1 gallon of beer daily. Deprived of vitamin C, sailors fell prey to scurvy. By adding fresh fruit to their diet, Lind fortified their immune systems so that British sailors no longer perished on extended voyages. From Lind s Treatise on the Scurvy (1753) comes the following poignant excerpt: ${ }^{35}$

On the 20th of May, 1747, I selected 12 patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. . . . The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of 6 days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine than a gargle for his mouth he became quite healthy before we came into

Plymouth which was on the 16th of June. The other was the best recovered in his condition; and being now pretty well, was appointed nurse to the rest of the sick. . . . Next to oranges, I thought the cyder had the best effects. It was indeed not very sound. However, those who had taken it, were in a fairer way of recovery than the others at the end of the fortnight, which was the length of time all these different courses were continued, except the oranges. The putrification of their gums, but especially their lassitude and weakness, were somewhat abated, and their appetites increased by it.

Lind published two books: ${ }^{65}$ An Essay on Preserving the Health of Seamen in the Royal Navy (1757) and Essay on Diseases Incidental to Europeans in Hot Climates (1768). Easily available, his books were translated into German, French, and Dutch. Lind s landmark emphasis on the crucial importance of dietary supplements antedates modern practices. His treatment regimen defeated scurvy, but 50 years had to pass with many more lives lost before the British Admiralty required fresh citrus fruit on all ships.

Joseph Black (1728 1799)
After graduating from the medical school in Edinburgh, Black became professor of chemistry at Glasgow. Experiments Upon Magnesia Alba, Quicklime, and Some Other Alcaline Substances (1756) determined that air contained carbon dioxide gas. He observed that carbonate (lime) lost half its weight after burning. Black reasoned that removing air from
 lime treated with acids produced a new substance he named fixed air, or carbon dioxide $\left(\mathrm{CaCO}_{3}=\mathrm{CaO}+\mathrm{CO}_{2}\right)$. Black s discovery that gas existed either freely or combined with other substances encouraged later experiments on the chemical composition of gases.

## Joseph Priestly (1733 1804)

Although Priestley discovered oxygen by heating red oxide of mercury in a closed vessel, he stubbornly clung to the phlogiston theory that had misled other scientists. Dismissing Lavoisier s (1743 1794) proof that respiration produced carbon dioxide and water, Priestley continued to believe in an immaterial constituent (phlogiston) that supposedly
 escaped from burning substances. He told the Royal Society about oxygen in 1772 and published Observations on Different Kinds of Air in 1773. Elated by his discovery, Priestley failed to grasp two facts that later research confirmed: (1) the


Priestleys London laboratory.
body needs oxygen and (2) cellular respiration produces carbon dioxide.

## Carl Wilhelm Scheele (1742 1786)

In one of history s great coincidences, Scheele, a Swedish pharmacist, discovered oxygen independently of Priestley. Scheele noted that heating mercuric oxide released fire-air (oxygen); burning other substances in fire-air produced violent reactions. When different mixtures contacted air inside a sealed container, the air volume decreased by $25 \%$ and could
 not support combustion. Scheele named the gas that extinguished fire foul air. In a memorable experiment, he added two bees to a glass jar immersed in lime water containing fire-air (illustration at right). After a few days, the bees remained alive, but the level of lime water had risen in the bottle and become cloudy. Scheele concluded that
 fixed air replaced the fire-air to sustain the bees. At the end of 8 days, the bees died despite ample honey inside the container. Scheele blamed their demise on phlogiston, which he felt was hostile to life. What Scheele called foul-air (phlogisticated air in Priestley s day) was later identified as nitrogen.

Just like Priestley, Scheele refused to accept Lavoisier s explanations concerning respiration. Although Scheele adhered to the phlogiston theory, he discovered, in addition to oxygen, chlorine, manganese, silicon, glycerol, silicon tetrafluoride, hydrofluoric acid, and copper arsenite (named

Scheele s green in his honor). Scheele also experimented with silver salts and how light influenced them (which became the basis of modern photography). He was the first and only student of pharmacy elected in 1775 into the prestigious Swedish Royal Academy of Sciences (www.kva.se/en/).

## Henry Cavendish (1731 1810)

Cavendish and his contemporaries Black and Priestley began to identify the constituents of carbohydrates, lipids, and proteins. On Factitious Air (1766) describes a highly flammable substance, later identified as hydrogen, which was liberated when acids combined with metals. Experiments in Air (1784) showed that inflammable air (hydrogen) combined with deflogisticated air (oxygen) produced water. Cavendish performed meticulous calculations using a sensitive torsion balance to measure the value of the gravitational constant $G$ that allowed him to compute the mass of the earth $\left(5.976 \times 10^{24} \mathrm{~kg}\right)$. His work eventually played an important role in the development of the space sciences, especially modern rocketry that led to space exploration (see Chapter 27).

## Antoine Laurent Lavoisier (1743 1794)

Lavoisier ushered in modern concepts of metabolism, nutrition, and exercise physiology (www. sportsci.org/news/history/lavoisier/ lavoisier.html). His discoveries in respiration chemistry and human nutrition were as essential to these fields as Harvey s discoveries were to circulatory physiology and medicine. Lavoisier paved the way for studies of energy balance by recog-
 nizing for the first time that the elements carbon, hydrogen, nitrogen, and oxygen involved in metabolism neither appeared suddenly nor disappeared mysteriously. He supplied basic truths: Only oxygen participates in animal respiration, and the caloric liberated during respiration is itself the source of the combustion. In the early 1770s, Lavoisier was the first person to conduct experiments on human respiration. According to Lusk, ${ }^{43}$ Lavoisier told of his experiments in a letter written to a friend dated November 19, 1790, as follows:

The quantity of oxygen absorbed by a resting man at a temperature of 26 C is 1200 pouces de France ( 1 cubic pouce $=$ 0.0198 L ) hourly. (2) The quantity of oxygen required at a temperature of 12 C rises to 1400 pouces. (3) During the digestion of food the quantity of oxygen amounts to from 1800 to 1900 pouces. (4) During exercise 4000 pouces and over may be the quantity of oxygen absorbed.

These discoveries, fundamental to modern concepts of energy balance, could not protect Lavoisier from the

A. Lavoisier supervises the first true exercise physiology experiment (heart rate and oxygen consumption measured as the seated subject at the right breathes through a copper pipe while pressing a foot pedal to increase external work). Sketched by Madame Lavoisier (sitting at the far left taking notes). B. The equipment of Lavoisiers laboratory from the mid-1700s can be viewed at Mus e des Arts et M tiers in Paris, France (60 rue Reaumur. Take the metro to exit Arts et Metiers; photo taken by F. Katch).
intolerance of his revolutionary countrymen. The Jacobean tribunal beheaded him in 1794. Yet once more, thoughtless resistance to innovative science temporarily delayed the triumph of truth.

## Lazzaro Spallanzani (1729 1799)

An accomplished Italian physiologist, Spallanzani debunked spontaneous generation as he studied fertilization and contraception in animals. In a famous study of digestion, he refined regurgitation experiments similar to those of the French scientist, Ren -Antoine Fercault de R aumur (1683 1757). R aumur s Digestion in Birds (1752) told
 how he recovered partially digested food from the gizzard of a kite. ${ }^{43}$ Spallanzani swallowed a sponge tied to the end of a string and then regurgitated it. He found that the sponge had absorbed a substance that dissolved bread and various animal tissues, thus indirectly observing how gastric juices function. His experiments with animals showed that the tissues of the heart, stomach, and liver consume oxygen and liberate carbon dioxide, even in creatures without lungs.

Spallanzani s idea that respiration and combustion took place within the tissues was novel and appeared posthumously in 1804. A century later, this phenomenon would be called internal respiration. ${ }^{2}$

## 19th Century Metabolism and Physiology

The untimely death of Lavoisier did not terminate fruitful research in nutrition and medicine. During the next half century, scientists discovered the chemical composition of carbohydrates, lipids, and proteins and further clarified the energy balance equation. ${ }^{12}$

## Claude Louis Berthollet

 (1748 1822)A French chemist and contemporary of Lavoisier, Berthollet (in white lab coat in illustration at right) identified the volatile substances associated with animal tissues. One of these substances, nitrogen, was produced when ammonia gas burned in oxygen. Berthollet showed that normal tissues did not contain ammonia. He believed that hydrogen united with nitrogen during fermentation to produce ammonia. Berthollet took exception to Lavoisier s ideas concerning the amount of heat liberated
 when the body oxidized an equal weight of carbohydrate or fat. According to Berthollet, the quantity of heat liberated in the incomplete oxidation of a substance equaled the difference between the total caloric value of the substance and that of the products formed.

## Joseph Louis Proust (1755 1826)

Proust proved that a pure substance isolated in the laboratory or found in nature would always contain the same elements in the same proportions. Known as the Law of Definite Proportions, Proust s ideas about the chemical constancy of substances provided an important milestone for future nutritional explorers, helping them analyze the major nutrients and calculate energy metabolism as meas-


## Louis-Joseph Gay-Lussac (1778 1850)

In 1810, Gay-Lussac, a pupil of Berthollet, analyzed the chemical composition of 20 animal and vegetable substances. He placed the vegetable substances into one of three categories depending on their proportion of hydrogen to oxygen atoms. One class of compounds he called saccharine (later identified as carbohydrate) was accepted by William Prout in his classification of the three basic macronutrients.

## William Prout (1785 1850)

Following up the studies of Lavoisier and S guin on muscular activity and respiration, Prout, an Englishman, measured the carbon dioxide exhaled by men exercising to fatigue (Annals of Philosophy, 1813). Moderate exercise such as walking raised carbon dioxide production to an eventual plateau. This observation heralded the modern
 concept of steady-state gas exchange kinetics in exercise. Although Prout could not determine the exact amount of carbon dioxide respired because there were no instruments to measure respiration rate, he nevertheless observed that carbon dioxide concentration in expired air decreased dramatically in fatiguing exercise.

## Fran ois Magendie (1783 1855)

In 1821, Magendie founded the first journal for the study of experimental physiology (Journal de Physiologie Exp rimentale), a field he literally created. The next year, he showed that anterior spinal nerve roots control motor activities and posterior roots control sensory functions.

Magendie s accomplishments were not limited to neural physiology. Unlike others who claimed that the tissues derived their nitrogen from the air, Magendie argued that the food they consumed provided the nitrogen. To prove his point, he studied animals subsisting on nitrogen-free diets. He described his 1836 experiment as follows (http://JN.nutrition.org/cgi/reprint/121/11_Suppl/S1.pdf):
... I took a dog of three years old, fat, and in good health, and put it to feed upon sugar alone, and gave it distilled water to drink: it had as much as it chose of both. . . . It appeared to
thrive very well in this way of living the first 7 or 8 days; it was brisk, active, ate eagerly, and drank in its usual manner. It began to get meagre upon the second week, though it had always a good appetite, and took about 6 or 8 ounces of sugar in 24 hours. . . . In the third week its leanness increased, its strength diminished, the animal lost its liveliness, and its appetite was much lessened. At this period there was developed, first upon one eye, and then upon the other, a small ulceration in the center of the transparent cornea; it increased very quickly, and in a few days it was more than a line in diameter; its depth increased in the same proportion; the cornea was very soon entirely perforated, and the humours of the eye ran out. This singular phenomenon was accompanied with an abundant secretion of the glands of the eyelids.

It, however, became weaker and weaker, and lost its strength; and though the animal took from 3 to 4 ounces of sugar every day, it became at length so weak that it could neither chew nor swallow; for the same reason every other motion was impossible. It expired the 32nd day of the experiment. I opened it with every suitable precaution; I found a total want of fat; the muscles were reduced by more than five-sixths of their ordinary size; the stomach and the intestines were also much diminished in volume, and strongly contracted.

The excrements, that were also examined by M. Chevreul, contained very little azote (nitrogen), whilst they generally present a great deal . . A third experiment produced similar results, and thence I considered sugar incapable of supporting dogs of itself.

## William Beaumont (1785 1853)

One of the most fortuitous experiments in medicine began on June 6, 1822, at Fort Mackinac on the upper Michigan peninsula (www.sportsci.org/ news/history/beaumont/beaumont. html). As fort surgeon, Beaumont tended the accidental shotgun wound that perforated the abdominal wall and stomach of a young French Canadian, Samata St. Martin, a voyageur for the American
 Fur Company.

The wound healed after 10 months but continued to provide new insights concerning digestion. Part of the wound formed a small natural valve that led directly into the stomach. Beaumont turned St. Martin on his left side, depressing the valve, and then inserted a tube the size of a large quill five or six inches into the stomach. He began two kinds of experiments on the digestive processes from 1825 to 1833 . First, he observed the fluids discharged by the stomach when different foods were eaten (in vivo); second, he extracted samples of the stomach s content and put them into glass tubes to determine the time required for external digestion (in vitro).

Beaumont revolutionized concepts about digestion. For centuries, the stomach was thought to produce heat that
somehow cooked foods. Alternatively, the stomach was portrayed as a mill, a fermenting vat, or a stew pan. ${ }^{d}$

Beaumont published the first results of his experiments on St. Martin in the Philadelphia Medical Recorder in January 1825 and full details in his Experiments and Observations on the Gastric Juice and the Physiology of Digestion (1833). ${ }^{21}$ Beaumont ends his treatise with a list of 51 inferences based on his 238 separate experiments. Although working away from the centers of medicine, Beaumont used findings from Spallanzini, Carminiti, Viridet, Vauquelin, Tiedemann and Gmelin, Leuret and Lassaigne, Montegre, and Prout. Even with their information, he still obeyed the scientific method, basing all his inferences on direct experimentation. Beaumont concluded:

> Pure gastric juice, when taken directly out of the stomach of a healthy adult, unmixed with any other fluid, save a portion of the mucus of the stomach with which it is most commonly, and perhaps always combined, is a clear, transparent fluid; inodorous; a little saltish; and very perceptibly acid. Its taste, when applied to the tongue, is similar to thin mucilaginous water, slightly acidulated with muriatic acid. It is readily diffusible in water, wine or spirits; slightly effervesces with alkalis; and is an effectual solvent of the materia alimentaria. It possess the property of coagulating albumen, in an eminent degree; is powerfully antiseptic, checking the putrefaction of meat; and effectually restorative of healthy action, when applied to old, fetid sores, and foul, ulcerating surfaces.

Beaumont s accomplishment is even more remarkable because the United States, unlike England, France, and Germany, provided no research facilities for experimental medicine. Little was known about the physiology of digestion. Yet Beaumont, a backwoods physiologist, ${ }^{12}$ inspired future studies of gastric emptying, intestinal absorption, electrolyte balance, rehydration, and nutritional supplementation with sports drinks.

## Michel Eugene Chevreul (1786 1889)

During his long life, Chevreul carried on a 200-year family tradition of studying chemistry and biology. His Chemical Investigations of Fat (1823) described different fatty acids. In addition, he separated cholesterol from biliary fats, coined the term margarine, and was first to show that lard consisted of two main fats (a solid he called stearine and the other a liquid called elaine). Chevreul also demon-
 strated that sugar from a diabetic s urine resembled cane sugar.

## Jean Baptiste Boussingault (1802 1884)

Boussingault s studies of animal nutrition paralleled later studies of human nutrition. He calculated the effect of calcium, iron, and other nutrient intake (particularly nitrogen) on energy balance. His pioneering work among Columbians formed the basis for his recommendations that they receive iodine to counteract goi-
 ter. Boussingault also turned his attention to plants. He showed that the carbon within a plant came from atmospheric carbon dioxide. He also determined that a plant derived most of its nitrogen from the nitrates in the soil, not from the atmosphere, as previously believed.

## Gerardus Johannis Mulder (1802 1880)

Professor of chemistry at Utrecht, Netherlands, Mulder analyzed albuminous substances he named proteine. He postulated a general protein radical identical in chemical composition to plant albumen, casein, animal fibrin, and albumen. This protein would contain substances other than nitrogen available only from plants. Because
 animals consume plants, substances from the plant kingdom, later called amino acids, served to build their tissues. Unfortunately, an influential German chemist, Justus von Liebig (1803 1873) attacked Mulder s theories about protein so vigorously that they fell out of favor.

Despite the academic controversy, Mulder strongly advocated society s role in promoting quality nutrition. He asked, Is there a more important question for discussion than the nutrition of the human race? Mulder urged people to observe the golden mean by eating neither too little nor too much food. He established minimum standards for his nation s food supply that he believed should be compatible with optimum health. In 1847, he gave these specific recommendations: laborers should consume 100 g of protein daily; those doing routine work about 60 g . He prescribed 500 g of carbohydrate as starch and included some fat without specifying an amount.

## Justus von Liebig (1803 1873)

Embroiled in professional controversies, Liebig nevertheless established a large, modern chemistry laboratory that attracted numerous students (www.sportsci.org/news/history/ liebig/liebig.html). He developed unique equipment to analyze

[^4]

Hundreds of chemists trained at Liebigs Giessen laboratory, many achieving international reputations for pioneering discoveries in chemistry. Liebigs interests included many topics in chemistry, not just those strictly related to chemistry. His research into chemical compounds produced the foundations of the dye industry and new, brilliant colors. (Photo courtesy of Magnus Mueller, Liebig Museum, Giessen, Germany.)
inorganic and organic substances. Liebig restudied protein compounds (alkaloids discovered by Mulder) and concluded that muscular exertion (by horses or humans) required mainly proteins, not just carbohydrates and fats. Liebig s influential Animal Chemistry (1842) communicated his ideas about energy metabolism.

Liebig dominated chemistry; his theoretical pronounce-
 ments about the relation of dietary protein to muscular activity were usually accepted without critique by other scientists until the 1850s. Despite his pronouncements, Liebig never carried out a physiologic experiment or performed nitrogen balance studies on animals or humans. Liebig demeaned physiologists, believing them incapable of commenting on his theoretic calculations unless they themselves achieved his level of expertise.

By midcentury, physiologist Adolf Fick (1829 1901) and chemist Johannes Wislicenus (1835 1903) challenged Liebig s dogma concerning protein s role in exercise. Their simple experiment measured changes in urinary nitrogen during a mountain climb. The protein that broke down could not have supplied all the energy for the hike. The result discredited Liebig s principal assertion regarding the importance of protein metabolism in supplying energy for vigorous exercise.

Although erroneous, Liebig s notions about protein as a primary exercise fuel worked their way into popular writings. By the turn of the 20th century, an idea that survives today seemed unassailable: Athletic prowess requires a large protein intake. He lent his name to two commercial products: Liebig s Infant Food, advertised as a replacement for breast milk, and Liebig s Fleisch Extract (meat extract) that supposedly conferred special benefits to the body. Liebig argued that consuming his extract and meat would help the body perform
extra work to convert plant material into useful substances. Even today, fitness magazines tout protein supplements for peak performance with little except anecdotal confirmation. Whatever the merit of Liebig s claims, debate continues, building on the metabolic studies of W. O. Atwater (1844 1907), F. G. Benedict (1870 1957), and R. H. Chittenden (1856 1943) in the United States and M. Rubner (1854 1932) in Germany. ${ }^{12}$

## Henri Victor Regnault (1810 1878)

With his colleague Jules Reiset, Henri Regnault, professor of chemistry and physics at the University of Paris, used closed-circuit spirometry to determine the respiratory quotient (RQ; carbon dioxide oxygen) in dogs, insects, silkworms, earthworms, and frogs (1849). Animals were placed in a sealed, 45 -L bell jar surrounded by a water jacket (see illustration below). A potash solution filtered the carbon dioxide gas produced during respiration. Water rising in a glass receptacle forced oxygen into the bell jar to replace the quantity consumed during energy metabolism. A thermometer recorded temperature, and a manometer measured variations in chamber pressure. For dogs, fowl, and rabbits deprived of food, the RQ was lower than when the same animals consumed meat. Regnault and Reiset reasoned that starving animals subsist on their own tissues. Foods never were completely destroyed during metabolism because urea and uric acid were recovered in the urine.


Regnault established relationships between different body sizes and metabolic rates. These ratios preceded the law of surface area and allometric scaling procedures now used in exercise science. Regnault and Reiset related oxygen consumption to heat production and body size in animals:

> The consumption of oxygen absorbed varies greatly in different animals per unit of body weight. It is ten times greater in sparrows than in chickens. Since the different species have the same body temperature, and the smaller animals present a relatively larger area to the environmental air, they experience a substantial cooling effect, and it becomes necessary that the sources of heat production operate more energetically and that respiration increase.

## Claude Bernard (1813 1878)

Claude Bernard, typically acclaimed as the greatest physiologist of all time, succeeded Magendie as professor of medicine at the Coll ge de France (www.sportsci.org/ news/history/bernard/bernard. html). Bernard interned in medicine and surgery before serving as laboratory assistant (pr parateur) to Magendie in 1839. Three years later, he
 followed Magendie to the H tel-Dieu (hospital) in Paris. For the next 35 years, Bernard discovered fundamental properties concerning physiology. He participated in the explosion of scientific knowledge in the midcentury. Bernard indicated his single-minded devotion to research by producing a doctorate thesis on gastric juice and its role in nutrition ( $D u$ sac gastrique et de son $r$ le dans la nutrition, 1843). Ten years later, he received the Doctorate in Natural Sciences for his study entitled Recherches sur une nouvelle fonction du foie, consider comme organe producteur
de mati re sucr e chez lhomme et les animaux (Research on a new function of the liver as a producer of sugar in man and animals). Before this seminal research, scientists assumed that only plants could synthesize sugar, and that sugar within animals must derive from ingested plant matter. Bernard disproved this notion by documenting the presence of sugar in the hepatic vein of a dog whose diet lacked carbohydrate.

Bernard s experiments that profoundly affected medicine include:

1. Discovery of the role of the pancreatic secretion in the digestion of lipids (1848)
2. Discovery of a new function of the liver-the internal secretion of glucose into the blood (1848)
3. Induction of diabetes by puncture of the floor of the fourth ventricle (1849)
4. Discovery of the elevation of local skin temperature upon section of the cervical sympathetic nerve (1851)
5. Production of sugar by washed excised liver (1855) and the isolation of glycogen (1857)
6. Demonstration that curare specifically blocks motor nerve endings (1856)
7. Demonstration that carbon monoxide blocks the respiration of erythrocytes (1857)

Bernard s work also influenced other sciences. ${ }^{21}$ His discoveries in chemical physiology spawned physiological chemistry and biochemistry, which in turn a century later spawned molecular biology. His contributions to regulatory physiology helped the next generation of scientists understand how metabolism and nutrition affected exercise. Bernard s influential Introduction l tude de la m decine exp rimentale (Introduction to the Study of Experimental Medicine, 1865) illustrates the self-control that enabled him to succeed despite external disturbances. Bernard urged researchers to vigorously observe, hypothesize, and then test their hypothesis. In the last third of the book, Bernard shares his strategies for verifying results. His disciplined approach


Students observing Dr. Bernard (white apron, no hat) perform a dissection as part of their medical training. Bernards students were thoroughly trained to conduct rigorous experiments (with controls), careful checking and rechecking of experimental observations, and application of related knowledge from disparate disciplines.
remains valid, and exercise physiologists would profit from reading this book.

## Edward Smith (1819 1874)

Edward Smith, physician, public health advocate, and social reformer, promoted better living conditions for Britain s lower class, including prisoners (www.sportsci.org/news/ history/smith/smith.html). He believed those in prison were maltreated because they received no additional food while toiling on the exhausting punitive treadmill. Smith had observed prisoners climbing up a treadwheel, whose steps
 resembled the side paddle wheels of a Victorian steamship. Prisoners climbed for 15 minutes, after which they were allowed a 15-minute rest, for a total of 4 hours of work three times a week. To overcome resistance from a sail on the prison roof attached to the treadwheel, each man traveled the equivalent of 1.43 miles up a steep hill.

Curious about this strenuous exercise, Smith conducted studies on himself. He constructed a closed-circuit apparatus (facemask with inspiratory and expiratory valves; see below) to measure carbon dioxide production while climbing at Brixton prison. ${ }^{22} \mathrm{He}$ expired 19.6 more grams of carbon while climbing for 15 minutes and resting for 15 minutes than he expired while resting. Smith estimated that if he climbed and rested for 7.5 hours, his daily total carbon output would increase $66 \%$. Smith analyzed the urine of four prisoners over a 3-week period to show that urea output was related to the nitrogen content of the ingested foods, while carbon dioxide related more closely to exercise intensity.

Smith inspired two German researchers to validate the prevailing idea that protein alone powered muscular contraction. Adolf Eugen Fick (1829 1901), a physiologist at the University of Zurich, and Johannes Wislicenus (1835 1903), professor of chemistry at Zurich, questioned whether protein oxidation or oxidation of carbohydrates and fats supplied energy

for muscular work. In 1864, they climbed Mt. Faulhorn (2681-m elevation to the lodge) in the Swiss Alps. Prior to the climb, they eliminated protein from their diet, reasoning that nonprotein nutrients would have to supply them energy. They collected their urine before and immediately after the ascent and the following morning. They calculated the external energy equivalent of the $1956-\mathrm{m}$ climb by multiplying body mass by the vertical distance. This external energy requirement exceeded protein catabolism reflected by nitrogen in the urine. Therefore, they concluded that the energy from protein breakdown hardly contributed to the exercise energy requirement. Again, these findings posed a serious challenge to Liebig s claim that protein served as the primary source of muscular power.

## Health and Hygiene Influence in the United States

By the early 1800s in the United States, ideas about health and hygiene were strongly promoted by European scienceoriented physicians and experimental anatomists and physiologists. ${ }^{22,23}$ Prior to 1800 , only 39 first edition American-authored medical books had been published; a few medical schools had been started in the 13 colonies (College of Philadelphia, 1765; Harvard Medical School, 1782); seven medical societies existed (the New Jersey State Medical Society being the first in $1766^{7,8}$ ), and only one medical journal was available (Medical Repository, published in 1797). Outside of the United States, 176 medical journals were being published, but by 1850 the number in the United States had increased to $117 .{ }^{63}$

Medical journal publications in the United States had increased tremendously during the first half of the 19th century, concurrent with a steady growth in the number of scientific contributions, yet European influences still affected the thinking and practice of U.S. medicine. ${ }^{45}$ This influence was particularly apparent in the information explosion that reached the public through books, magazines, newspapers, and traveling health salesmen who peddled an endless array of tonics, elixirs, and other products for purposes of optimizing health and curing disease. The hot topics of the early 19th century (also true today) included nutrition and dieting (slimming), general information concerning exercise, how best to develop overall fitness, training (or gymnastic) exercises for recreation and sport preparation, and all matters relating to personal health and hygiene.

By the middle of the 19th century, fledgling medical schools in the United States began to graduate their own students, many of whom assumed positions of leadership in the academic world and allied medical sciences. Interestingly, physicians had the opportunity either to teach in medical school and conduct research (and write textbooks) or become associated with departments of physical education and hygiene. There, they would oversee programs of physical training for students and athletes. ${ }^{42}$

Within this framework, we begin our discussion of the early physiology and exercise physiology pioneers with Austin Flint, Jr., MD, a respected physician, physiologist, and
successful textbook author (Table 1, page xix, lists his texts). His writings provided reliable information for those wishing to place their beliefs about exercise on a scientific footing.

## Austin Flint, Jr., MD: American Physician Physiologist

Austin Flint, Jr., MD (1836 1915) was one of the first influential American pioneer physician scientists whose writings contributed significantly to the burgeoning literature in physiology. Flint served as professor of physiology and physiological anatomy in the Bellevue Hospital Medical College of New York, and chaired the Department of Physiology and Microbiology from 1861 to 1897 . In 1866, he published a series of five classic textbooks, the first titled The Physiology of Man; Designed to Represent the Existing State of Physiological Science as Applied to the Functions of the Human Body. Vol. 1; Introduction; The Blood; Circulation; Respiration. Eleven years
 later, Flint published The Principles and Practice of Medicine, a synthesis of his first five textbooks, which consisted of 987 pages of meticulously organized sections with supporting documentation. The text included 4 lithograph plates and 313 woodcuts of detailed anatomic illustrations of the body s major systems, along with important principles of physiology. In addition, there were illustrations of equipment used to record physiologic phenomena, such as Etienne-Jules Marey s (1830 1904) early cardiograph for registering the wave form and frequency of the pulse and a refinement of one of Marey s instruments, the sphygmograph, for making pulse measurements-the forerunner of modern cardiovascular instrumentation (FIG. 2).

Dr. Flint, one of six generations of physicians spanning the years 1733 to 1955 , was well trained in the scientific method. In 1858, he received the American Medical Association s prize for basic research on the heart, and his medical school thesis, titled The Phenomena of Capillary Circulation, was published in 1878 in the American Journal of the Medical Sciences. A characteristic of Flint s textbooks was his admiration for the work of other scholars. These included the noted French physician Claude Bernard (1813 1878); the celebrated observations of Dr. William Beaumont; and William Harvey s momentous discoveries.

Dr. Flint was a careful writer. This was a refreshing approach, particularly because so many authorities in physical training, exercise, and hygiene in the United States and abroad were uninformed and unscientific about exercise and its possible role in health care. In his 1877 textbook, Flint


Figure 2 - Mareys advanced sphygmograph, including portions of four original tracings of the pulse under different conditions. It was not until the next century in 1928 that Boas and Goldschmidt (cited in the 1932 Boas and Goldschmidt text; see Table 1) reported on their human experiments with the first electronic cardiotachometer. (Goldschmidt had invented the pulse resonator for recording pulse rate in 1927.)
wrote about many topics related to exercise. The following sample passages are quoted from Flint s 1877 book to present the flavor of the emerging science of exercise physiology in the late 19th century:

1. Influence of posture and exercise on pulse rate (pp. 52 53)

It has been observed that the position of the body has a very marked influence upon the rapidity of the pulse. Experiments of a very interesting character have been made by Dr. Guy and others, with a view to determine the difference in the pulse in different postures. In the male, there is a difference of about ten beats between standing and sitting, and fifteen beats between standing and the recumbent posture. In the female, the variations with position are not so great. The average given by Dr. Guy is, for the male-standing, 81; sitting, 71; lying, 66; and for the female-standing, 91 ; sitting, 84; lying, 80. This is given as the average of a large number of observations.

Influence of age and sex. In both the male and female, observers have constantly found a great difference in the rapidity of the heart s action at different periods of life.

During early life, there is no marked and constant difference in the rapidity of the pulse in the sexes; but, toward the age of puberty, the development of the sexual peculiarities is accompanied with an acceleration of the heart s action in the female, which continues even into old age. The differences at different ages are shown in the following table, compiled from the observations of Dr. Guy:

Influence of Exercise, etc.-It is a fact generally admitted that muscular exertion increases the frequency of the pulsations of the heart; and the experiments just cited show that the difference in rapidity, which is by some attributed to change in posture (some positions, it is fancied, offering fewer obstacles to the current of blood than others), is mainly due to muscular exertion. Everyone knows, indeed, that the action of the heart is much more rapid after violent exertion, such as running, lifting, etc. Experiments on this point date from quite a remote period. Bryan Robinson, who published a treatise on the Animal Economy in 1734, states, as the result of observation, that a

| Ages <br> (Years) | Average Pulsations |  |
| :--- | :---: | :---: |
|  | Men | Women |
| 2 to 7 | 97 | 98 |
| 8 to 14 | 84 | 94 |
| 14 to 21 | 76 | 82 |
| 21 to 28 | 73 | 80 |
| 28 to 35 | 70 | 78 |
| 35 to 42 | 68 | 78 |
| 42 to 49 | 70 | 77 |
| 49 to 56 | 67 | 76 |
| 56 to 63 | 68 | 77 |
| 63 to 70 | 70 | 78 |
| 70 to 77 | 67 | 81 |
| 77 to 84 | 71 | 82 |

man in the recumbent position has 64 pulsations per minute; sitting, 68; after a slow walk, 78; after walking four miles in one hour, 100; and 140 to 150 after running as fast as he could. This general statement, which has been repeatedly verified, shows the powerful influence of the muscular system on the heart. The fact is so familiar that it need not be farther dwelt upon.
2. Influence of muscular activity on respiration (pp. 150 151)

Nearly all observers are agreed that there is a considerable increase in the exhalation of carbonic acid during and immediately following muscular exercise. In insects, Mr. Newport has found that a greater quantity is sometimes exhaled in an hour of violent agitation than in twenty-four hours of repose. In a drone, the exhalation in twenty-four hours was 0.30 of a cubic inch, and during violent muscular exertion the exhalation in one hour was 0.34 . Lavoisier recognized the great influence of muscular activity upon the respiratory changes. In treating of the consumption of oxygen, we have quoted his observations on the relative quantities of air vitiated in repose and activity.

The following results of the experiments of Dr. Edward Smith on the influence of exercise are very definite and satisfactory:

In walking at the rate of two miles an hour, the exhalation of carbonic acid during one hour was equal to the quantity produced during $1^{4}{ }_{5}$ hour of repose with food, and $2^{1}{ }_{2}$ hours with, and $3^{1}{ }_{2}$ hours without food.

One hour s labor at the tread-wheel, while actually working the wheel, was equal to $4^{1}{ }_{2}$ of rest with food, and 6 hours without food.

The various observers we have cited have remarked that, when muscular exertion is carried so far as to produce great fatigue and exhaustion, the exhalation of carbonic acid is notably diminished.
3. Influence of muscular exercise on nitrogen elimination (pp. 429 430)

We have had an opportunity of settling definitely the vexed question of the influence of muscular exercise upon elimination
of nitrogen. ${ }^{e}$ In 1871, we made an exceedingly elaborate series of observations upon Mr. Weston, the pedestrian. Of these we can only give here a brief summary. Mr. Weston walked for five consecutive days as follows: First day, 92 miles; second day, 80 miles; third day, 57 miles; fourth day, 48 miles; fifth day, 40.5 miles. The nitrogen of the food was compared with the nitrogen excreted for three periods; viz, five days before the walk, five days walking, and five days after the walk. A trusty assistant was with Mr. Weston day and night for the fifteen days; the food was weighted and analyzed; the excreta were collected; and other observations were made during the entire period. The analyses were made independently, under the direction of Prof. R.O. Doremus, who had no idea of the results until we had classified and tabulated them. The conclusions were most decided, and, as far as possible, all the physiological conditions were fulfilled. As regards the proportion of nitrogen eliminated to the nitrogen of the food, the general results were as follows:

For the 5 days before the walk, with an average exercise of about 8 miles daily, the nitrogen eliminated was $92: 82$ parts for 100 parts of nitrogen ingested. For the five days of the walk, for every hundred parts of nitrogen ingested, there were discharged $153: 99$ parts. For the five days after the walk, when there was hardly any exercise, for every hundred parts of nitrogen ingested, there were discharged 84:63 parts. During the walk, the nitrogen excreted was in direct ratio to the amount of exercise; and, what was still more striking, the excess of nitrogen eliminated over the nitrogen of food almost exactly corresponded with a calculation of the nitrogen of the muscular tissue wasted, as estimated from the loss of weight of the body. Full details of the method of investigation, the processes employed, etc., are given in our original paper.

Through his textbooks and writings, Austin Flint, Jr., influenced the first medically trained and scientifically oriented professor of physical education, Edward Hitchcock, Jr., MD. Hitchcock quoted Flint about the muscular system in his syllabus of Health Lectures, required reading for all students enrolled at Amherst College between 1861 and 1905.

## The Amherst College Connection

Two physicians, father and son, pioneered the American sports science movement. Edward Hitchcock, DD, LLD (1793 1864), was a professor of chemistry and natural history at Amherst College and also served as president of the college from 1845 1854. He convinced the college president in 1861 to allow his son Edward [(1828 1911); Amherst undergraduate (1849); Harvard medical degree (1853)] to assume the duties of his anatomy course. Subsequently, Edward Hitchcock, Jr., was officially appointed on August 15, 1861, as Professor of Hygiene and Physical Education with full academic rank in the Department of Physical Culture at an annual salary of $\$ 1000$, a position he held almost continuously
${ }^{e}$ Flint A Jr. On the physiological effects of severe and protracted muscular exercise, with special reference to its influence upon the excretion of nitrogen. New York Medical Journal, 1871;xiii:609, et seq.
until 1911. This was the second such appointment in physical education to an American college in the United States. ${ }^{f}$

The Hitchcocks geared their textbook to college physical education (Hitchcock E., Hitchcock E., Jr., Elementary Anatomy and Physiology for Colleges, Academies, and Other Schools, New York: Ivison, Phinney \& Co., 1860; Edward Hitchcock, Sr., had previously published a textbook on hygiene in 1831). The Hitchcock and Hitchcock anatomy and physiology book predated Flints anatomy and physiology text by 6 years. Topics covered were listed in numerical order by subject, and considerable attention was devoted to the physiology of species other than humans. The text included questions at the bottom of each page concerning the


Dr. Edward Hitchcock
(1793 1864)


Dr. Edward Hitchcock, Jr., MD (1828 1911) topics under consideration, making the textbook a study guide or workbook, not an uncommon pedagogic feature (Cutter, 1848; see Table 1). Figure 3 shows sample pages on muscle structure and function from the Hitchcock and Hitchcock text.

From 1865 to approximately 1905, the Hitchcocks syllabus of Health Lectures (a 38-page pamphlet titled The Subjects and Statement of Facts Upon Personal Health Used for the Lectures Given to the Freshman Classes of Amherst College) was part of the required curriculum. The topics included hygiene and physical education, with brief quotations about the topic, including a citation for the quote. In addition to quoting Austin Flint, Jr., regarding care of the muscles,
The condition of the muscular system is an almost unfailing evidence of the general state of the body, other quotations
peppered each section of the pamphlet, some from wellknown physiologists such as Englishman Thomas Huxley (1825 1895; http://aleph0.clarku.edu/huxley/) and Harvard s Henry Pickering Bowditch (1840 1911; cofounder of the American Physiological Society in 1887 and American editor of the Journal of Physiology). For example, with regard to physical education and hygiene, Huxley posited, The successful men in life are those who have stored up such physical health in youth that they can in an emergency work sixteen hours in a day without suffering from it. Concerning food and digestion, Bowditch stated: A scientific or physiological diet for an adult, per day, is two pounds of bread, and threequarters of a pound of lean meat, and in regard to tobacco use, Tobacco is nearly as dangerous and deadly as alcohol, and a man with tobacco heart is as badly off as a drunkard.
Other quotations were used for such tissues as skin. Dr. Dudley A. Sargent (1849 1924; pioneer Harvard physical educator) told readers, Wear dark clothes in winter and light in summer. Have three changes of underclothing-heavy flannels for winter, light flannels for spring and fall, lisle thread, silk or open cotton for summer.

## Anthropometric Assessment of Body Build

During the years 1861 to 1888 , Dr. Hitchcock, Jr., obtained 6 measures of segmental height, 23 girths, 6 breadths, 8 lengths, 8 measures of muscular strength, lung capacity, and pilosity (amount of hair on the body) from almost every student who attended Amherst College. From 1882 to 1888, according to Hitchcock, his standardization for measurement was improved based on suggestions of Dr. W. T. Brigham of Boston and Dr. Dudley A. Sargent (Yale medical degree, 1878; assistant professor of physical training and director of Harvard s Hemenway Gymnasium).

In 1889, Dr. Hitchcock and his colleague in the Department of Physical Education and Hygiene, Hiram H. Seelye, MD (who also served as college physician from 1884 1896), published a 37-page anthropometric manual that included five tables of anthropometric statistics of students from 1861 to 1891. This resource compendium provided detailed descriptions for taking measurements that also included eye testing and an examination of the lungs and heart before testing subjects for muscular strength. In the last section of the manual, Dr. Seelye wrote detailed instructions for using the various pieces of gymnasium apparatus for enlarging and strengthening the neck, to remedy round or stooping shoulders, to

[^5]
## CIIAPTER SECOND.

THE MOVING POWERS OF THE SYSTEM.-MYOLOGY, OR THE IIISTORY OF THE MUSCLES.

## DEFINITIONS AND DESCRIPTIONS.

228. Mieroscopic Structure of Muscle.-The Muscles, known as flesh or dean meat, compose a large part of the extremities, and the covering of the trunk. To the naked eye they appear to be fibrous, and, with the assistance of the microscope, these fibers are found to be bundles - called Fasci-culi-of still smaller fibers, called Ultimate Fibers. These seem to be polygonal in form, and with an average diameter of $\frac{1}{5} \frac{1}{0}$ th of an inch in man, though in some of the lower animals their size is much less.

Fiew of the stages of development of Muscular Fiber. 1, A Muscular Fiber of Animal life enclosed in its Sheath or Myolemma. 2, An Ultimate Fibril of tho same. 3, A more highly magnified View of Fig. 1, showing the true nature of the Longitudinal Strixe, as well as the mode of formation of the Transverse Strix. The Myolemma is here so thin as to permit the Cltimate Fibrils to be seen through it. 4, A Muscular Fibre of Organic life with two of its Nuclei; taken from the Urinary Bladder, and magnifled 600 Diameters. 5, A Muscular Fibre of Organic life from the Stomach, magnifled the same.
229. Fibrils. - The ulti-
 mate fibers are still further divisible into what are termed Fibrils. These have an average diameter of about ${ }_{\bar{\top} \bar{\sigma} \frac{1}{0} \bar{\pi}}$ th

[^6]108


A Tiew of the Fragments of Striped elementary Fibers, showing a clearage in opposite directions-magnifled 300 Diameters. 1, The Longitudinal Cle:vage. 2, The Transverso Cleavage, the Longitudinal Lines being scarcely visible. 3, Incomplete Fracture, following the opposite surfaces of a Dise which stretches across the Interval and retains the two Fragments in connexion. The Edge and Surface of this Dise are seen to be minutely tance between thanules corresponding in size to the thick ness of the Dise and to the dis-
 by violence from each other at the broken enil of the Fiber 7 . The two appearanes common'y presented by the scparated single Fibrills: ; more hiphly mannifed, at 7 the spaces are rectanirular, at S the borders are sealloped and the spaces beal-like of an inch, and number about 650 in each ultimate fiber. They are unprotected by any covering, while both the fasicu-

Fig. 122.
 lus and ultimate fiber are everywhere protected by a delicate sheath called the Sarcolemma.
230. Organic, or Unstriped, and Animal, or Striped Fi-bers.-All the muscles of the body are divided into two classes, according to their function. Those necessary for carrying on the vital functions, such as breathing and digestion, are called Organic, and those under the control of the will Animal Fibers. In addition to their use as a means of distinction, they may be known by their appearance under the micro-
What is the Sareolemma? On what "ement of muscle i.s this wanting? 2:0. Givo the two functional classeis of the anuocles.

Figure 3 - Examples from the Hitchcocks text on structure and function of muscles. (Reproduced from Hitchcock E, Hitchcock E Jr. Elementary anatomy and physiology for colleges, academies, and other schools. New York: Ivison, Phinney \& Co., 1860:132, 137. Materials courtesy of Amherst College Archives and permission of the Trustees of Amherst College, 1995.)
increase the size of the chest and the capacity of the lungs, to strengthen and enlarge the arm, abdominal muscles, and weak back, and to enlarge and strengthen the thighs, calves, legs and ankles. The Hitchcock and Seelye manual, the first of its kind devoted to an analysis of anthropometric and strength data based on detailed measurements, influenced other departments of physical education in the United States
(e.g., Yale, Harvard, Wellesley, Mt. Holyoke) to include anthropometric measurements as part of the physical education and hygiene curriculum. ${ }^{g}$

One reason for the early interest in anthropometric measurement was to demonstrate that engaging in daily, vigorous exercise produced desirable results, particularly for muscular development. Although none of the early physical education

[^7]

Figure 4 Changes in selected girth measurements of Amherst College men over 4 years of college using Behnkes reference man standards (presented in Chapter 28). A. The average body mass of the freshman class in 1882 was 59.1 kg (stature, 171.0 cm ). B. Four years later, average body mass increased $5.5 \mathrm{~kg}(11.3 \mathrm{lb})$ and stature increased by 7.4 cm (2.9 in).
scientists used statistics to evaluate the outcomes of exercise programs, it is instructive to apply modern methods of anthropometric analysis to the original data of Hitchcock on entering students at Amherst College in 1882 and on their graduation in 1886. Figure 4 shows how the average student changed in anthropometric dimensions throughout 4 years of college in relation to Behnkes reference standards presented in Chapter 28. Note the dramatic increase in biceps girth and decreases in the nonmuscular abdomen and hip regions. Although data for a nonexercising control group of students were not available, these changes coincided with daily resistance training prescribed in the Hitchcock and Seelye Anthropometric Manual. This training used Indian club or barbell swinging exercises (Fig. 5) and other strengthening modalities (horizontal bar, rope and ring exercises, parallel bar exercises, dipping machine, inclined presses with weights, pulley weights, and rowing machine workouts). The Hitchcock data presentation, a first of its kind initially reported in the Anthropometric Manual in March 1892, used bodily stature as the basis of comparison from measurements of 1322 students between 17 and 26 years of age. The strength tests are derived from 20,761 items. The Hitchcock anthropometric and strength studies were acknowledged in the first formal American textbook on anthropometry published in 1896 by Jay W. Seaver, MD (1855 1915), physician and lecturer on personal hygiene at Yale University. Table 3 presents a sample of the average and best (maximal) anthropometric and strength measures at Amherst College from 1861 to 1900.

While Hitchcock was performing pioneering anthropometric studies at the college level, the military was making the first detailed anthropometric, spirometric, and muscular strength measurements on Civil War soldiers in the early


Figure 5 Dr. Edward Hitchcock, Jr. (second from right, with beard) observing the students perform barbell exercises in the Pratt Gymnasium of Amherst College. (Photo courtesy of Amherst College Archives and by permission of the Trustees of Amherst College, 1995.)

1860s, published in 1869 by Gould (cited in Table 1). The specially trained military anthropometrists used a unique device, the andrometer (Fig. 6), to secure the physical dimensions to the nearest $1 / 10$ th of an inch of soldiers for purposes of fitting uniforms. The andrometer was originally devised in 1855 by a tailor in Edinburgh, Scotland, commissioned by the British government to determine the proper size for British soldiers clothing. This device was set by special gauges to adjust sliders for measurement of total height; breadth of the neck, shoulders, and pelvis; and the length of the legs and

TABLE 3 - Average and Best Anthropometric and Strength Records of Amherst College from 1861 to 1900 Inclusive

|  | Average |  |  | Maximal |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Metric | English |  | Metric | English |  | Held By |

${ }^{\mathrm{a}}$ Weight in kg or lb ; height in cm or in; girths in mm or in; strength in kg or lb .
From Hitchcock E., et al. An anthropometric manual, 4th ed. Amherst, MA: Carpenter and Morehouse, 1900.
height to the knees and crotch. Each examiner received 2 days of practice to perfect measurement technique before assignment to different military installations (e.g., Fort McHenry in Baltimore, Naval Rendezvous in New York City, Marine Barracks at the Brooklyn Navy Yard, and bases in South


Figure 6 - The andrometer, first used by the United States Sanitary Commission at numerous military installations along the Atlantic seaboard during the early 1860s, sized soldiers for clothing.

Carolina; Washington, DC; Detroit; and New Orleans). Data were compiled on the actual and relative proportions of 15,781 men ( Whites, Blacks, Indians ) between the ages of 16 and 45 years. One purpose of these military studies was to determine relationships among the anthropometric and other physical measurements, and to gather demographic and anthropologic statistics on enlisted and commissioned soldiers in the infantry, cavalry, and artillery. These early investigations about muscular strength and body dimensions served as prototypical studies whose measurement techniques led the way to many later studies conducted in the military about muscular strength and human performance per se. Most laboratories in exercise physiology today include assessment procedures to evaluate aspects of muscular strength and body composition. ${ }^{58,69}$

Figure 7A and B show two views of the instrument used to evaluate muscular strength in the military studies; C and D show the early spirometers used to evaluate pulmonary dimensions. The strength device predates the various strengthmeasuring instruments shown in Figure 8 used by Hitchcock (Amherst), Sargent (Harvard), and Seaver (Yale), as well as anthropometric measuring instruments used in their batteries of physical measurements. The inset shows the price list of some of the equipment from the 1889 and 1890 Hitchcock manuals on anthropometry. Note the progression in complexity of the early spirometers and strength devices used in the 1860 military studies (Fig. 7), and the more modern equipment of the 18891905 period displayed in Figure 8. Figure 9 includes three uncovered photographs (circa 1897 1901) of the strength-testing equipment (Kellogg s Universal Dynamometer) acquired by Dr. Hitchcock in 1897 to assess the strength of arms (panel A), anterior trunk and forearm


Figure 7 - A. and B. Instrument used to evaluate muscular strength in the military studies of Gould in 1869. The illustration on the left shows the general look of the device, while the right side shows the internal arrangement without face-plate. Gould described the procedure for measuring muscular strength as follows: The man stands upon the movable lid of the wooden packing box, to which the apparatus is firmly attached, and grasps with both hands the rounded extremities of a wooden bar, of convenient shape and adjustable in height. The handle is conveniently shaped for firm and easy grasp, its height well suited for application and the full muscular power, and the mechanism such as to afford results which are to all appearance very trustworthy. This was not the first dynamometer; Gould cites Regnier (no date given), who published a description of a dynamometer to measure the strength of Parisians; and P ron, who carried a dynamometer on an expedition to Australia. Other researchers in Europe had also used dynamometers to compare the muscular strength of men of different races. Figure 22.1C (Chapter 22) shows the modern back-leg lift dynamometer still used for assessing muscular strength as part of physical fitness test procedures. C. and D. Spirometers (or dry gas meters), manufactured by the American Meter Company of Philadelphia, were used to measure vital capacity. According to Gould, the spirometers needed to be rugged . . . to undergo the rough usage inseparable from transportation by army trains or on military railroads, which are in danger of being handled roughly at some unguarded moment by rude men. . . The spirometers were graduated in cubic centimeters and were furnished with a mouth-piece of convenient form, connected with the instrument by flexible tubing. (Gould, 1869; see Table 1.)
supinators (panel B), and leg extensors, flexors, and adductors (panel C). ${ }^{h}$

## The First Exercise Physiology Laboratory and Associated Degree Program in the United States

The first formal exercise physiology laboratory in the United States was established in 1891 at Harvard University and housed in a newly created Department of Anatomy, Physiology, and Physical Training at the Lawrence Scientific School. ${ }^{23,41}$ Several instructors in the initial undergraduate BS degree program in Anatomy, Physiology, and Physical Training started at the same time were Harvard-trained physicians; others—including Henry Pickering Bowditch, renowned professor of physiology who discovered the all-ornone principle of cardiac contraction and treppe, the staircase phenomenon of muscular contraction, and William T. Porter,
also a distinguished physiologist in the Harvard Medical School-were respected for their rigorous scientific and laboratory training.

## George Wells Fitz, MD: A Major Influence

An important influence in creating the new departmental major and recruiting top scientists as faculty in the Harvard program was George Wells Fitz, MD (1860 1934). Fitz vociferously supported a strong, science-based curriculum in preparing the new breed of physical educators. The archival records show that the newly formed major was grounded
 in the basic sciences, including formal coursework in exercise

[^8]

Figure 8 • Anthropometric instruments used by Hitchcock, Seaver, and Sargent. Sargent, also an entrepreneur, constructed and sold specialized strength equipment used in his studies. A. Metric graduated scale. B. Height meter. C. Sliding anthropometer. D. Cloth tape measure, with an instrument made by the Narragansett Machine Co. at the suggestion of Dr. Gulick (head of the Department of Physical Training of the YMCA Training School, Springfield, MA) in 1887. The modern version of this tape, now sold as the Gulick tape, was for attachment to the end of a tape to indicate the proper tension, so that the pressure may be always alike. (Seaver, 1896; see Table 1.) E. Calipers for taking body depths. F. Several types of hand dynamometers, including push holder and pull holder instruments. G. Back and leg dynamometer, also used to measure the strength of the pectoral and retractor muscles of the shoulders. H. Vital capacity spirometer and Hutchinsons wet spirometer. I. Two stethoscopes. The soft rubber bell was used to secure perfect coaptation to the surface of the chest. (Seaver, 1896; see Table 1.) The Albion Stethoscope was preferred because it could be conveniently carried in the pocket. J. Parallel bars for testing arm extensors during push-ups and testing of flexors in pull-ups. In special situations, physiology laboratories used Mareys cardiograph to record pulse, but the preferred instrument was a pneumatic kymograph (or sphygmograph; see Fig. 2). The inset table shows a price comparison for the testing equipment from the 1889 and 1890 Hitchcock manuals. Note the yearly variation in prices. (Inset courtesy of Amherst College Archives, reproduced by permission of the Trustees of Amherst College, 1995.)


Figure 9 - Kelloggs Universal Dynamometer, acquired by Dr. Hitchcock to test the muscular strength of Amherst College students. From 1897 to 1900, strength measurements were taken on 328 freshmen, 111 sophomores, and 88 seniors, including retests of 58 individuals. Arm strength was measured bilaterally for the forearms and for the latissimus dorsi, deltoid, pectoral, and shoulder retractor muscles. Trunk measurements included the anterior trunk, and anterior and posterior neck. The leg measurements included the leg extensors and flexors and thigh adductors. A. Arm pull. B. Anterior trunk (standing) and forearm supinators (sitting). C. Legs. (Photos courtesy of Amherst College Archives and by permission of the trustees of Amherst College, 1995.)
physiology, zoology, morphology (animal and human), anthropometry, applied anatomy and animal mechanics, medical chemistry, comparative anatomy, remedial exercises, physics, gymnastics and athletics, history of physical education, and English. Physical education students took general anatomy and physiology courses in the medical school; after 4 years of study, graduates could enroll as second-year medical students and graduate in 3 years with an MD degree. Dr. Fitz taught the physiology of exercise course; thus, we believe he was the first person to formally teach such a course. It included experimental investigation and original work and thesis, including 6 hours a week of laboratory study. The course prerequisites included general physiology at the medical school or its equivalent. The purpose of the course was to introduce the student to the fundamentals of physical education and provide training in experimental methods related to exercise physiology. Fitz also taught a more general course titled The Elementary Physiology of The Hygiene of Common Life, Personal Hygiene, Emergencies. The course included one lecture and one laboratory section a week for a year (or three times a week for half a year). The official course description stated: This is a general introductory course intended to give the knowledge of human anatomy, physiology and hygiene which should be possessed by every student; it is suitable also for those not intending to study medicine or physical training. Fitz also taught a course called Remedial Exercises: The Correction of Abnormal Conditions and Positions. Course content included observations of deformities such as spinal curvature (and the corrective effects of specialized exercises) and the selection and application of proper exercises, and in
the diagnosis of cases when exercise is unsuitable. Several of Fitz s scientific publications dealt with spinal deformities. In addition to the remedial exercise course, students took a required course, Applied Anatomy and Animal Mechanics: Action of Muscles in Different Exercises. This thrice-weekly course, taught by Dr. Dudley Sargent, was the forerunner of modern biomechanics courses. Its prerequisite was general anatomy at the medical school or its equivalent. Sargent designed numerous exercise machines with pulleys and weights (www.ihpra.org/ imagesa/sargentex.jpg), many of which he sold to individuals and schools.

Nine men graduated with BS degrees from the Department of Anatomy, Physiology, and Physical Training up to 1900. The aim of the major was to prepare students to become directors of gymnasia or instructors in physical training, to provide students with the necessary knowledge about the science of exercise, and to offer suitable training for entrance to the medical school. The stated purpose of the new exercise physiology research laboratory from Harvard s Widner Library catalogs of courses, was as follows:

A large and well-equipped laboratory has been organized for the experimental study of the physiology of exercise. The object of this work is to exemplify the hygiene of the muscles, the conditions under which they act, the relation of their action to the body as a whole affecting blood supply and general hygienic conditions, and the effects of various exercises upon muscular growth and general health.

With the activities of the department in full operation, its outspoken and critical director Dr. Fitz was not afraid to speak
his mind about academic topics. For example, Fitz reviewed a new physiology text (American Text-Book of Physiology, edited by William H. Howell, PhD, MD) in the March 1897 issue of the American Physical Education Review (Vol II, No. 1, p. 56). The review praised Dr. Howell s collection of contributions from outstanding physiologists (such as Bowditch, Lee, Lusk, and Sewall) and attacked an 1888 French book by Lagrange that some historians consider the first important text in exercise physiology. ${ }^{i 6}$ The following is Fitz s review:

No one who is interested in the deeper problems of the physiology of exercise can afford to be without this book [referring to Howell s Physiology text], and it is to be hoped it may be used as a text-book in the normal schools of physical training. These schools have been forced to depend largely on Lagrange s physiology of exercise for the discussion of specific problems, or at least for the basis of such discussions. The only value Lagrange has, to my mind, is that he seldom gives any hint of the truth, and the student is forced to work out his own problems. This does very well in well-taught classes, but, Alas! for those schools and readers who take his statements as final in matters physiological. We have a conspicuous example of the disastrous consequences in Treve s contribution of the Cy clopaedia of Hygiene on Physical Education, in which he quotes freely from Lagrange and rivals him in the absurdity of his conclusions.

The time has surely come for a thoroughly scientific investigation of the physiological problems involved in physical exercise and the promulgation of the exact and absolute. It is not too much to hope that the use of the American Text-Book of Physiology by training schools and teachers, may aid to bring about this much needed consummation.

For unknown reasons, but coinciding with Fitz s untimely departure from Harvard in $1899,{ }^{j 46}$ the department changed its curricular emphasis (the term physical training was dropped from the department title), thus terminating at least temporarily this unique experiment in higher education.

One of the legacies of the Fitz-directed Harvard experience between 1891 and 1899 was the training it provided to the cadre of young scholars who began their careers with a strong scientific basis in exercise and training and its relationship to health. Unfortunately, it would take about another
quarter century before the next generation of science-oriented physical educators (led by such world-class physiologists as Nobel laureate A. V. Hill and 1963 ACSM Honor Award recipient David Bruce Dill, not physical educators) would once again exert a strong influence on the physical education curriculum.

## Exercise Studies in Research Journals

Another notable event in the growth of exercise physiology occurred in 1898: the appearance of three articles dealing with physical activity in the first volume of the American Journal of Physiology. ${ }^{k}$ This was followed in 1921 with the publication of the prestigious journal Physiological Reviews (http://physrev.physiology.org/). Table 4 lists the articles in this journal (and two from the Annual Review of Physiology) from the first review of the mechanisms of muscular contraction by A. V. Hill (www.sportsci.org/news/history/hill/hill. html) in 1922, to Professor Francis Hellebrandt s classic review of exercise in 1940. The German applied physiology publication Internationale Zeitschrift fur angewandte Physiologie einschliesslich Arbeitsphysiologie (1929 1973) was a significant journal for research in exercise physiology. The current title of this journal is European Journal of Applied Physiology and Occupational Physiology. The Journal of Applied Physiology (http://jap.physiology.org/) was first published in 1948. Its first volume contained the now-classic paper on ratio expressions of physiologic data with reference to body size and function by J. M. Tanner, a must-read for exercise physiologists. The journal Medicine and Science in Sports was first published in 1969. Its aim was to integrate both medical and physiologic aspects of the emerging fields of sports medicine and exercise science. The official name of this journal was changed in 1980 (Volume 12) to Medicine and Science in Sports and Exercise (www.ms-se.com).

## The First Textbook in Exercise Physiology: The Debate Continues

What was the first textbook in exercise physiology? Several recent exercise physiology texts give the distinction of being first to the English translation of Fernand Lagrange s book, The Physiology of Bodily Exercise, originally published in

[^9]
## TABLE 4 • Review Articles About Exercise, 19221940

## Year Author and Article

Hill AV. The mechanism of muscular contraction. Physiol Rev 1922;2:310.
Cathcart EP. The influence of muscle work on protein metabolism. Physiol Rev 1925;5:225.
Cobb S. Review on the tonus of skeletal muscle. Physiol Rev 1925;5:518.
Vernon HM. Industrial fatigue in relation to atmospheric conditions. Physiol Rev 1928;8:1.
Eggleton P. The position of phosphorus in the chemical mechanism of muscle contraction. Physiol Rev 1929;9:432.
Richardson HB. The respiratory quotient (including: The source of energy used for muscular exertion). Physiol Rev 1929;9:61. Gasset HS. Contracture of skeletal muscle. Physiol Rev 1930;10:35.
Milroy TH. The present status of the chemistry of skeletal muscular contraction. Physiol Rev 1931;11:515.
Baetzer AM. The effect of muscular fatigue upon resistance. Physiol Rev 1932;12:453.
Hill AV. The revolution in muscle physiology. Physiol Rev 1932;12:56.
Jordan HE. The structural changes in striped muscle during contraction. Physiol Rev 1933;13:301.
Steinhaus AH. Chronic effects of exercise. Physiol Rev 1933;13:103.
Hinsey JC. The innervation of skeletal muscle. Physiol Rev 1934;14:514.
Dill DB. The economy of muscular exercise. Physiol Rev 1936;16:263.
Fenn WO. Electrolytes in muscle. Physiol Rev 1936;16:450.
Anderson WW, Williams HH. Role of fat in diet. Physiol Rev 1937;17:335.
Bozler E. Muscle. Annu Rev Physiol 1939;1:217.
Dill DB. Applied physiology. Annu Rev Physiol 1939;1:551. Millikan GA. Muscle hemoglobin. Physiol Rev 1939;19:503.
Tower SS. The reaction of muscle to denervation. Physiol Rev 1939;19:1. Hellebrandt FA. Exercise. Annu Rev Physiol 1940;2:411.

French in $1888 .{ }^{6,66,69}$ To deserve such historical recognition, we believe the work should meet the following three criteria:

1. Provide sound scientific rationale for major concepts
2. Provide summary information (based on experimentation) about important prior research in a particular topic area (e.g., contain scientific references to research in the area)
3. Provide sufficient factual information about a topic area to give it academic legitimacy

After reading the Lagrange book in its entirety, we came to the same conclusion as George Wells Fitz. Specifically, it was a popular book about health and exercise with a scientific title. It is our opinion that the book is not a legitimate scientific textbook of exercise physiology based on any reasonable criteria of the time. Despite Lagrange s assertion that the focus of his book assessed physiology applied to exercise and not hygiene and exercise, it is informed by a 19th-century hygienic perspective, not science. We believe Fitz would accept our evaluation.

There was much information available to Lagrange from existing European and American physiology textbooks about the digestive, muscular, circulatory, and respiratory systems, including some limited information on physical training, hormones, basic nutrition, chemistry, and the biology of muscular contraction. Admittedly, this information was relatively
scarce, but well-trained physiologists Flint, Howell, Martin, Huxley, Dalton, Carpenter, and Combe had already produced high-quality textbooks that contained relatively detailed information about physiology in general, with some reference to muscular exercise. ${ }^{46}$ We now understand why Fitz was so troubled by the Lagrange book. By comparison, the two-volume text by Howell titled An American Text-Book of Physiology was impressive; this edited volume contained articles from acknowledged American physiologists at the forefront of physiologic research. This textbook was a high-level physiology text even by today standards. In his quest to provide the best possible science for his physical education students, Fitz could not tolerate a book that did not live up to his expectations for excellence. In fact, the Lagrange book contained fewer than 20 reference citations, and most of these were ascribed to French research reports or were based on observations of friends performing exercise. This plethora of anecdotal reports must have given Fitz fits.

Lagrange, an accomplished writer, wrote extensively on exercise. Despite the titles of several of his books, ${ }^{l}$ Lagrange was not a scientist, but probably a practicing physical culturist. Bibliographic information about Lagrange is limited in the French and American archival records of the period-a further indication of his relative obscurity as a thinker of distinction. As far as we know, there have been no citations to his work in any physiology text or scientific article. For these

[^10]reasons, we contend the Lagrange book does not qualify as the first exercise physiology textbook. ${ }^{m}$

## Other Early Exercise Physiology Research Laboratories

The Nutrition Laboratory at the Carnegie Institute in Washington, DC, had been created in 1904 to study nutrition and energy metabolism, and the first research laboratories established in physical education in the United States to study exercise physiology were at George Williams College (1923), the University of Illinois (1925), and Springfield College (1927). However, the real impact of laboratory research in exercise physiology (along with many other research specialties) occurred in 1927 with the creation of the 800 -square-foot Harvard Fatigue Laboratory in the basement of Morgan Hall of Harvard University s Business School. ${ }^{33}$ The outstanding work of this laboratory during the next two decades established the legitimacy of exercise physiology on its own merits as an important area of research and study. Another exercise physiology laboratory started before World War II was the Laboratory of Physiological Hygiene at the University of California, Berkeley, in 1934. The syllabus for the Physiological Hygiene course (taught by professor Frank Kleeberger), the precursor of contemporary exercise physiology courses, contained 12 laboratory experiments. ${ }^{49}$ Several years later, Dr. Franklin M. Henry assumed responsibility for the laboratory. Dr. Henry began publishing the results of different experiments in various physiology-oriented journals, including the Journal of Applied Physiology, Annals of Internal Medicine, Aviation Medicine, War Medicine, and Science. Henry s first research project as a faculty member in the Department of Physical Education (published in 1938) concerned the validity and reliability of the pulse ratio test of cardiac efficiency; ${ }^{27,28,29}$ a later paper dealt with predicting aviators bends. Henry applied his training in experimental psychology to exercise physiology topics, including individual differences in the kinetics of the fast and slow components of the oxygen uptake and recovery curves during light- and moder-ate-cycle ergometer exercise; muscular strength; cardiorespiratory responses during steady-rate exercise; assessment of heavy-work fatigue; determinants of endurance performance; and neural control factors related to human motor performance (Fig. 10).

## Contributions of the Harvard Fatigue Laboratory (1927 1946)

Many of the great scientists of the 20th century with an interest in exercise were associated with the Harvard Fatigue Laboratory. This research facility was established by Lawrence J.

Henderson, MD (1878 1942), renowned chemist and professor of biochemistry at the Harvard Medical School. The first and only scientific director of the Fatigue Laboratory was David Bruce Dill (1891 1986; www.theaps.org/about/pres/introdbd.htm), a Stanford PhD in physical chemistry. Dill was transformed from a biochemist to an experimental physiologist while at the Fatigue Laboratory and was an influential
 driving force behind the laboratory s numerous scientific accomplishments. His early academic association with Boston physician Arlen Vernon Bock (a student of famous high-altitude physiologist Dr. Barcroft at Cambridge, England, ${ }^{5}$ and Dill s closest friend for 59 years) and contact with 1922 Nobel laureate Archibald Vivian (A. V.) Hill (for his discovery related to heat production in muscles) provided Dill with the confidence to successfully coordinate the research efforts of dozens of scholars from 15 different countries. A. V. Hill convinced Bock to write a third edition of Bainbridge s text Physiology of Muscular Activity. Bock, in turn, invited Dill to coauthor the book republished in $1931 .{ }^{17}$

Over a 20-year period, at least 352 research papers, numerous monographs, and a book ${ }^{33}$ were published in areas of basic and applied exercise physiology, including methodologic refinements concerned with blood chemistry analysis and simplified methods for analyzing the fractional concentrations of expired air. Research at the Fatigue Laboratory included many aspects of short-term responses and chronic physiologic adaptations to exercise under environmental stresses produced by exposure to altitude, heat, and cold. ${ }^{20}$ Most of the key human exercise experiments were conducted using treadmill and bicycle ergometer exercise, but several important studies used animals. The human and animal studies framed the cornerstone for research in modern laboratories of exercise physiology, particularly those related to the assessment of physical working capacity and fitness, cardiovascular and hemodynamic responses during maximal exercise, kinetics of oxygen consumption and substrate use, metabolism during exercise and recovery, and maximal oxygen consumption. Detailed discussions of each of these topics appear in various chapters of this seventh edition.

Like the first exercise physiology laboratory established at Harvard s Lawrence Scientific School in 1892, the Harvard Fatigue Laboratory demanded excellence in research and scholarship. Particularly noteworthy was the cooperation among scientists from around the world that fostered lasting collaborations. Furthermore, many of the scientists who had

[^11]

Figure 10 - A. Professor Franklin Henry supervising 50-yard sprints (at 5-yd intervals) on the roof of Harmon Gymnasium at UC Berkeley. Henrys study ${ }^{28}$ was prompted by A. V. Hills 1927 observations concerning the viscosity factor of muscular contraction that at first helped to explain the large decline in metabolic efficiency at fast rates of movement and that the oxygen requirement of running increased with the cube of speed. Henry verified that metabolic efficiency was not correlated with a muscle viscosity factor. ${ }^{26,27}$ B. Henry making limb and trunk anthropometric measurements on a sprinter during continuous studies of the force-time characteristics of the sprint start ${ }^{29}$ to further evaluate A . V. Hills theoretical equation for the velocity of sprint running. C. Henry recording the timing of the initial movements of blocking performance in football players. ${ }^{44}$
contact with the Fatigue Laboratory profoundly affected a new generation of exercise physiologists in the United States and abroad. Noteworthy were Ancel Keys (1904 2004), who established the Laboratory of Physiology and Physical Education (later renamed the Laboratory of Physiological Hygiene) at the University of Minnesota; Henry L. Taylor (Keys and Taylor were mentors to exercise physiologist Elsworth R. Buskirk, formerly at the NIH and later the Noll Laboratory at Pennsylvania State University); Robert E. Johnson at the Human Environmental Unit at the University of Illinois; Sid Robinson at Indiana University; Robert C. Darling at the Department of Rehabilitation Medicine at Columbia University; Harwood S. Belding, who started the Environmental Physiology Laboratory at the University of Pittsburgh; C. Frank Consolazio of the U.S. Army Medical Research and Nutrition Laboratory at Denver; Lucien Brouha, who headed the Fitness Research Unit at the University of Montreal, and then went to the Dupont Chemical Company in Delaware; and Steven M. Horvath, who established the Institute of Environmental Stress at the University of California, Santa Barbara, where he worked with visiting scientists and mentored graduate students in the Biology Department and Department of Ergonomics and Physical Education. After the Fatigue Laboratory was unfortunately forced to close in 1946, Dill continued as the deputy director of the U.S. Army Chemical Corps Medical Laboratory in Maryland for 13 years (1948 1961). Thereafter, he worked with Sid Robinson at Indiana University s physiology department. He then started the Desert Research Institute (connected with the University of Nevada at Las Vegas), where he studied the physiologic responses of men and animals to hot environments, a topic that culminated in a book on the subject. ${ }^{19}$

The group of scholars associated with the Harvard Fatigue Laboratory mentored the next generation of students who continue to make significant contributions to the field of exercise physiology. The monograph by Horvath and Horvath ${ }^{33}$ and the chronology by Dill ${ }^{19}$ are the best direct sources of historical information about the Harvard Fatigue Laboratory. Exercise physiology continued to expand after the closing of the Fatigue Laboratory. Subsequent efforts probed the full range of physiologic functions. The depth and breadth of these early investigations, summarized in Table 5 provided much of the current knowledge base for establishing exercise physiology as a respectable academic field of study.

## Research Methodology Textbook Focusing on Physiologic Research

In 1949, the Research Section of the Research Council of the Research Section of the American Association for Health, Physical Education, and Recreation, or AAHPER (an outgrowth of the American Association for the Advancement of Physical Education created in 1885), sponsored publication of the first textbook devoted to research methodology in physical education. ${ }^{1}$ Thomas Cureton, PhD, (1901 1992; ACSM Honor Award, 1969) a pioneer researcher in physical fitness evaluation and director of the exercise physiology research

TABLE 5 - Areas of Investigation at the Harvard Fatigue Laboratory that Helped to Establish Exercise Physiology as an Academic Discipline

1. Specificity of the exercise prescription.
2. Genetic components of an exercise response.
3. Selectivity of the adaptive responses by diseased populations.
4. Differentiation between central and peripheral adaptations.
5. The existence of cellular thresholds.
6. Actions of transmitters and the regulation of receptors.
7. Feed-forward and feedback mechanisms that influence cardiorespiratory and metabolic control.
8. Matching mechanisms between oxygen delivery and oxygen demand.
9. The substrate utilization profile with and without dietary manipulations.
10. Adaptive responses of cellular and molecular units.
11. Mechanisms responsible for signal transduction.
12. The behavior of lactate in cells.
13. The plasticity of muscle fiber types.
14. Motor functions of the spinal cord.

15 . The ability of hormonally deficient animals to respond to conditions of acute exercise and chronic disease.
16. The hypoxemia of severe exercise.

From Tipton CM. Personal communication to F. Katch, June 12, 1995. From a presentation made to the American Physiological Society Meetings, 1995.
laboratory he established at the University of Illinois in 1944, appointed Dr. Henry to chair the committee to write the chapter on physiologic research methods. The other committee members were respected scientists in their own right and included the following: Anna Espenshade (PhD in psychology from Berkeley, specialist in motor development and motor performance during growth); Pauline Hodgson (Berkeley PhD in physiology who did postdoctoral work at the Harvard Fatigue Laboratory); Peter V. Karpovich, MD (originator of the Physiological Research Laboratory at Springfield College); Arthur H. Steinhaus, PhD (director of the research laboratory at George Williams College, one of the 11 founders of the American College of Sports Medicine, and research physiologist who authored an important review article [Physiological Reviews, 1933] about chronic effects of exercise); and distinguished Berkeley physiologist Hardin Jones, PhD (Donner Research Laboratory of Medical Physics at Berkeley).

The book chapter by this distinguished committee stands as a hallmark of research methodology in exercise physiology. The 99 references, many of them key articles in this thenembryonic field, covered such exercise-related topics as the heart and circulation, blood, urine and kidney function, work, lung ventilation, respiratory metabolism and energy exchange, and alveolar air.

Another masterful compendium of research methodologies published 14 years later, Physiological Measurements of Metabolic Functions in Man, by C. F. Consolazio and colleagues, provided complete details about specific measurements in exercise physiology. ${ }^{16}$ Several sections in this book
contained material previously published from the Harvard Fatigue Laboratory one year before its closing in $1946{ }^{34}$ and from another book dealing with metabolic methods published in $1951 .{ }^{15}$

## THE NORDIC CONNECTION (DENMARK, SWEDEN, NORWAY, AND FINLAND)

Denmark and Sweden have made a significant historical impact on physical education as an academic field. In 1800, Denmark was the first European country to include physical training (military-style gymnastics) as a requirement in the public school curriculum. Since that time, Danish and Swedish scientists have made outstanding contributions to research in both traditional physiology and exercise physiology.

## Danish Influence

In 1909, the University of Copenhagen endowed the equivalent of a Chair in Anatomy, Physiology, and Theory of Gymnastics. ${ }^{43}$ The first docent was Johannes Lindhard, MD (1870 1947). He later teamed with August Krogh, PhD (1874 1949; www.sportsci.org/ news/history/krogh/krogh.html), an eminent scientist specializ-


Professors August Krogh and Johannes Lindhard in the early 1930s. ing in physiological chemistry and research instrument design and construction, to conduct many of the now classic experiments in exercise physiology. For example, Krogh and Lindhard investigated gas exchange in the lungs, pioneered studies of the relative contribution of fat and carbohydrate oxidation during exercise (see Focus on Research, Chapter 8), measured the redistribution of blood flow during different exercise intensities, and measured cardiorespiratory dynamics in exercise (including cardiac output using nitrous oxide gas, a method described by a German researcher in 1770).

By 1910, Krogh and his wife Marie (a physician) had proven through a series of ingenious, decisive experiments ${ }^{37} 40$ that diffusion was how pulmonary gas exchange occurred-not by secretion of oxygen from lung tissue into the


Marie and August Krogh blood during exercise and exposure to altitude, as postulated by Scottish physiologist Sir John Scott Haldane (1860 1936) and Englishman James Priestley. ${ }^{25}$ By 1919, Krogh had published reports of a series of experiments (with three appearing in the Journal of

Physiology, 1919) concerning the mechanism of oxygen diffusion and transport in skeletal muscles. The details of these early experiments are included in Krogh s 1936 textbook, ${ }^{37}$ but he also was prolific in many other areas of science. ${ }^{36} 40$ In 1920, Krogh received the Nobel Prize in physiology or medicine for discovering the mechanism of capillary control of blood flow in resting and exercising muscle (in frogs). To honor the achievements of this renowned scientist (which included 300 scientific articles), an institute for physiologic research in Copenhagen was named for him.

Three other Danish researcher physiologists, Erling Asmussen (1907 1991; ACSM Citation Award, 1976, and ACSM Honor Award, 1979), Erik Hohw -Christensen (1904 1996; ACSM Honor Award, 1981), and Marius Nielsen (1903 2000) conducted pioneering studies in exercise physiology. These three musketeers, as Krogh referred to them, published numerous research papers from the 1930s to the 1970s. Asmussen, initially an assistant in Lindhards laboratory, became a productive researcher specializing in muscle fiber architecture and mechanics. He also published papers


The three musketeers, Drs. Erling Asmussen (left), Erik Hohw Christensen (center), and Marius Nielsen (right) (1988 photo). with Nielsen and Christensen as coauthors on many applied topics including muscular strength and performance, ventilatory and cardiovascular response to changes in posture and exercise intensity, maximum working capacity during arm and leg exercise, changes in oxidative response of muscle during exercise, comparisons of positive and negative work, hormonal and core temperature response during different intensities of exercise, and respiratory function in response to decreases in oxygen partial pressure. As evident in his classic review article ${ }^{14}$ of muscular exercise that cites many of his own studies (plus 75 references from other Scandinavian researchers), Asmussen s grasp of the importance of the study of biologic functions during exercise is as relevant today as it was more than 41 years ago when the article was published. He clearly defines exercise physiology within the context of biologic science:

The physiology of muscular exercise can be considered a purely descriptive science: it measures the extent to which the human organism can adapt itself to the stresses and strains of the environment and thus provides useful knowledge for athletes, trainers, industrial human engineers, clinicians, and workers in rehabilitation on the working capacity of humans and its limitations. But the physiology of muscular exercise is also part of the general biological science, physiology, which attempts to explain how the living organism functions, by means of the chemical and physical laws that govern the inanimate world. Its important role in physiology lies in the fact that muscular exercise more than most other conditions, taxes the functions to their uttermost. Respiration, circulation, and heat
regulation are only idling in the resting state. By following them through stages of increasing work intensities, a far better understanding of the resting condition is also achieved. Although the physiology of muscular exercise must be studied primarily in healthy subjects, the accumulated knowledge of how the organism responds to the stresses of exercise adds immensely to the understanding of how the organism adapts itself to disease or attempts to eliminate its effects by mobilizing its regulatory mechanisms.

Christensen became Lindhards student in Copenhagen in 1925. Together with Krogh and Lindhard, Christensen published an important review article in 1936 that described physiologic dynamics during maximal exercise. ${ }^{14}$ In his 1931 thesis, Christensen reported on studies of cardiac output with a modified Grollman acetylene method; body temperature and blood sugar concentration during heavy cycling exercise; comparisons of arm and leg exercise; and the effects of training. Together with Ov Hansen, he used oxygen consumption and the respiratory quotient to describe how diet, state of training, and exercise intensity and duration affected carbohydrate and fat use. Interestingly, the concept of carbohydrate

A. Bengt Saltin taking muscle biopsy of gastrocnemius muscle. (Photo courtesy of Dr. David Costill.) B. Saltin (hand on hip) during an experiment at the August Krogh Institute, Copenhagen. (Photo courtesy Per-Olof strand.)
loading was first discovered in 1939! Other notable studies included core temperature and blood glucose regulation during light-to-heavy fatiguing exercise at various ambient temperatures. A study by Christensen and Nielsen in 1942 used finger plethysmography to study regional blood flow (including skin temperature) during brief periods of constant-load cycle ergometer exercise. ${ }^{13}$ Experiments published in 1936 by physician Ol Bang, inspired by his mentor Ejar Lundsgaard, described the fate of blood lactate during exercise of different intensities and durations. ${ }^{4}$ The experiments of Christensen, Asmussen, Nielsen, and Hansen were conducted at the Laboratory for the Theory of Gymnastics at the University of Copenhagen. Today, the August Krogh Institute (www.aki. ku.dk/index.asp?sprog=EN\&level=\&page=\&indhold=) carries on the tradition of basic and applied research in exercise physiology. Since 1973, Swedish-trained scientist Bengt Saltin (the only Nordic researcher besides Erling Asmussen to receive the ACSM Citation Award, 1980, and ACSM Honor Award, 1990; former student of Per-Olof strand, discussed in the next section; see Interview with Bengt Saltin in Section 4) has been a professor and continues his significant scientific studies as professor and director of the Copenhagen Muscle Research Centre, University of Copenhagen, Denmark.

## Swedish Influence

Modern exercise physiology in Sweden can be traced to Per Henrik Ling (1776 1839), who in 1813 became the first director of Stockholms Royal Central Institute of Gymnastics. ${ }^{3}$ Ling, a specialist in fencing, developed a system of medical gymnastics. This system, which became part of the school curriculum of Sweden in 1820, was based on his studies of anatomy and physiology.

Lings son Hjalmar also had


Hjalmar Ling a strong interest in medical gymnastics and physiology and anatomy, in part owing to his attendance at lectures by French physiologist Claude Bernard in Paris in 1854. Hjalmar Ling published a book on the kinesiology of body movements in 1866. As a result of the Lings philosophy and influence, the physical educators who graduated from the Stockholm Central Institute were well schooled in the basic biologic sciences, in addition to being highly proficient in sports and games. Currently, the College of Physical Education (Gymnastik-Och Idrottsh gskolan) and Department of Physiology in the Karolinska Institute Medical School in Stockholm continue to sponsor studies in exercise physiology.

Per-Olof strand, MD, PhD (1922 ) is the most famous graduate of the College of Physical Education (1946); in 1952, he presented his thesis to the Karolinska Institute Medical School. strand taught in the Department of Physiology in the College of Physical Education from 1946 to 1977.


P-O. strand, Department of Physiology, Karolinska Institute, Stockholm. A. Measuring maximal performance of Johnny Nilsson, Olympic Gold Medal speed skater, 1964. B. Maximal oxygen consumption measured during cycle ergometer exercise, 1958. C. Laboratory experiment, 1955. D. Invited lecture, 1992 International Conference on Physical Activity, Fitness and Health, Toronto.

When the College of Physical Education became a department of the Karolinska Institute, strand served as professor and department head from 1977 to 1987. Christensen was strands mentor and supervised his doctoral dissertation, which included data on the physical working capacity of both sexes ages 4 to 33 years. This important studyalong with collabo rative studies
with his wife Irma Ryhmingestablished a line of research that propelled strand to the forefront of experimental exercise physiology, for which he achieved worldwide fame. ${ }^{n}$ Four papers published by strand in 1960, with Christensen as one of the authors, stimulated further studies on the physiologic responses to intermittent exercise. strand has mentored an impressive group of exercise physiologists, including such superstars as Bengt Saltin and Bj rn Ekblom. Table 6 is a sampling of contributions to the exercise physiology literature by strand and Saltin in books, book chapters, monographs, and research articles. As further evidence of their phenomenal international influence, the bottom part of the table includes the number of times each was cited in the scientific literature from 1996 through April 2001.

Two Swedish scientists at the Karolinska Institute, Drs. Jonas Bergstr m and Erik Hultman, performed important experiments with the needle biopsy procedure that have provided a new vista from which to study exercise physiology. With this procedure, it became relatively easy to conduct invasive studies of muscle under various exercise conditions, training, and nutritional status.


Drs. Jonas Bergstr m (left) and Eric Hultman, Karolinska Institute, mid-1960s. Collaborative work with other Scandinavian researchers (Saltin and Hultman from Sweden and Lars Hermanson from Norway) and leading researchers in the United States (e.g., Phillip Gollnick [1935 1991; Washington State University] and David Costill, retired Ball State University) contributed a unique new dimension to the study of the physiology of muscular exercise.

## Norwegian and Finnish Influence

The new generation of exercise physiologists trained in the late 1940s analyzed respiratory gases by means of a highly accurate sampling apparatus that measured relatively small quantities of carbon dioxide and oxygen in expired air. The method of analysis (and also the analyzer) was developed in 1947 by Norwegian scientist Per Scholander (1905 1980). A diagram of Scholanders micrometer gas analyzer ${ }^{62}$ is presented in Chapter 8, Figure 8.7, along with its larger counterpart, the Haldane analyzer.

[^12]
## TABLE 6 • Selected Contributions to the Exercise Physiology Literature by Swedish Exercise Physiologists Per-Olof strand and Bengt Saltin

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strand P-O Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952.
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Saltin B, et al. Skeletal muscle blood flow in humans and its regulation during exercise. Acta Physiol Scand 1998;162:421.
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|  |  | Number of Citations in the Scientific Literature (1996 2001) |  |  |  |  |
| :--- | ---: | :---: | :---: | ---: | ---: | ---: |
| Year | $\mathbf{1 9 9 6}$ | $\mathbf{1 9 9 7}$ | $\mathbf{1 9 9 8}$ | $\mathbf{1 9 9 9}$ | $\mathbf{2 0 0 0}$ | $\mathbf{2 0 0 1}^{\boldsymbol{a}}$ |
| strand | 7526 | 6502 | 6485 | 7834 | 8523 | 3822 |
| Saltin | 20,332 | 16,780 | 17,272 | 21,441 | 18,060 | 14,524 |

Source: Science Citation Index. Numbers refer to the total number of citations ( hits ) in the published literature (including books).
${ }^{a}$ Through April 30, 2001.

Another prominent Norwegian researcher was Lars A. Hermansen (1933 1984; ACSM Citation Award, 1985) from the Institute of Work Physiology, who died prematurely. Nevertheless, his many contributions include a classic 1969 article entitled Anaerobic Energy Release that appeared in the first volume of Medicine and Science in Sports. ${ }^{30}$ Other papers included work with exercise physiologist K. Lange Andersen. ${ }^{31}$

In Finland, Martti Karvonen, MD, PhD (ACSM Honor Award, 1991) from the Physiology Department of the Institute of Occupational Health, Helsinki, is best known for a method to predict optimal exercise training heart rate, the so-called Karvonen formula (see Focus on Research, Chapter 15). He also conducted studies dealing with exercise performance and the role of exercise in longevity. In 1952, Lauri Pikhala, a physiologist, suggested that obesity was the consequence and not the cause of physical unfitness. Ilkka Vuori, starting in the early 1970s, reported on hormone responses to exercise.


Lars A. Hermansen (1933 1984). Institute of Work Physiology, Oslo.

## TABLE 7 - Nordic Researchers ${ }^{a}$ Awarded the <br> ACSM Honor Award and ACSM Citation Award

Martti J. Karvonen, 1991
${ }^{a}$ Born and educated in a Nordic country.

## ACSM Honor Award

Per-Olof strand, 1973
Erling Asmussen, 1979
Erik Hohw -Christensen, 1981
Bengt Saltin, 1990

## ACSM Citation Award

Erling Asmussen, 1976
Bengt Saltin, 1980
Lars A. Hermansen, 1985
C. Gunnar Blomqvist, 1987

Paavo Komi, from the Department of Biology of Physical Activity, University of Jyv skyl, has been Finland s most prolific researcher, with numerous experiments published in the combined areas of exercise physiology and sport biomechanics. Table 7 lists the Nordic researchers who have received the prestigious ACSM Honor Award or ACSM Citation Award.

## OTHER CONTRIBUTORS TO THE KNOWLEDGE BASE IN EXERCISE PHYSIOLOGY

In addition to the distinguished American and Nordic applied scientists profiled earlier, there have been many other giants in the field of physiology and experimental science ${ }^{o}$ who have made monumental contributions that indirectly added to the knowledge base in exercise physiology. The list includes:

Sir Joseph Barcroft (1872 1947). High-altitude research physiologist who pioneered fundamental work concerning the functions of hemoglobin, later confirmed by Nobel laureate August Krogh. Barcroft also performed experiments to determine how cold affected the central nervous system. For up to one hour, he would lie without


Marie Krogh collects data at Barcrafts high-altitude experimental station to assess oxygen tension of gases. clothing on a couch in subfreezing temperature and record his subjective reactions.

Christian Bohr (1855 1911). Professor of physiology in the medical school at the University of Copenhagen who mentored August Krogh, and father of nuclear physicist Niels Bohr. Bohr studied with Carl Ludwig in Leipzig in 1881 and 1883 , publishing papers on the solubility of gases in various fluids, including oxygen absorption in distilled water and in solutions containing hemo-
 globin. Krogh s careful experiments using advanced instruments (microtonometer) disproved Bohr s secretion theory that both oxygen and carbon dioxide were secreted across the lung epithelium in opposite directions based on the time required for equalization of gas tension in blood and air.

John Scott Haldane (1860 1936; www.faqs.org/health/ bios/55/John-Scott-Haldane.html). Conducted research in mine safety, investigating principally the action of dangerous gases (carbon monoxide), the use of rescue equipment, and the incidence of pulmonary disease. He devised a decompression apparatus for the safe ascent of deep-sea divers. The British Royal Navy and the United States Navy adopted tables based on this work. In 1905, he discovered that carbon dioxide acted on the brain s respiratory center to regu-


Haldane investigating carbon monoxide gas in an English coal mine at the turn of the 20th century. late breathing. In 1911, he and several other physiologists organized an expedition to Pikes Peak, Colorado, to study the effects of low oxygen pressures at high altitudes. Haldane also showed that the reaction of oxyhemoglobin with ferricyanide rapidly and quantitatively released oxygen and formed methemoglobin. The amount of liberated oxygen could be accurately calculated from the increased gas pressure in the closed reaction system at constant temperature and volume. Haldane devised a microtechnique to fractionate a sample of a mixed gas into its component gases (see Chapter 8, Haldane apparatus). Haldane founded the Journal of Hygiene.

Otto Meyerhof (1884 1951; nobelprize.org/nobel_ prizes/medicine/laureates/1922/meyerhof-bio.html).
Meyerhof s experiments on the energy changes during cellular respiration led to discoveries on lactic acid related to muscular activity, research that led to the Nobel Prize (with A.V. Hill in 1923). In 1925, Meyerhof extracted from muscle the enzymes that convert glycogen to lactic acid. Subsequent research confirmed work done by Gustav Embden in 1933; together they discovered the


[^13]pathway that converts glucose to lactic acid (the Embden Meyerhof pathway).

Nathan Zuntz (1847 1920). Devised the first portable metabolic apparatus to assess respiratory exchange in animals and humans at different altitudes; proved that carbohydrates were precursors for lipid synthesis. He maintained that dietary lipids and carbohydrates should not be consumed equally for proper nutrition. He pro-
 duced 430 articles concerning blood and blood
 gases, circulation, mechanics and chemistry of respiration, general metabolism and metabolism of specific foods, energy metabolism and heat production, and digestion.

Zuntz tests his portable, closed-circuit spirometer carried on his back. This device made it possible for the first time to measure $\mathrm{O}_{2}$ consumed and $\mathrm{CO}_{2}$ produced during ambulation.

Karl von Voit (1831 1908; www.bookrags.com/biography/ karl-von-voit-wsd/) and his student Max Rubner (1854 1932). Discovered the isodynamic law and the calorific heat values of proteins, lipids, and carbohydrates; Rubner s surface area law states that resting heat production is proportional to body surface area and that consuming food in-
 creases heat production. Voit disproved Liebig s assertion that protein was a primary energy fuel by showing that protein breakdown does not increase in proportion to exercise duration or intensity.

Max Joseph von Pettenkofer (1818 1901). Perfected the respiration calorimeter to study human and animal metabolism; discovered creatinine, an amino acid in urine. The top chamber of the figure in top right-hand column shows the entire calorimeter. The cut-away image shows a human experiment where



Human respiration calorimeter.
fresh air was pumped into the sealed chamber and vented air sampled for carbon dioxide.

Eduard F. W. Pfl ger (1829 1910). First demonstrated that minute changes in the partial pressure of blood gases affect the rate of oxygen release across capillary membranes, thus proving that blood flow alone does not govern how tissues receive oxygen.


Wilbur Olin Atwater (1844 1907;
www.sportsci.org/news/history/atwater/atwater.html).
Published data about the chemical composition of 2600 American foods currently used in databases of food composition Also performed human calorimetric experiments and confirmed that the law of conservation of energy governs transformation of matter in the human body.


Russel Henry Chittenden (1856 1943; www.sportsci .org/news/history/chittenden/ chittenden.html). Refocused attention on the minimal protein requirement of humans while resting or exercising; concluded that no debilitation occurred if protein intake equaled 1.0 g kg body mass ${ }^{1}$ in either normal or athletic young men. Chittenden received the first PhD in physi-
 ological chemistry given by an American university.

Some scholars ${ }^{12}$ regard Chittenden as the father of biochemistry in the United States-he believed that physiological chemistry would provide basic tools for researchers to study important aspects of physiology and provided the impetus for incorporating biochemical analyses in exercise physiology.

Frederick Gowland Hopkins (1861 1947; www.sportsci .org/news/history/hopkins/hopkins.html). Nobel Prize in 1929 for isolating and identifying the structure of the amino acid tryptophan. Hopkins collaborated with W. M. Fletcher (mentor to A. V. Hill) to study muscle chemistry. Their classic 1907 paper in experimental physiology used new methods to isolate lactic acid in muscle. Fletcher and Hopkins s chemical methods reduced the muscle s
 enzyme activity prior to analysis to isolate the reactions. They found that a muscle contracting under low oxygen conditions produced lactate at the expense of glycogen. Conversely, oxygen in muscle suppressed lactate formation. The researchers deduced that lactate forms from a nonoxidative (anaerobic) process during contraction; during recovery in a noncontracted state, an oxidative (aerobic) process removes lactate with oxygen present.

Francis Gano Benedict (1870 1957; www.sportsci.org/ news/history/benedict/benedict.html). Conducted exhaustive studies of energy metabolism in newborn infants, growing children and adolescents, starving persons, athletes, and vegetarians. Devised metabolic standard tables based on sex, age, height, and weight to compare energy metabolism in normals and patients. His last monograph, Vital Energetics, A
 Study in Comparative Basal Metabolism (Carnegie Institution Monograph no. 503, 1938), refers to many of his approximately 400 publications.

## CONTRIBUTIONS OF WOMEN TO SCIENCE AT THE DAWN OF THE 20TH CENTURY

The triumphs and accomplishments during the evolution of exercise physiology reveal a glaring absence of credit to the contributions of women from the 1850 s and continuing for the next 100 years. Many reasons can explain this occurrencebut it was not from women s lack of interest in pursuing a
career in the sciences. Rather, women who wished to stand with male colleagues found the going difficult. Opposition included hostility, ridicule, and professional discrimination, typically in chemistry, physics, and medicine, but also in related fields such as botany, biology, and mathematics. A few women did break through the almost exclusively maledominated fields to make significant contributions despite such considerable hurdles. The leadership at the top of the scientific culture (college presidents, academic deans, curriculum and personnel committees, governing bodies, heads of departments, and review boards for grants and journals) subtly and directly repressed women $s$ attempts to even enter some fields, let alone achieve parity with male scientists. Subtle discrimination included assignment to underequipped, understaffed, and substandard laboratory facilities; having to teach courses without proper university recognition; disallowing membership on graduate thesis or dissertation committees; and having a male colleague s name appear first (or only) on research publications, regardless of his involvement. Male supervisors typically presented the results of joint work at conferences and seminars when the woman clearly worked as the lead scientist. Direct suppression included outright refusal to hire women to teach at the university or college level. For those who were hired, many could not directly supervise graduate student research projects. Women also routinely experienced shameful inequity in salary received or were paid no salary as assistants.

The Nobel Prize in the sciences, the most prestigious award for discoveries in physics, chemistry, and physiology or medicine, has honored 300 men but only 10 women since the award originated in 1901. The Karolinska Institute in Stockholm (http://ki.se/ki/jsp/polopoly.jsp?d=130\&l=en) selects the Nobel laureates in physiology or medicine, and the Swedish Academy of Sciences awards the prizes in chemistry and physics. Considerable controversy has emerged over the years about the role of in-fighting and politics in the selection process. The difference in the gender-specific pool of outstanding scientists cannot adequately explain the disparity between male and female Nobel winners. However, reading about the lives and times of the 10 female winners, including others who by all accounts probably deserved the honor, gives a better appreciation for the inequity. Each of the 10 female laureates and the other 3 world-class scientists (chronicled in Scientific Contributions of Thirteen Outstanding Female Scientists, available online at http://thepoint.lww.com/mkk7e) overcame huge nonscientific issues before achieving their eventual scientific triumphs.

In a way, some of the same problems faced by women in academia and the private sector over the years help to explain the relatively slow ascendance of women to positions of prominence during the first 100 years of modern exercise physiology. A salient example comes from reviewing the historical record of the ACSM from its inception on January 8, 1955, to the present. Of the 11 founders, one was a woman
(Josephine L. Rathbone, PhD, specialist in physical education and rehabilitation). Eighteen months later, three other women joined Dr. Rathbone (Dorothy Ainsworth, PhD, from Smith College, MA; Anna Espenshare, PhD, from UC Berkeley; and Clair Langdon, EdD, from Oregon State College) as part of the 54 original Charter ACSM members.

From ACSM s founding, ${ }^{7}$ it would take 33 years before a woman was elected the organization s president. Barbara L. Drinkwater, PhD, from the Institute of Environmental Stress at UC Santa Barbara, became ACSM s first woman president (see Interview with Barbara L. Drinkwater in Section 5). This breakthrough allowed many other women to assume the top administrative roles within ACSM, including the 20082009 president, Melinda Millard-Stafford, PhD, Georgia Institute of Technology. From 1955 to 1980, only Drs. Rathbone and Drinkwater served as officers of the College (as vice presidents); from 1981 to 1992, three additional women achieved elective office (Christine Wells, PhD, Arizona State University; Betty Atwater, PhD , University of Arizona; Mona Shangold, MD, Georgetown Medical Center). Since 2000, many women have served as vice presidents. Until 1996, no woman received the prestigious ACSM Honor Award, delivered the Wolffe Memorial Lecture, or won a New Investigator or Scholar Award. That changed in 1996 when Barbara Drinkwater became the first female to receive the Honor Award (and Priscilla Clarkson, 2005).

In addition to female ACSM presidents, many women currently hold key positions as deans, associate deans, chairs of departments of exercise science and kinesiology, principal investigators on major research grants, and directors of exercise physiology laboratories.

We hope the legacy of the women pioneers in the related fields of exercise physiology inspires other female students to strive for excellence in their particular specialty. Successful women scientists often must surmount many obstacles along the way to achieve success and recognition. They all shared common traits-an unyielding passion for science and uncompromising quest to explore new ground where others had not ventured. As you progress in your own careers, we hope that you too will experience the pure joy of discovering new truths in exercise physiology. Perhaps the achievements of women scientists from outside our field will serve as a gentle reminder to support the next generation of scientists from their accomplishments and passion for their field.

## SUMMARY

This introductory section on the historical development of exercise physiology illustrates that interest in exercise and health had its roots with the ancients. During the next 2000 years, the field we now call exercise physiology evolved from a symbiotic (albeit, sometimes rocky) relationship between the classically trained physicians, the academically based anatomists and physiologists, and a small cadre of physical educators who struggled to achieve their identity and academic credibility through research and experimentation in the basic and applied sciences. The physiologists used exercise to
study the dynamics of human physiology, and the early physical educators often adapted the methodology and knowledge of physiology to study human responses to exercise.

Beginning in the mid-1850s in the United States, there was a small but slowly growing effort to raise standards for the scientific training of physical education and hygiene specialists who were primarily involved in teaching at the college and university level. The creation of the first exercise physiology laboratory at Harvard University in 1891 contributed to an already burgeoning knowledge explosion in basic physiology. Originally, medically trained physiologists made the significant scientific advances in most of the subspecialties now included in the exercise physiology course curriculum. They studied oxygen metabolism, muscle structure and function, gas transport and exchange, mechanisms of circulatory dynamics, and neural control of voluntary and involuntary muscular activity.

The field of exercise physiology also owes a debt of gratitude to the pioneers of the physical fitness movement in the United States, notably Thomas K. Cureton (1901 1993; ACSM charter member; ACSM Honor Award, 1969) at the University of Illinois, Champaign-a prolific, insightful researcher who trained four generations of physical educators, beginning in 1941. Many of these pioneers assumed leadership positions as professors with teaching and research responsibilities in exercise physiology at numerous colleges and universities in the United States and throughout the world.

Although we have focused on the contributions of selected early American scientists and physical educators and their counterparts from the Nordic countries to the development of modern-day exercise physiology, we would be neglectful not to acknowledge the numerous contributions from many scholars in other countries. The group of foreign contributors, many still active, includes but certainly is not limited to the following individuals: Roy Shephard, School of Physical and Health Education, University of Toronto (ACSM Citation Award, 1991; ACSM Honor Award, 2001); Claude Bouchard, Pennington Biomedical Research Center, Baton Rouge, LA (ACSM Citation Award, 1992; ACSM Honor Award, 2002); Oded Bar-Or, McMaster University, Hamilton, Ontario, Canada (ACSM Citation Award, 1997; ACSM Presidents Lecture); Rodolfo Margaria and P. Cerretelli, Institute of Human Physiology, Medical School of the University of Milan; M. Ikai, School of Education, University of Japan; Wildor Holloman, Director of the Institute for Circulation, Research and Sports Medicine, and L. Brauer and H. W. Knipping, Institute of Medicine, University of Cologne, Germany (in 1929, they described the vita maxima now called the maximal oxygen consumption); L. G. C. E. Pugh, Medical Research Council Laboratories, London; Z. I. Barbashova, Sechenov Institute of Evolutionary Physiology, Leningrad, U.S.S.R.; Sir Cedric Stanton Hicks, Human Physiology Department, University of Adelaide, Australia; Otto Gustaf Edholm, National Institute for Medical Research, London, England; John Valentine George Andrew Durnin, Department of Physiology, Glasgow University, Scotland; Reginald Passmore, Department of Physiology,

University of Edinburgh, Scotland; Ernst F. Jokl (ACSM founder and charter member), Witwatersrand Technical College, Johannesburg, South Africa, and later the University of Kentucky; C. H. Wyndham and N. B. Strydom, University of the Witwatersrand, South Africa. There were also many early German scientific contributions to exercise physiology and sports medicine. ${ }^{32}$

## CONCLUDING COMMENT

One theme unites the history of exercise physiology: the value of mentoring by those visionaries who spent an extraordinary amount of their careers infecting students with love for hard science. These demanding but inspiring relationships developed researchers who, in turn, nurtured the next generation of productive scholars. This applies not only to the current group of exercise physiologists, but also to scholars of previous generations. Siegel ${ }^{64}$ cites Payne, ${ }^{57}$ who in 1896 wrote the following about Harvey s 1616 discovery of the mechanism of the circulation, acknowledging the discoveries of the past:

No kind of knowledge has ever sprung into being without an antecedent, but is inseparably connected with what was known before. . . . We are led back to Aristotle and Galen as the real predecessors of Harvey in his work concerning the heart. It was the labors of the great school of Greek anatomists . . . that the problem though unsolved, was put in such a shape that the genius of Harvey was enabled to solve it. . . . The moral is, I think, that the influence of the past on the present is even more potent than we commonly suppose. In common and trivial things, we may ignore this connection; in what is of enduring worth we cannot.

We end our overview of the history of exercise physiology with a passage from an American physiology and hygiene textbook written more than 140 years ago by J. C. Dalton, MD, a professor of physiology in the College of Physicians and Surgeons in New York City. It shows how current themes in exercise physiology share a common bond with what was known and advocated at that time (the benefits of moderate physical activity, walking as an excellent exercise, the appropriate exercise intensity, the specificity of training, the importance of mental well-being). Even the new thoughts and ideas of Dalton penned in 1869 had their roots in antiquityreinforcing to us the importance of maintaining a healthy respect for the past.

Exercise. The natural force of the muscular system requires to be maintained by constant and regular Exercise. If all of the muscles, or those of any particular part, be allowed to remain for a long time unused they diminish in size, grow softer, and finally become sluggish and debilitated. By use and exercise, on the contrary, they maintain their vigor, continue plump and firm to the touch, and retain all the characters of their healthy organization. It is very important, therefore, that the muscles should be trained and exercised by sufficient daily use. Too
much confinement by sedentary occupation, in study, or by simple indulgence in indolent habits, will certainly impair the strength of the body and injuriously affect the health. Every one who is in a healthy condition should provide for the free use of the muscles by at least two hours exercise each day; and this exercise can not be neglected with impunity, any more than the due provision of clothing and food.

The muscular exercise of the body, in order to produce its proper effect, should be regular and moderate in degree. It will not do for any person to remain inactive during the greater part of the week, and then take an excessive amount of exercise on a single day. An unnatural deficiency of this kind cannot be compensated by an occasional excess. It is only a uniform and healthy action of the parts that stimulates the muscles and provides for their nourishment and growth. Exercise that is so violent and long-continued as to produce exhaustion or unnatural fatigue is an injury instead of an advantage, and creates a waste and expenditure of the muscular force instead of its healthy increase.

Walking is therefore one of the most useful kinds of exercise, since it calls into easy and moderate action nearly all the muscles of the body, and may be continued for a long time without fatigue. Riding on horseback is also exceedingly efficacious, particularly as it is accompanied by a certain amount of excitement and interest that acts as an agreeable and healthy stimulus to the nervous system. Running and leaping, being more violent should be used more sparingly. For children, the rapid and continuous exercise that they spontaneously take in their various games and amusements in the open air is the best. The exact quantity of exercise to be taken is not precisely the same for different persons, but should be measured by its effect. It is always beneficial when it has fully employed the muscular powers without producing any sense of excessive fatigue or exhaustion.

In all cases, also, the exercise that is taken should be regular and uniform in degree, and should be repeated as nearly as possible for the same time every day.

As a student of Exercise Physiology, you are about to embark on an exciting journey into the world of human physiologic response and adaptation to physical activity. We hope our tour of the beginnings of exercise physiology inspires you in your studies to begin your own journey to new discoveries.

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# Interview with Dr. Charles M. Tipton 



Education: BA (Springfield College in Springfield, MA); MA, PhD in physiology, with minors in biochemistry and anatomy (University of Illinois, Champaign, IL)<br>Current Affiliation: Professor Emeritus of Physiology and Surgery at the College of Medicine at the University of Arizona<br>Honors and Awards: See Appendix E, online at http://thepoint.lww.com/mkk7e.<br>Research Focus: The physiologic effects of short- and long-term exercise and their responsible mechanisms<br>Memorable Publication: Tipton CM, et al. The influence of exercise, intensity, age, and medication on resting systolic blood pressure of SHR populations. J Appl Physiol 1983;55:1305.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

Dr. Tipton is well known for his contributions as an investigator in exercise physiology, his educational vision in establishing the gold standard for graduate training in the exercise sciences, and his leadership and driving energy. For almost 25 years, Professor Tipton has excelled as
an investigator by using animal models to study the acute and chronic effects of exercise on connective tissue, hormones, metabolism, and the cardiovascular system. This broad scope of knowledge has enabled him to build a graduate training program with an international reputation that has produced researchers and educators who have subsequently achieved prominence in the exercise sciences.

What first inspired you to enter the exercise science field? What made you decide to pursue your degree and/or line of research?

- My experiences in athletics and as a physical fitness instructor in an infantry division convinced me that I should secure an education on the G.I. Bill of Rights to be able to teach health and physical education while coaching in a rural high school. Once I realized that I did not enjoy my chosen career, I returned to the University of Illinois for more education in health education. To support a growing family, I secured a summer and part-time position as a $4-\mathrm{H}$ Club fitness specialist who conducted fitness tests and clinics through the state of Illinois. When it became apparent that I had to have more physiology and biochemistry to explain what I was testing and advocating, I knew I had to be a physiologist with an expertise in exercise physiology. So I transferred to the Physiology Department, and the rest is history.


## What influences did your undergraduate education have on your final career choice?

> Very little. Although I had the late Peter V. Karpovich as my exercise physiology instructor at Springfield College, he did not stimulate, motivate, or encourage me to become one. My mind set was to teach and coach in a rural high school, and everything in the undergraduate curriculum or experience was to help me achieve that goal.

Who were the most influential people in your career, and why?

- The drive to learn and acquire more education was imprinted by my father, who had to leave school in the eighth grade to help support the family. Early on in graduate school at the University of Illinois, I became interested in the physiological and biochemical foundations of physical fitness by the interesting and
evangelical lectures of Thomas K. Cureton of the Physical Education Department. However, my interest in physiological research and its scientific foundations was stimulated, developed, and perfected by Darl M. Hall, a critical and caring research scientist in the Illinois Extension Service, who had the responsibility of testing the fitness levels of $4-\mathrm{H}$ Club members. He made me recognize that functional explanations require in-depth scientific knowledge and encouraged me to transfer into the Physiology Department to secure such information. Once in physiology, I became exposed to the unique scholarship of Robert E. Johnson and to his example of the scientific attributes necessary to become a productive exercise physiologist. Inherent in this profile of recognition is the fact that without the love and support of my wife, Betty, and our four children, my transition to the various departmentsand survival of a poverty state-would have never occurred.


## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect

$>$ To me, the most interesting and stimulating aspect of exercise physiology was the planning, testing, and evaluation of one s hypotheses. The least enjoyable were the administrative aspects of supervising a laboratory and in the conduct of research.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

> Exercise science evolved from the discipline of physical education and includes exercise physiology. My most meaningful contribution to the field was the planning and implementation of a rigorous, science-based PhD graduate program in exercise physiology at the University of Iowa, which served as a model for other departments of physical education to follow. It was important to me because it attracted many outstanding individuals to the University of Iowa, who became dear friends and help paved the way for exercise science to become an academic entity.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

$>$ Research requires more than intellectual curiosity and infectious enthusiasm. It is an exciting occupation that demands hard work while requiring an individual to be disciplined, dedicated, and honest. A future researcher must acquire an education that enables him/her to be well prepared in mathematics and the biological and physical sciences, and the ability to communicate by written and verbal means. Lastly, seek a mentor whose research interests you and one who is concerned about you as a future researcher and not as a contributor to their vitae.

## What interests have you pursued outside of your professional career?

- Becoming a Civil War buff, enjoying the pleasures of dancing and listening to Dixieland jazz, exercising regularly, participating in road races, reading nonfiction, learning about poetry, being a member of a book club, watching televised sports, cheering for the Washington Redskins football team, and observing our grandchildren as they grow up.


Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 20 years?
$>$ It is my speculation that during the next 20 years exercise physiologists will be emphasizing and investigating molecular mechanisms in all of the known systems. Since the genome will have been characterized during this interval, exercise physiology genomics will have become a well-defined subdiscipline, and countless studies will be under way to determine the interactions between the genome and the exercise response in normal and diseased populations.

## You have the opportunity to give a last lecture. Describe its primary focus.

- It would be entitled Exercise Physiology in the Last Frontier and would pertain to what is known and unknown about exercising in a microgravity environment.



## Exercise Physiology




# Nutrition: The Base for Human Performance 

## OVERVIEW

Nutrition and exercise physiology share a natural linkage. Proper nutrition forms the foundation for physical performance; it provides the necessary fuel for biologic work and the chemicals for extracting and using the potential energy within this fuel. Nutrients from food also furnish essential elements for repairing existing cells and synthesizing new tissues.

Some may argue that a well-balanced diet readily provides adequate nutrients for exercise, so in-depth nutrition knowledge would offer little value to exercise physiologists. We maintain, however, that the study of exercise, energy capacities, and performance must highlight the relevance of energy sources and the role diverse nutrients play in energy release and transfer. With this knowledge and perspective, the exercise specialist can critically evaluate claims about special nutritional supplements, including dietary modifications to enhance physical performance. Because nutrients provide energy and regulate physiologic processes in exercise, improved athletic performance often links with dietary modification. Too often, individuals devote considerable time and effort striving to optimize exercise performance, only to fall short owing to inadequate, counterproductive, and sometimes harmful nutritional practices. The three chapters that follow present the six categories of nutrientscarbohydrates, lipids, proteins, vitamins, minerals, and waterand explore within the context of exercise physiology the following five questions related to nutrition:

## What are nutrients?

Where are they found?
What are their functions?
What role do they play in physical activity?
How does optimal nutrition impact exercise performance and training responsiveness?

# Interview with Dr. David L. Costill 



Education: BS (Ohio University, Athens, OH); MEd (Miami University, Oxford, OH ); PhD (Physiology, Ohio State University, Columbus, OH)

Current Affiliation: Professor Emeritus, John and Janice Fisher Chair in Exercise Science, Ball State University

Honors and Awards: See Appendix E, available online at
http://thepoint.lww.com/mkk7e
Research Focus: My research interest was aimed at several areas: body fluid balance, carbohydrate metabolism in human muscle, thermal regulation during exercise, physiologic characteristics of runners and swimmers, aging distance runners, and changes in muscle fiber function during bed rest and space flight.

Memorable Publication: Costill DL, et al. Skeletal muscle enzymes and fiber composition in male and female track athletes. J Appl Physiol 1976;40:149.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

In recognition of his lifetime of distinguished scientific achievement in the applied, basic and clinical aspects of exercise physiology and sports medicine through his research, teaching, lecturing, mentoring of students and colleagues, and professional leadership.

Professor Costill has been one of the pioneers in researching human performance and sports nutrition. He provided the scientific community with the first complete assessment of the physiological factors that determine distance-running performance. His early studies on carbohydrate metabolism and fluid replacement were foundational to understanding the fuel and fluid needs of the endurance athlete, and have provided the stimulus to what has become one of the most active areas in exercise research today. His studies of environmental limitation to endurance performance have contributed greatly to our understanding of how to best prepare individuals to exercise and compete in the heat. His personal interest in and dedication to distance running and swimming led him to conduct an unprecedented series of studies in both sports. The results of these studies have provided the physiologist, coach, and athlete with better understanding of the physiological basis for these sports.

His most recent research in the area of overtraining has made major contributions to the training of elite athletes.

Professor Costill has dedicated considerable time and energy to the education of scientists, clinicians, coaches and athletes, through his professional articles, books, and lecturing. No single scientist has impacted the sports community nationally or internationally more than Professor Costill, due largely to his ability to effectively communicate the results of his research and those of others.

Professor Costill has also had a tremendous impact on those who have trained with him as undergraduate students, graduate students, postdoctoral fellows, or visiting colleagues. Professor Costill s national and international professional leadership is widely acknowledged. He has served the American College of Sports Medicine in many ways, but most importantly as President during a critical time in the growth of the College. He has served as Editor-in-Chief of the International Journal of Sports Medicine.

Professor Costill s unceasing search for new insights into the mechanism underlying exercise and sports medicine has received the respect and admiration of the international scientific community. His prolific career has brought honor to his university, his students, his colleagues, and the American College of Sports Medicine.

## What first inspired you to enter the exercise science field?

- Growing up in Ohio, I was always interested in biology and physiology, although I never thought of it in those terms. Even as an 8 -year-old, I needed to know why animals differed and what made them work.

In college, I was more interested in anatomy and physiology than in physical education. But I was a poor student who was satisfied with taking all the activities classes and easy grades that I was able to attain. My primary interest was staying eligible for swimming. During my senior year at OSU, I signed up
for an independent study and was assigned a research project with 30 rats. The project never amounted to much, but I was left on my own and learned that the research process was challenging.

My first introduction to exercise physiology was as a graduate student at Miami University in Ohio. A faculty member (Fred Zeckman) in the Department of Zoology offered an exercise physiology class to about six students. Again, the class project involved data collection, a process Id already found interesting. After teaching high school general science and biology for 3 years, as well as coaching three teams, I decided it was time to see if I could get the credentials to become a coach at a small college. I began working toward a doctorate in higher education. At the same time, I became close friends with Dick Bowers and Ed Fox, fellow graduate students who were majoring in exercise physiology under the direction of Dr. D. K. Mathews. It wasnt long before they persuaded me to switch over to work in the laboratory with them.

## What influence did your undergraduate education have on your final career choice?

$>$ It enabled me to get a degree and a teaching job. It was not until I had been teaching for several years that I identified what I really wanted to do. After one year at OSU, I moved to Cortland (SUNY), where I coached cross-country track and swimming for 2 years. Although I enjoyed coaching, I just couldnt take the recruiting and continual exposure to 18 -year-olds. So I decided to focus my energy on research. Exercise physiology gave me a chance to do research in an area that held numerous practical questions. My early studies with runners were a natural, considering the experience Id had in coaching runners at Cortland. Interestingly, a few of those runners (e.g., Bob Fitts and Bob Gregor) have become well-known in the exercise science field.

## Who were the most influential people in your career, and why?

> Dr. Bob Bartels: Bob was my college swimming coach. First, he kept me on the freshman team, even though I was one of the least talented. There were moments during my senior year (as co-captain) when Im sure he had second thoughts! Bob was also instrumental in getting me admitted to Miami University and OSU. Without his efforts, Id probably still be teaching junior high science in Ohio.

Dr. David Bruce (D. B.) Dill: I worked with Bruce in the summer of 1968. His words of wisdom and advice headed me in the right direction. Drs. Bengt Saltin and Phil Gollnick: Because I received my PhD after only one year at OSU, I had
little research background and no postdoctoral experience. In 1972, I spent 6 months with Bengt and Phil in Bengts laboratory in Stockholm. I learned a great deal working with them and the gang (Jan Karlsson, Bj rn Ekblom, E. H. Christensen, P. O. strand, and others), which I consider to be my postdoctoral experience.


## What has been the most interesting/enjoyable aspect of your involvement in science?

> Most interesting: Meeting people! The professional contact and friendships I had with other scientists (Charles Tipton, Skip Knuttgen, Jack Wilmore, Lars Hermansen, Harm Kuipers, Mark Hargreaves, Reggie Edgerton, Bill Fink, Clyde Williams, Per Blom, George Sheehan, astronauts from STS78 flight, and others).

Most enjoyable: Following the success of my former students. Since I was a student with little talent but a good work ethic, I tended to recruit those types as graduate students. They were not always the ones with the high GPAs, but they were motivated and knew how to work. A number of them have become well known in our field, including Bill Evans, Ed Coyle, Mike Sherman, Mark Hargreaves, Bob Fitts, Bob Gregor, Paul Thompson, Carl Foster, Joe Houmard, Rick Sharp, Larry Armstrong, Rob Robergs, John Ivy, Hiro Tanaka, Mike Flynn, Scott and Todd Trappe, Abe Katz, Pete Van Handel, Darrell Neufer, Matt Hickey, and others.

One of the most enjoyable aspects of my research has been the opportunity to work with some very interesting subjects such as Bill Rogers, Steve Prefontaine, Alberto Salazar, Matt Biondi, Derek Clayton, Shella Young, Frank Shorter, Kenny Moore, and Ken Sparks.

## What was the least interesting/enjoyable aspect?

> I have never liked writing books or chasing after grant money, but I knew that was essential to expand the laboratory and upgrade facilities to continue to do research. Also, seeing students with great talent fail to live up to full potential. Not every student achieved the level of success I expected, but their lives were often altered by events outside the laboratory. I always view my students as a part of my family, so when they had troubles and/or were unsuccessful, it was like watching my own kids struggle.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

> There are six keys to success as a researcher: (1) Identify a worthy question; (2) Design a protocol that will give you the best possible answer; (3) Make sure the question is fundable; in other words, it must be a problem that an outside source is willing to support financially; (4) Be good at and enjoy collecting data. Precision in the laboratory is essential if you want to generate a clear answer to your question; (5) Be capable of reducing the data to an intelligible form and writing a clear/concise paper that is publishable in a creditable journal; and (6) Be capable of presenting your research at scientific forums, as this helps to establish your scientific creditability.

## What interests have you pursued outside of your professional career?

> Photography (1949 1955): I went to college to study photography (I won three national photo contests in high school) but switched to physical education during my sophomore year.

Distance running (1965 1982): I started running for fitness and eventually ran 16 marathons in the late 1970s and early 1980s. Knee injuries forced me back to swimming in 1982. Masters Swimming (1982 present): After training for 6 months, Doc Counsilman, the famed Indiana University swim coach, talked me into entering a Masters meet, where he promptly beat me in a 500-yard freestyle event. My graduate students Rick Sharp and John Troup convinced me to shave down and compete in one more meet. Subsequently, I performed almost as well as I had in college, so I was hooked. At the age of 60 I could still beat my best college times and set six age-group national records.

I have two passions: aviation and auto restoration. I also enjoy fishing, camping, and canoeing. We have a cottage in northern Wisconsin where we spend as much time in the summer as possible. But I always like to come back to the small town of Muncie where there is no traffic, a nice house, good airport, and all the activities of the University.

## Where do you see the exercise physiology field heading in the next 20 years?

> This field has moved from whole body measurements (handgrip and vital capacity) to molecular biology (single muscle fiber physiology). To fully understand the physiology of exercise, the answers lie at the subcellular level. Students need solid training in chemistry and molecular biology in order to contribute to knowledge over the next 20 years.


## CHAPTER

 1
## Carbohydrates, Lipids, and Proteins

## CHAPTER OBJECTIVES

- Distinguish among monosaccharides, disaccharides, and polysaccharides
> Identify the two major classifications of dietary fiber and their roles in overall health
- Discuss physiologic responses to different dietary carbohydrates in the development of type 2 diabetes and obesity
- Quantify the amount, energy content, and distribution of carbohydrate within an averagesized man
- Summarize carbohydrate s role as an energy source, protein sparer, metabolic primer, and central nervous system fuel
> Outline the dynamics of carbohydrate metabolism during physical activity of various intensities and durations
- Contrast the speed of energy transfer from carbohydrate and fat combustion
- Discuss how diet affects muscle glycogen levels and endurance exercise performance
- Give an example of a food source of each of the diverse fatty acids (including trans- and omega-3 fatty acids), its physiologic functions, and its possible role in coronary heart disease
> List major characteristics of high- and low-density lipoprotein cholesterol and discuss the role of each in coronary heart disease
> Make prudent recommendations for dietary lipid intake, including cholesterol and types of fatty acids
- Quantify the amount, energy content, and distribution of fat within an average-sized woman
> Outline the dynamics of fat metabolism during physical activity of different intensities and durations
- List four functions of fat in the body
> Discuss how aerobic training affects fat and carbohydrate catabolism during exercise
- Explain how aerobic training affects fat-burning adaptations within skeletal muscle
- Define the terms essential amino acid and nonessential amino acid and give food sources for each
- Discuss the advantages and potential limitations of a vegetarian diet in maintaining good health and a physically active lifestyle
> Outline the dynamics of protein metabolism during physical activity of various intensities and durations
> Provide a rationale for increasing protein intake above the Recommended Dietary Allowance (RDA) for individuals who perform strenuous endurance or resistance-exercise training
- Describe the alanine glucose cycle and how the body uses amino acids for energy during exercise

The carbohydrate, lipid, and protein nutrients provide energy to maintain bodily functions during rest and physical activity. Aside from their role as biologic fuel, these nutrients, called macronutrients, preserve the structural and functional integrity of the organism. This chapter discusses each macronutrients general structure, function, and dietary source. We emphasize their importance in sustaining physiologic function during physical activities of differing intensity and duration.

## Part 1 CARBOHYDRATES

## KINDS AND SOURCES OF CARBOHYDRATES

Atoms of carbon, hydrogen, and oxygen combine to form a basic carbohydrate (sugar) molecule in the general formula $\left(\mathrm{CH}_{2} \mathrm{O}\right)_{n}$, where $n$ ranges from 3 to 7 carbon atoms with hydrogen and oxygen atoms attached by single bonds. Except for lactose and a small amount of glycogen from animal origin, plants provide the carbohydrate source in the human diet. Carbohydrates classify as monosaccharides, oligosaccharides, and polysaccharides. The number of simple sugars linked within each of these molecules distinguishes each carbohydrate form.

## Monosaccharides

The monosaccharide represents the basic unit of carbohydrates. Glucose, also called dextrose or blood sugar, consists of a 6-carbon (hexose) compound formed naturally in food or in the body through digestion of more complex carbohydrates. Gluconeogenesis, the bodys process for making new sugar, occurs primarily in the liver from the carbon residues of other compounds (generally amino acids, but also glycerol, pyruvate, and lactate). After absorption by the small intestine, glucose either (1) becomes available as an energy source for cellular metabolism, (2) forms glycogen for storage in the liver and muscles, or (3) converts to fat (triacylglycerol) for later use as energy. Figure 1.1 illustrates glucose along with other carbohydrates formed in plants from photosynthesis. Glucose consists of 6 carbon, 12 hydrogen, and 6 oxygen atoms $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}\right)$. Each carbon atom has four bonding sites that can link to other atoms, including carbons. Carbon bonds
not linked to other carbons are free to hold hydrogen (with only one bond site), oxygen (with two bond sites), or an oxygen hydrogen combination (hydroxyl, or OH). Fructose and galactose, two other simple sugars with the same chemical formula as glucose, have a slightly different C-H-O linkage and are thus different substances with distinct biochemical characteristics.

Fructose (fruit sugar or levulose), the sweetest sugar, occurs in large amounts in fruits and honey. Some fructose moves directly from the digestive tract into the blood, but all eventually converts to glucose in the liver. Galactose does not exist freely in nature; rather, it combines with glucose to form milk sugar in the mammary glands of lactating animals. The body converts galactose to glucose for use in energy metabolism.

## Oligosaccharides

Oligosaccharides (from the Greek oligo, meaning $\mathfrak{~} \mathfrak{d}$ few) form when 2 to 10 monosaccharides bond chemically. The major oligosaccharides, the disaccharides, or double sugars, form when two monosaccharide molecules combine. Monosaccharides and disaccharides collectively make up the simple sugars. These sugars are packaged commercially under a variety of namesbrown sugar, corn syrup, fruit syrup, molasses, barley malt, invert sugar, honey, and fiatural sweeteners.

Disaccharides all contain glucose. The three principal disaccharides are:

- Sucrose (glucose + fructose), the most common dietary disaccharide, contributes up to $25 \%$ of the total calories consumed in the United States. It occurs naturally in most foods that contain carbohydrates, especially beet and cane sugar, brown sugar, sorghum, maple syrup, and honey.
- Lactose (glucose + galactose), a sugar not found in plants, exists in natural form only in milk as milk sugar. The least sweet of the disaccharides, lactose when artificially processed often becomes an ingredient in carbohydrate-rich, high-calorie liquid meals.
- Maltose (glucose + glucose) occurs in beer, breakfast cereals, and germinating seeds. Also called malt sugar, this sugar cleaves into two glucose molecules yet makes only a small contribution to the carbohydrate content of the diet.


Figure 1.1 Three-dimensional ring structure of the simple sugar glucose molecule formed during photosynthesis when energy from sunlight interacts with water, carbon dioxide, and the green pigment chlorophyll.

## Polysaccharides

Polysaccharide describes the linkage of from three up to thousands of sugar molecules. Polysaccharides form during the chemical process of dehydration synthesis, a waterlosing reaction that forms a more complex carbohydrate molecule. Both plant and animal sources contribute to these large chains of linked monosaccharides.

## Plant Polysaccharides

Starch and fiber are the common forms of plant polysaccharides.

Starch, the storage form of carbohydrate in plants, occurs in seeds, corn, and various grains of bread, cereal, pasta, and pastries. Starch exists in two forms:

1. Amylose, a long straight chain of glucose units twisted into a helical coil
2. Amylopectin, a highly branched monosaccharide linkage (Fig. 1.2).

The relative proportion of each form of starch in a plant species determines the characteristics of the starch, including its digestibility. Starches with a relatively large amount of amylopectin digest and absorb rapidly, whereas starches with high amylose content break down (hydrolyze) at a slower rate.

The term complex carbohydrate describes dietary starch, which represents the most important dietary source of carbohydrate in the U.S. diet, accounting for approximately $50 \%$ of the total intake.

Fiber, classified as a nonstarch, structural polysaccharide, includes cellulose, the most abundant organic molecule

## A. Straight chain linkage in amylose starch arranged in a helical coil



## B. Branch point in amylopectin starch



Figure 1.2 The two forms of plant starch. A. Straight-chain linkage with unbranched bonding of glucose residues (glycosidic linkages) in amylose. B. Branch point in the highly branched amylopectin starch molecule. The amylopectin structure appears linear, but it exists as a helical coil.
on earth. Fibrous materials resist chemical breakdown by human digestive enzymes, although a small portion ferments by action of bacteria in the large intestine and ultimately participates in metabolic reactions following intestinal absorption. Fibers occur exclusively in plants; they comprise the structure of leaves, stems, roots, seeds, and fruit coverings.

Health Implications of Fiber Deficiency. Much of the interest in dietary fiber originates from studies that link high fiber intake, particularly whole-grain cereal fibers, with a lower occurrence of obesity, systemic inflammation, insulin resistance and type 2 diabetes, hypertension, the metabolic syndrome, digestive disorders (including diverticular disease and cancers of the mouth, pharynx, larynx, esophagus, and stomach), elevated blood cholesterol, and heart disease. ${ }^{20,55,56,64}$ The Western diet contains considerable fiberfree animal foods and loses much of its natural plant fiber
through processing. Americans typically consume about 12 to 15 g of fiber daily, short of the Food and Nutrition Board of the National Academy of Sciences recommendations of 38 g for men and 25 g for women up to age 50 , and 30 g for men and 21 g for women over age $50 .{ }^{23}$ (Note: Appendix A is available online at http://thepoint.lww.com/mkk7e and shows the relationship between metric units and U.S. units, including common expressions of work, energy, and power.)

Fibers retain considerable water and thus give bulk to the food residues in the intestinal tract. Fiber intake modestly reduces serum cholesterol in humans by lowering the lowdensity lipoprotein fraction of the cholesterol profile. Particularly effective are the water-soluble, mucilaginous fibers such as psyllium seed husk, $\beta$-glucan, pectin, and guar gum present in oats, beans, brown rice, peas, carrots, cornhusk, and many fruits. ${ }^{10,16,37}$ Dietary fiber exerts no effect on high-density lipoproteins (see p. 24). The water-insoluble fibers cellulose,

## TABLE 1.1 Fiber Content of Common Foods (Listed in Order of Total Fiber Content)

|  | Serving Size | Total Fiber (g) | Soluble Fiber (g) | Insoluble Fiber (g) |
| :--- | :---: | :---: | :---: | :---: |
| $100 \%$ bran cereal | $1 / 2$ cup | 10.0 | 0.3 | 9.7 |
| Peas | $1 / 2$ cup | 5.2 | 2.0 | 3.2 |
| Kidney beans | $1 / 2$ cup | 4.5 | 0.5 | 4.0 |
| Apple | 1 small | 3.9 | 2.3 | 1.6 |
| Potato | 1 small | 3.8 | 2.2 | 1.6 |
| Broccoli | $1 / 2$ cup | 2.5 | 1.1 | 1.4 |
| Strawberries | $3 / 4$ cup | 2.4 | 0.9 | 1.5 |
| Oats, whole | $1 / 2$ cup | 1.6 | 0.5 | 1.1 |
| Banana | 1 small | 1.3 | 0.6 | 0.7 |
| Pasta | $1 / 2$ cup | 0.5 | 0.2 | 0.8 |
| Lettuce | $1 / 2$ cup | 0.5 | 0.2 | 0.3 |
| White rice | $1 / 2$ cup |  | 0 | 0.5 |

many hemicelluloses, and lignin and cellulose-rich products (wheat bran) do not lower cholesterol. The potential protective effect of fiber on colon cancer risk remains a debated topic. ${ }^{7,26,61}$

Heart disease and obesity protection may relate to dietary fibers regulatory role in reducing insulin secretion by slowing nutrient absorption by the small intestine following a meal. Fiber consumption may also confer heart disease protection through beneficial effects on blood pressure, insulin sensitivity, and blood clotting characteristics. ${ }^{50,85}$ On the negative side, excessive fiber intake inhibits intestinal absorption of the minerals calcium, phosphorus, and iron. Present nutritional wisdom advocates a diet that contains 20 to 40 g of fiber (depending on age) per day (ratio of 3:1 for water-insoluble to soluble fiber) by following the recommendations of the MyPyramid from the U.S. Department of Agriculture (see Chapter 3, p. 89). Table 1.1 lists the fiber content of some common foods and Table 1.2 presents a sample daily 2200kCal menu that includes 31 g of fiber ( 21 g of insoluble fiber). Total lipid calories equal $30 \%$ (saturated fat $10 \%$ ), protein
equals $16 \%$, and carbohydrate equals $54 \%$ of total calories ingested. Figure 1.3 shows possible mechanisms by which dietary fiber lowers blood cholesterol (Fig. 1.3A) and blood glucose (Fig. 1.3B).

## Not All Carbohydrates Are Physiologically Equal.

 Digestion rates of different carbohydrate sources possibly explain the link between carbohydrate intake and diabetes and excess body fat. Foods containing dietary fiber slow carbohydrate digestion, minimizing surges in blood glucose. In contrast, low-fiber processed starches (and simple sugars in soft drinks) digest quickly and enter the blood at a relatively rapid rate (high glycemic index foods; see Chapter 3). The blood glucose surge after consuming refined, processed starch and simple sugar stimulates overproduction of insulin by the pancreas to accentuate hyperinsulinemia, elevate plasma triacylglycerol concentrations, and accelerate fat synthesis. Consistently eating such foods may eventually reduce the bodys sensitivity to insulin (i.e., peripheral tissues become more resistant to
## TABLE 1.2 Sample Daily Menu for Breakfast, Lunch, and Dinner ( 2200 kCal ) Containing 31 g of Dietary Fiber ${ }^{a}$



[^14]

Figure 1.3 A. Possible mechanism by which dietary fiber lowers blood cholesterol. (CHO, carbohydrate; HMG-CoA reductase, hydroxy-3-methylglutaryl-coenzyme A reductase). B. Possible mechanisms by which dietary water-soluble fiber lowers blood glucose. (Modified from McIntosh M, Miller C. A diet containing food rich in soluble and insoluble fiber improves glycemic control and reduces hyperlipidemia among patients with type 2 diabetes. Nutr Rev 2001;59:52.)
insulins effects), thus requiring progressively more insulin to optimize blood sugar levels. Type 2 diabetes results when the pancreas cannot produce sufficient insulin to regulate blood glucose, causing it to rise. Regular exercise exerts a potent
influence to improve insulin sensitivity, independent of body fat levels, thereby reducing the insulin requirement for a given glucose uptake. ${ }^{45}$ Chapter 20 discusses exercise, diabetes, and the associated risk of the metabolic syndrome.

Know Your Fiber

| Food | High Fiber | Moderate Fiber | Low Fiber |
| :---: | :---: | :---: | :---: |
| Bread, cereal, rice, pasta breads (1 slice) cereals ( $1 / 2$ cup) | $5 \mathrm{~g} /$ serving <br> No product available All-Bran , Bran Buds $100 \%$ bran flakes | $2 \mathrm{~g} / \mathrm{serving}$ <br> Whole wheat, rye, $40 \%$ bran, shredded wheat | $0.5 \mathrm{~g} /$ serving White, bagel (1/2), roll (1/2), English muffin (1/2) Cheerios , Rice Krispies |
| Rice/pasta (1/2 cup) | No product available | Whole wheat pasta, brown rice | macaroni, pasta, white rice |
| Fruits (1 medium or $1 / 2$ cup) | $4 \mathrm{~g} /$ serving Berries, prunes | $2 \mathrm{~g} /$ serving <br> Apple, apricot, banana, orange, raisins | $1 \mathrm{~g} /$ serving Melon, canned fruit, juices |
| Vegetables (1/2 cup) | $4 \mathrm{~g} /$ serving <br> Peas, broccoli, spinach, kidney beans, dried peas | $2 \mathrm{~g} /$ serving <br> Green beans, carrots, eggplant, cabbage, corn | $1 \mathrm{~g} /$ serving <br> Asparagus, cauliflower, celery, lettuce, tomatoes, zucchini, peppers, potatoes w/o skins, onions |

## Glycogen: The Animal Polysaccharide

Glycogen is the storage carbohydrate within mammalian muscle and liver. It forms as a large polysaccharide polymer synthesized from glucose in the process of glucogenesis (catalyzed by the enzyme glycogen synthase). Irregularly shaped, glycogen ranges from a few hundred to 30,000 glucose molecules linked together, much like links in a chain of sausages, with branch linkages for joining additional glucose units (see inset stage 4, Fig. 1.4) Its compact structure produces the dense glycogen granules within cells, which vary in composition, subcellular location, and metabolic regulation and responsiveness. These glycosomes contain glycogen and the proteins that regulate its metabolism. ${ }^{69}$

Figure 1.4 shows that glycogen biosynthesis involves adding individual glucose units to an existing glycogen polymer. Stage 4 of the figure shows an enlarged view of the chemical configuration of the glycogen molecule. Overall, glycogen synthesis is irreversible. Glycogen synthesis requires energy, as one adenosine triphosphate (ATP: stage 1) and one uridine triphosphate (UTP: stage 3) degrade during glucogenesis.

How Much Glycogen Does the Body Store? Figure 1.5 shows that a well-nourished $80-\mathrm{kg}$ man stores approximately 500 g of carbohydrate. Of this, muscle glycogen accounts for the largest reserve (approximately 400 g ), followed by 90 to 110 g as liver glycogen (highest concentration, representing 3 to $7 \%$ of the livers weight), with only about 2 to 3 g as blood glucose. Because each gram of either glycogen or glucose contains approximately 4 calories ( kCal ) of energy, the average person stores about 2000 kCal as carbohydrateenough total energy to power a 20-mile run at high intensity.

The body stores comparatively little glycogen, so its quantity fluctuates considerably through dietary modifications. For example, a 24 -hour fast or a low-carbohydrate, normal-calorie diet nearly depletes glycogen reserves. In contrast, maintaining a carbohydrate-rich diet for several days almost doubles the bodys carbohydrate stores compared with levels attained with a typical, well-balanced diet. The bodys upper limit for glycogen storage averages about 15 g per kilogram (kg) of body mass, equivalent to 1050 g for a $70-\mathrm{kg}$ man and 840 g for a $56-\mathrm{kg}$ woman.

Several factors determine the rate and quantity of glycogen breakdown and resynthesis. During exercise, intramuscular glycogen provides the major carbohydrate energy source for active muscles. In addition, liver glycogen rapidly reconverts to glucose (regulated by a specific phosphatase enzyme) for release into the blood as an extramuscular glucose supply for exercise. The term glycogenolysis describes this reconversion of glycogen to glucose. Depletion of liver and muscle glycogen by dietary restriction of carbohydrates or intense exercise stimulates glucose synthesis. This occurs through gluconeogenic metabolic pathways from the structural components of other nutrients, particularly proteins.

Hormones play a key role in regulating liver and muscle glycogen stores by controlling circulating blood sugar levels. Elevated blood sugar causes the beta $(\beta)$ cells of the pancreas to secrete additional insulin; this facilitates cellular glucose uptake and inhibits further insulin secretion. This type of feedback regulation maintains blood glucose at an appropriate physiologic concentration. In contrast, when blood sugar falls below normal, the pancreass alpha ( $\alpha$ ) cells secrete glucagon to normalize blood sugar concentration. Known as the ínsulin antagonist hormone ( www. glucagon.com), glucagon elevates blood glucose by stimulating the livers glycogenolytic and gluconeogenic pathways. Chapter 20 contains further discussion of hormonal regulation in exercise.

## RECOMMENDED INTAKE OF CARBOHYDRATES

Figure 1.6 lists the carbohydrate content of selected foods. Cereals, cookies, candies, breads, and cakes provide rich carbohydrate sources. Fruits appear as less valuable carbohydrate sources because of their large water content. However, the dried portion of these foods, sold as a dehydrated product, contains almost pure carbohydrate.

For a sedentary $70-\mathrm{kg}$ person, daily carbohydrate intake typically amounts to about 300 g or between 40 and $50 \%$ of total calories. For more physically active people and those involved in exercise training, carbohydrates should equal about $60 \%$ of daily calories or 400 to 600 g , predominantly as unrefined, fiber-rich fruits, grains, and vegetables. During periods of intense exercise training, we recommend that carbohydrate intake increase to $70 \%$ of total calories consumed ( 8 to 10 g per kg of body mass).

Nutritious dietary carbohydrate sources consist of fruits, grains, and vegetables, yet this does not represent the usual source of carbohydrate intake for all people. The typical American consumes about $50 \%$ of carbohydrate as simple sugars whose intake comes primarily from sugars added in food processing as sucrose and high-fructose corn syrup. These sugars do not come in a nutrient-dense package characteristic of the simple sugars found naturally in fruits and vegetables.

## ROLE OF CARBOHYDRATES IN THE BODY

Carbohydrates serve four important functions related to energy metabolism and exercise performance.

## 1. Energy Source

Carbohydrates primarily serve as an energy fuel, particularly during high-intensity exercise. Energy derived from the catabolism of blood-borne glucose and muscle glycogen



Figure 1.5 Distribution of carbohydrate energy in an average $80-\mathrm{kg}$ man.
powers the contractile elements of muscle and other forms of biologic work.

Sufficient daily carbohydrate intake for physically active individuals maintains the bodys relatively limited glycogen stores. However, once cells reach their maximum capacity for glycogen storage, excess sugars convert to and store as fat. The interconversion of macronutrients for energy storage explains how body fat can increase when dietary carbohydrate exceeds energy requirements, even if the diet contains little lipid.

## 2. Protein Sparer

Adequate carbohydrate intake helps to preserve tissue protein. Normally, protein serves a vital role in tissue maintenance, repair, and growth and to a considerably lesser degree as a nutrient energy source. Depletion of glycogen reservesreadily occurring with starvation, reduced energy and/or carbohydrate intake, and strenuous exercisedramatically affects the


Figure 1.6 Percentage of carbohydrate (relative to food s total weight) in common foods arranged by food type. The insert in each bar displays the number of grams of carbohydrate per ounce $(28.4 \mathrm{~g})$ of the food.
metabolic mixture of fuels for energy. In addition to stimulating fat catabolism, glycogen depletion triggers glucose synthesis from the labile pool of amino acids (protein). This gluconeogenic conversion offers a metabolic option for augmenting carbohydrate availability (and maintaining plasma glucose levels) even with insufficient glycogen stores. The price paid, however, strains the bodys protein levels, particularly muscle protein. In the extreme, this reduces lean tissue mass and adds a solute load on the kidneys, forcing them to excrete the nitrogenous byproducts of protein breakdown.

## INTEGRATIVE QUESTION

Discuss the rationale for recommending adequate carbohydrate intake rather than an excess of protein to increase muscle mass through heavy resistance training.

Figure 1.4 Glycogen synthesis consists of a four-stage process. Stage 1. ATP donates a phosphate to glucose to form glucose 6-phosphate. This reaction involves the enzyme hexokinase. Stage 2. The enzyme phosphoglucomutase catalyzes the isomerization of glucose 6-phosphate to glucose 1-phosphate. Stage 3. The enzyme uridyl transferase reacts with glucose 1 -phosphate to form UDP-glucose (a pyrophosphate forms in the degradation of uridine triphosphate [UTP]). Stage 4. UDPglucose attaches to one end of an already existing glycogen polymer chain. This forms a new bond (known as a glycoside bond) between the adjacent glucose units, with concomitant release of UDP. For each glucose unit added, two molecules of high-energy phosphate (ATP and UDP) convert to two molecules of ADP and inorganic phosphate. The inset at the upper right of Stage 4 shows a low-resolution view of glycogen; the atomic arrangement of the circled area of the inset appears beneath the inset.

## 3. Metabolic Primer/Prevents Ketosis

Components of carbohydrate catabolism serve as primer substrate for fat oxidation. Insufficient carbohydrate breakdowneither through limitations in glucose transport into the cell (e.g., diabetes where insulin production wanes or insulin resistance increases) or glycogen depletion through inadequate diet or prolonged exerciseeauses fat mobilization to exceed fat oxidation. The lack of adequate byproducts of glycogen catabolism produces incomplete fat breakdown with accumulation of ketone bodies (acetoacetate and $\beta$-hydroxybutyrate, acetone-like byproducts of incomplete fat breakdown). In excess, ketone bodies increase body fluid acidity to produce a potentially harmful condition called acidosis or, specifically with regard to fat breakdown, ketosis. Chapter 6 continues the discussion of carbohydrate as a primer for fat catabolism.

## 4. Fuel for the Central Nervous System

The central nervous system requires an uninterrupted stream of carbohydrate for proper function. Under normal conditions, the brain metabolizes blood glucose almost exclusively as its fuel source. In poorly regulated diabetes, during starvation, or with a prolonged low-carbohydrate intake, the brain adapts after about 8 days and metabolizes larger amounts of fat (as ketones) for fuel. Chronic low-carbohydrate, high-fat diets also induce adaptations in skeletal muscle that increase fat use during low-to-moderate exercise levels, thus sparing muscle glycogen.

Blood sugar usually remains regulated within narrow limits for two main reasons:

1. Glucose serves as a primary fuel for nerve tissue metabolism.
2. Glucose represents the sole energy source for red blood cells.

At rest and during exercise, liver glycogenolysis (glycogen-to-glucose conversion) maintains normal blood glucose levels, usually at $100 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ (deciliter or 100 mL ). In prolonged exercise such as marathon running (or similar duration-intense activities), blood glucose concentration eventually falls below normal levels because liver glycogen depletes, while active muscle continues to catabolize the available blood glucose. Symptoms of clinically reduced blood glucose (hypoglycemia: $<45 \mathrm{mg}$ glucose $\cdot \mathrm{dL}^{-1}$ of blood) include weakness, hunger, mental confusion, and dizziness. This ultimately impairs exercise performance and can contribute to central nervous system fatigue associated with prolonged exercise. Sustained and profound hypoglycemia can trigger unconsciousness and produces irreversible brain damage. ${ }^{71}$

## CARBOHYDRATE DYNAMICS IN EXERCISE

Biochemical and biopsy techniques (see Chapter 18) and labeled nutrient tracers assess the energy contribution of nutrients during physical activity. Such data indicate that two
factors, intensity and duration of effort and the fitness and nutritional status of the exerciser, largely determine the fuel mixture in exercise. ${ }^{13,27}$

The liver increases glucose release to active muscle as exercise progresses from low to high intensity. Simultaneously, muscle glycogen supplies the predominant carbohydrate energy source during the early stages of exercise and as intensity increases. ${ }^{32}$ Compared to fat and protein use, carbohydrate remains the preferential fuel in intense aerobic exercise because it rapidly supplies energy (adenosine triphosphate, or ATP) via oxidative processes. During anaerobic exercise (requiring glycolysis reactions; see Chapter 6), carbohydrate becomes the sole fuel ATP resynthesis. Just 3 days of a diet with only $5 \%$ carbohydrate considerably depresses all-out exercise capacity. ${ }^{48}$

Carbohydrate availability in the metabolic mixture controls its use for energy. In turn, carbohydrate intake dramatically affects its availability. The concentration of blood glucose provides feedback regulation of the livers glucose output; an increase in blood glucose inhibits hepatic glucose release during exercise. ${ }^{36}$ Carbohydrate availability during exercise helps regulate fat mobilization and its use for energy. ${ }^{15,17}$ For example, increasing carbohydrate oxidation by ingesting high-glycemic carbohydrates prior to exercise (with accompanying hyperglycemia and hyperinsulinemia) inhibits two processes: (1) long-chain fatty acid oxidation by skeletal muscle and (2) free fatty acid (FFA) liberation from adipose tissue. Adequate carbohydrate availability (and resulting increased catabolism) may also inhibit transport of long-chain fatty acids into the mitochondria, thus controlling the exercise metabolic mixture.

## High-Intensity Exercise

Neural humoral factors during intense exercise increase the output of epinephrine, norepinephrine, and glucagon and decrease insulin release. These hormonal responses activate glycogen phosphorylase (indirectly via activation of cyclic adenosine monophosphate, or cyclic AMP; see Chapter 20), the enzyme that facilitates glycogenolysis in the liver and active muscles. Think of glycogen phosphorylase as the controller of the glycogen glucose interconversion to regulate circulating glucose concentration in the bloodstream. Because muscle glycogen provides energy without oxygen, it contributes considerable energy in the early minutes of exercise when oxygen use fails to meet oxygen demands. As exercise continues, blood-borne glucose increases its contribution as a metabolic fuel. For example, blood glucose may supply up to $30 \%$ of the total energy of vigorously active muscles, with the remaining carbohydrate energy supplied by muscle glycogen.

One hour of high-intensity exercise decreases liver glycogen by about 55\%; a 2-hour strenuous workout almost depletes the glycogen of the liver and exercised muscles. Figure 1.7 illustrates that the muscles uptake of circulating blood glucose increases sharply during the initial stage of cycling exercise and continues to increase as exercise continues. After 40 minutes, glucose uptake rises 7 to 20 times the uptake at rest, depending on exercise intensity. The advantage of


| Intense exercise | $\square$ | Moderate exercise |
| :--- | :--- | :--- |
| $75 \%-90 \%$ | $\square$ | $\square$ Mild exercise |
| $\mathbf{V O} 0_{2 \text { max }}$ | $\mathrm{VO}_{2 \text { max }}$ | $25 \%-60 \%$ |
|  |  | $\mathrm{VO}_{2 \text { max }}$ |

Figure 1.7 Generalized response for blood glucose uptake by the leg muscles during cycling in relation to exercise duration and intensity. Exercise intensity is expressed as a percentage of $\mathrm{VO}_{2 \text { max }}$.
a selective dependence on carbohydrate metabolism during intense aerobic exercise derives from its rate of energy transfer, which is twice that of fat or protein. ${ }^{77}$ In addition, carbohydrate generates almost $6 \%$ more energy than fat per liter of oxygen consumed. Chapter 6 discusses in more detail the energy release from carbohydrate under anaerobic and aerobic conditions.

## Moderate and Prolonged Exercise

Glycogen stored in active muscles supplies almost all of the energy in the transition from rest to moderate exercise. During the next 20 minutes, liver and muscle glycogen supply between 40 and $50 \%$ of the energy requirement, with the remainder provided by fat catabolism and a limited amount of protein. In essence, the nutrient mixture for energy depends on the relative exercise intensity. During low-intensity exercise, fat serves as the main energy substrate throughout exercise (see Fig. 1.20). As exercise continues and muscle glycogen decreases, blood glucose becomes the major source of carbohydrate energy, while fat catabolism furnishes an increasingly greater percentage of the total energy. Eventually, the livers glucose output fails to keep pace with glucose use by muscle, and plasma glucose concentration decreases. In such cases, circulating blood glucose may reach hypoglycemic levels.

Figure 1.8 depicts the metabolic profile during prolonged exercise in the glycogen-depleted and glycogen-loaded states. As submaximal exercise progresses in the glycogen-depleted
state, blood glucose levels fall and circulating fat (predominantly as free fatty acids, or FFA) increases dramatically compared with exercise under glycogen-loaded conditions. Concurrently, the contribution of protein to the energy expenditure increases. Exercise intensity (expressed as percentage of maximum) also progressively decreases under the glycogendepleted condition. At the end of 2 hours, an exerciser can only maintain about $50 \%$ of the initial exercise intensity. Reduced power output results directly from the relatively slow rate of aerobic energy release from fat oxidation, which now becomes the primary energy source. Any of the following seven potential rate-limiting metabolic processes that precede the citric acid cycle (see Chapter 6) could explain the relatively slower rate of fat oxidation compared with that of carbohydrate:

1. FFA mobilization from adipose tissue
2. FFA transport to skeletal muscle via circulation
3. FFA uptake by the muscle cell
4. FFA uptake by the muscle from triacylglycerols in chylomicrons and lipoproteins
5. Fatty acid mobilization from intramuscular triacylglycerols and cytoplasmic transport
6. Fatty acid transport into the mitochondria
7. Fatty acid oxidation within the mitochondria

Fatigue occurs when exercise continues to the point that compromises the content of liver and muscle glycogen. This occurs despite sufficient oxygen availability to muscle and an almost unlimited energy supply available from stored fat. Endurance athletes commonly refer to this sensation of fatigue as bonking, or " hitting the wall. Because skeletal muscle lacks the phosphatase enzyme, which allows glucose exchange between cells, the relatively inactive muscles maintain their full glycogen content. What remains unclear is why muscle glycogen depletion coincides with the point of fatigue. The answer may relate to the following three factors:

1. Depressed availability of blood glucose for optimal central nervous system function
2. Muscle glycogens role as a frimer in fat breakdown
3. Slower rate of energy release from fat compared to carbohydrate breakdown

## Effect of Diet on Muscle Glycogen Stores and Endurance

Diet composition profoundly affects glycogen reserves and subsequent exercise performance. In the classic experiment ${ }^{6}$ illustrated in Figure 1.9, six subjects maintained normal caloric intake for 3 days but consumed most of their calories as lipid and $5 \%$ or less as carbohydrate (high-fat diet). In the second condition (normal diet), the 3-day diet contained the recommended daily percentages of carbohydrate, lipid, and protein. The third diet provided $82 \%$ of the calories as carbohydrates (high-carbohydrate diet). The glycogen content


Figure 1.8 Dynamics of nutrient metabolism in the glycogen-loaded and glycogen-depleted states. During exercise with limited carbohydrate availability, plasma glucose levels (A) progressively decrease, while fat metabolism (B) progressively increases compared with similar exercise when glycogen loaded. In addition, protein use for energy (C), as indicated by plasma levels of 3-OH butyrate, remains considerably higher with glycogen depletion. After 2 hours, exercise capacity (D) decreases to about $50 \%$ of maximum in exercise begun in the glycogen-depleted state. (From Wagenmakers AJM, et al. Carbohydrate supplementation, glycogen depletion, and amino acid metabolism. Am J Physiol 1991;260:E883.)
of the quadriceps femoris muscle, determined from needle biopsy specimens, averaged 0.63 g of glycogen per 100 g wet muscle with the high-fat diet, 1.75 g for the normal diet, and 3.75 g for the high-carbohydrate diet.

Endurance capacity during cycling exercise varied considerably, depending on what diet was consumed for 3 days before the exercise test. With the normal diet, exercise lasted an average of 114 minutes, whereas endurance averaged only 57 minutes with the high-fat diet. The highcarbohydrate diet improved endurance performance by more than three times that of the high-fat diet. Interestingly, the point of fatigue coincided with the same low level of muscle glycogen under the three diet conditions. These findings, complemented by the recent research of others, ${ }^{24,30}$ conclusively demonstrate the importance of muscle glycogen to sustain high-intensity exercise lasting more than 1 hour.

A carbohydrate-deficient diet rapidly depletes muscle and liver glycogen and negatively affects performance in
short-term anaerobic exercise and prolonged intense aerobic activities. These observations apply particularly to individuals who modify their diets by reducing carbohydrate intake below recommended levels. Reliance on starvation diets or other extreme diet forms (e.g., high-fat, low-carbohydrate diets or liquid-protein diets) proves counterproductive to optimize exercise performance. Reliance on low-carbohydrate diets makes it particularly difficult from an energy supply standpoint to engage regularly in longer-duration, vigorous physical activities. Chapter 3 discusses optimal provision for carbohydrate needs prior to, during, and in recovery from strenuous exercise.

## Summary

1. Carbon, hydrogen, oxygen, and nitrogen represent the basic structural units for most of the bodys bioactive substances. Carbon combined with oxygen and hydrogen form carbohydrates and lipids. Proteins


Figure 1.9 Classic experiment illustrating the effects of a high-fat low-carbohydrate ( CHO ) diet, a normal diet, and a high-carbohydrate-low-fat diet on the quadriceps femoris muscle s glycogen content and duration of endurance exercise on a bicycle ergometer. Endurance time with a high-carbohydrate diet is three times that on a low-carbohydrate diet. (Adapted from Bergstrom J, et al. Diet, muscle glycogen and physical performance. Acta Physiol Scand 1967;71:140.)
form when combinations of carbon, oxygen, and hydrogen bind with nitrogen and minerals.
2. Simple sugars consist of chains of 3 to 7 carbon atoms, with hydrogen and oxygen in the ratio of $2: 1$. Glucose, the most common simple sugar, contains a 6-carbon chain as $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$.
3. Three major classifications of carbohydrates include monosaccharides (sugars such as glucose and fructose), oligosaccharides (disaccharides such as sucrose, lactose, and maltose), and polysaccharides that contain three or more simple sugars to create plant starch and fiber and glycogen (the large glucose polymer from the animal kingdom).
4. Glycogenolysis describes the reconversion of glycogen to glucose; gluconeogenesis refers to glucose synthesis, particularly from protein sources.
5. Americans consume 40 to $50 \%$ of total caloric intake as carbohydrates, typically as simple sugars and refined starches. Excess consumption of simple sugars and other rapidly absorbed carbohydrates may have negative health consequences.
6. Carbohydrate, stored in limited quantity in liver and muscle, serves four important functions: (1) provides a major source of energy, (2) spares protein breakdown, (3) functions as a metabolic primer for fat catabolism, and (4) provides the required,
uninterrupted fuel supply for the central nervous system.
7. Muscle glycogen provides the primary energy substrate (fuel) during anaerobic exercise. The bodys glycogen stores (muscle glycogen and glucose from the liver) also contribute substantially to energy metabolism in longer-duration endurance-type activities.
8. Fat contributes about $50 \%$ of the energy requirement during light- and moderate-intensity exercise. Stored intramuscular fat and fat derived from adipocytes becomes important during prolonged exercise. In this situation, the fatty acid molecules (mainly as circulating FFAs) supply more than $80 \%$ of the exercise energy requirements.
9. A carbohydrate-deficient diet quickly depletes muscle and liver glycogen. This profoundly affects both all-out exercise capacity and the capacity to sustain high-intensity aerobic exercise.
10. Individuals who train at high intensities should consume between 60 and $70 \%$ of daily calories as carbohydrates, predominantly in unrefined, complex form ( 400 to $800 \mathrm{~g} ; 8$ to 10 g per kg of body mass).
11. When muscles supply of glycogen depletes, exercise intensity decreases to a level determined by the bodys ability to mobilize and oxidize fat.

## Part 2 LIPIDS

## THE NATURE OF LIPIDS

A lipid (from the Greek lipos, meaning fat) molecule has the identical structural elements as carbohydrate but differs in its linkage and number of atoms. Specifically, the lipids ratio of hydrogen to oxygen considerably exceeds that of carbohydrate. For example, the formula $\mathrm{C}_{57} \mathrm{H}_{110} \mathrm{O}_{6}$ describes the common lipid stearin with an $\mathrm{H}: \mathrm{O}$ ratio of 18.3:1; for carbohydrate, the ratio remains constant at 2:1.

Lipid, the general term for a heterogeneous group of compounds, includes oils, fats, waxes, and related compounds. Oils become liquid at room temperature, whereas fats remain solid. Approximately $98 \%$ of dietary lipid exists as triacylglycerol (see next section), while about $90 \%$ of the bodys total fat resides in the adipose tissue depots of the subcutaneous tissues.

## KINDS AND SOURCES OF LIPIDS

Plants and animals contain lipids in long hydrocarbon chains. Lipids, generally greasy to the touch, remain insoluble in water but soluble in the nonpolar organic solvents acetone, ether, chloroform, and benzene. According to common classification, lipids belong to one of three main groups: simple lipids, compound lipids, and derived lipids.

## Simple Lipids

The simple lipids, or heutral fats, consist primarily of triacylglycerolsa-term preferable to triglycerides among biochemists because it describes glycerol acylated by three fatty acids. The fats are ffeutral because at the pH of the cell they carry no electrically charged groups. These completely nonpolar molecules have no affinity for water. Triacylglycerols constitute the major storage form of fat in fat cells, or adipocytes. This molecule contains two different clusters of atoms. One cluster, glycerol, consists of a 3-carbon molecule that itself does not qualify as a lipid because of its high solubility in water. Three clusters of unbranched carbon-chained atoms, termed fatty acids, bond to the glycerol molecule. A carboxyl ( COOH ) cluster at one end of the fatty acid chain gives the molecule its acidic characteristics. Fatty acids have straight hydrocarbon chains with as few as 4 carbon atoms or more than 20, although chain lengths of 16 and 18 carbons are most common. As the fatty acids chain length increases, it becomes less water soluble and thus more oily, with fatty characteristics.

The synthesis (condensation) of the triacylglycerol molecule produces three molecules of water. Conversely, during hydrolysis, when lipase enzymes cleave the molecule into its constituents, three molecules of water attach at the points where the fat molecule splits. Figure 1.10 illustrates the basic structure of a saturated fatty acid and an unsaturated fatty


A No double bonds; fatty acid chains fit close together

## Unsaturated Fatty Acid



B Double bonds present; fatty acid chains do not fit close together
Figure 1.10 The presence or absence of double bonds between the carbon atoms is the major structural difference between saturated and unsaturated fatty acids. A. The saturated fatty acid palmitic acid has no double bonds in its carbon chain and contains the maximum number of hydrogen atoms. Without double bonds, the three saturated fatty acid chains fit together closely to form a hard fat. B. The three double bonds in linoleic acid, an unsaturated fatty acid, reduce the number of hydrogen atoms along the carbon chain. Insertion of double bonds into the carbon chain prevents close association of the fatty acids; this produces a softer fat, or an oil.
acid molecule. All lipid-containing foods consist of a mixture of different proportions of saturated and unsaturated fatty acids. Fatty acids are so named because the organic acid molecule $(\mathrm{COOH})$ forms part of their chemical structure. The body fat of humans contains both forms of fatty acids.

## Saturated Fatty Acids

A saturated fatty acid contains only single covalent bonds between carbon atoms; all of the remaining bonds attach to hydrogen. If the carbon within a fatty acid chain binds the maximum possible number of hydrogens, the fatty acid molecule is said to be saturated with respect to hydrogen, and hence the name saturated fatty acid.

Saturated fatty acids occur primarily in animal products such as beef ( $52 \%$ saturated fatty acids), lamb, pork, chicken, egg yolk, and dairy fats of cream, milk, butter ( $62 \%$ saturated fatty acids), and cheese. Saturated fatty acids from the plant kingdom include coconut and palm oil, vegetable shortening, and hydrogenated margarine; commercially prepared cakes, pies, and cookies contain plentiful amounts of these fatty acids.

## Unsaturated Fatty Acids

Unsaturated fatty acids contain one or more double bonds along their main carbon chain. Each double bond along the chain reduces the number of potential hydrogen-binding sites; the molecule, therefore, is said to be unsaturated with respect to hydrogen. A monounsaturated fatty acid contains one double bond along the main carbon chain; examples include canola oil, olive oil ( $77 \%$ monounsaturated fatty acids), peanut oil, and the oil in almonds, pecans, and avocados. A polyunsaturated fatty acid contains two or more double bonds along the main carbon chain; safflower, sunflower, soybean, and corn oil serve as examples. Figure 1.11 lists the contents of saturated, monounsaturated, and polyunsaturated fatty acids in common fats and oils (expressed in g per 100 g of the lipid). The inset table shows the hidden fat percentage in some popular foods. Several polyunsaturated fatty acids, most notably linoleic acid (an 18-carbon fatty acid with two double bonds present in cooking and salad oils), must originate from dietary sources because they serve as precursors of other fatty acids the body cannot synthesize, thus they are termed essential fatty acids. Linoleic acid maintains the integrity of plasma membranes and sustains growth, reproduction, skin maintenance, and general body functioning.

Fatty acids from plant sources generally remain unsaturated and liquefy at room temperature. In contrast, lipids containing longer (more carbons along the chain) and more saturated fatty acids exist as solids at room temperature; those with shorter and more unsaturated fatty acids remain soft. Oils exist as liquids and contain unsaturated fatty acids. The chemical process of hydrogenation changes oils to semisolid fats by bubbling liquid hydrogen under pressure into vegetable oil. This reduces the unsaturated fatty acids double bonds to single bonds so more hydrogens can attach to carbons along the chain. Firmer fat forms because adding hydrogen


| Hidden fat percentage of total calories |  |  |  |
| :--- | :---: | :--- | :---: |
| Food | Fat $\%$ | Food | Fat $\%$ |
| Brazil nuts | 67 | Lamb roast | 19 |
| Walnuts | 61 | Avocado | 16 |
| Almonds | 54 | Ice cream | 13 |
| Peanuts | 50 | Herring | 12 |
| Sunflower seeds | 47 | Poached eggs | 11 |
| Pork sausage | 44 | Tuna, canned | 8 |
| Pork roast | 30 | Poultry, dark meat | 7 |
| Cheese | 30 | Oatmeal, dry | 7 |
| Bologna | 28 | Salmon | 6 |
| Beef roast | 25 | Whole milk | 4 |
| Ham, cured | 22 | Poultry, light meat | 4 |
| Hamburger | 20 | Shredded wheat cereal | 2 |

Figure 1.11 Upper graph shows the composition of diverse fatty acids ( g per 100 g ) in common lipid sources in the diet. Lower table shows the hidden total fat percentage of total calories in popular foods. (Data from Food Composition Tables, United States Department of Agriculture.)
increases the lipids melting temperature. Hydrogenated oil behaves like a saturated fat; the most common hydrogenated fats include lard substitutes and margarine.

## Triacylglycerol Formation

Figure 1.12 outlines the sequence of reactions in triacylglycerol synthesis, a process termed esterification. Initially, a fatty acid substrate attached to coenzyme A forms fatty acyl-CoA, which then transfers to glycerol (as glycerol 3-phosphate). In subsequent reactions, two additional fatty acyl-CoAs link to the single glycerol backbone to form the composite triacylglycerol molecule. Triacylglycerol synthesis increases following a


Figure 1.12 Top. Triacylglycerol formation in adipocytes (and muscle) tissue involves a series of reactions (dehydration synthesis) that link three fatty acid molecules to a single glycerol backbone. The bottom portion of the figure summarizes this linkage.
meal for two reasons: (1) Food absorption increases blood levels of fatty acids and glucose and (2) relatively high levels of circulating insulin facilitate triacylglycerol synthesis.

## Triacylglycerol Breakdown

The term hydrolysis (more specifically lipolysis when applied to lipids) describes triacylglycerol catabolism to yield glycerol and the energy-rich fatty acid molecules. Figure 1.13 shows that lipolysis adds water in three distinct hydrolysis
reactions, each catalyzed by hormone-sensitive lipase. ${ }^{18}$ The mobilization of fatty acids via lipolysis predominates under four conditions:

1. Low-to-moderate intensity exercise
2. Low-calorie dieting or fasting
3. Cold stress
4. Prolonged exercise that depletes glycogen reserves

Triacylglycerol esterification and lipolysis occur in the cytosol of adipocytes. The fatty acids released during lipolysis


Figure 1.13 Triacylglycerol catabolism (hydrolysis or, more specifically, lipolysis) to its glycerol and fatty acid components involves a three-step process regulated by hormone-sensitive lipase (HSL).
can either reesterify to triacylglycerol following their conversion to a fatty acyl-CoA or exit from the adipocyte, enter the blood, and combine with the blood protein albumin for transport to tissues throughout the body. The term free fatty acid (FFA) describes this albumin fatty acid combination.

Lipolysis also occurs in tissues other than adipocytes. Hydrolysis of dietary triacylglycerol occurs in the small intestine, catalyzed by pancreatic lipase; lipoprotein lipase, an enzyme located on the walls of capillaries, catalyzes the hydrolysis of the triacylglycerols carried by the bloods lipoproteins. Adjacent adipose tissue and muscle cells take up the fatty acids released by the action lipoprotein lipase; these fatty acids are resynthesized to triacylglycerol for energy storage.

## Trans-Fatty Acids: The Unwanted Fat

Trans-fatty acids derive from the partial hydrogenation of unsaturated corn, soybean, or sunflower oil. A trans-fatty acid forms when one of the hydrogen atoms along the restructured carbon chain moves from its naturally occurring position (cis position) to the opposite side of the double bond that separates 2 carbon atoms (trans position). The richest trans-fat sources comprise vegetable shortenings, some margarines, crackers, candies, cookies, snack foods, fried foods, baked goods, salad dressings, and other processed foods made with partially hydrogenated vegetable oils.

Health concerns about trans-fatty acids centers on their possible detrimental effects on serum lipoproteins. ${ }^{3,53,54}$ A diet high in margarine and commercial baked goods (cookies,
cakes, doughnuts, pies) and deep-fried foods prepared with hydrogenated vegetable oils increases low-density lipoprotein cholesterol concentration by a similar amount as a diet high in saturated fatty acids. Unlike saturated fats, hydrogenated oils also decrease the concentration of beneficial high-density lipoprotein cholesterol. In light of the strong evidence that trans-fatty acids place individuals at increased risk for heart disease, ${ }^{83}$ the Food and Drug Administration (FDA) has mandated that food processors include the amount of trans-fatty acids on nutrition labels. The FDA estimates the average American consumes approximately 2.2 kg of trans fats yearly.

In July 2008, New York City became the nations first city to enforce a ban on essentially all trans fats in foods prepared in the Citys 24,000 eateriesfrem fast foods to fine dining.

## Lipids in the Diet

Figure 1.14 displays the approximate percentage contribution of some common food groups to the total lipid content of the typical American diet.

The average person in the United States consumes about $15 \%$ of total calories as saturated fatty acids, the equivalent of over 23 kg yearly. The relationship between saturated fatty acid intake and coronary heart disease risk has prompted health professionals to recommend two courses of action:

1. Replacing at least a portion of the saturated fatty acids and all trans-fatty acids with nonhydrogenated monounsaturated and polyunsaturated oils


Figure 1.14 Contribution from the major food groups to the lipid content of the typical American diet.
2. Balancing energy intake with regular physical activity to minimize weight gain and obtain the health benefits of regular exercise

From a health perspective, individuals should consume no more than $10 \%$ of total daily energy intake as saturated fatty acids (about 300 kCal , or 30 to 35 g for the average young adult male who consumes 3000 kCal ).

Fish Oils. The health profiles and dietary patterns of Greenland Eskimos, who consume large quantities of lipids from fish, seal, and whale that are high in two essential long-chain polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, show that these people have a low incidence of heart disease. These oils belong to the omega- $\mathbf{3}$ fatty acid family (also termed $n-3$; the last double bond begins 3 carbons from the end carbon), found primarily in the oils of shellfish and cold-water herring, sardines, and mackerel, and sea mammals. Regular intake of fish (minimum 2 servings weekly) and fish oil benefits the blood lipid profile, particularly plasma triacylglycerols, ${ }^{46}$ overall heart disease risk and mortality rate (chance of ventricular fibrillation and sudden death); ${ }^{1,19,42,86}$ Alzheimers disease; ${ }^{4,60}$ inflammatory disease risk; ${ }^{14}$ and (for smokers) the risk of contracting chronic obstructive pulmonary disease. ${ }^{68}$ One proposed mechanism for heart attack protection asserts that fish oil helps to prevent blood clot formation on arterial walls. It also may inhibit the growth of atherosclerotic plaques, reduce pulse pressure and total vascular resistance (increase arterial compliance), and stimulate endothelialderived nitric oxide (see Chapter 16) to facilitate myocardial perfusion. ${ }^{58}$

## Compound Lipids

Compound lipids, triacylglycerol components combined with other chemicals, represent about $10 \%$ of the bodys total fat content. One group of modified triacylglycerols, the phospholipids, contains one or more fatty acid molecules joined with a phosphorus-containing group and one of several nitrogen-containing molecules. These lipids form in all cells, although the liver synthesizes most of them. Phospholipids have four main functions:

1. Interacting with both water and lipid to modulate fluid movement across cell membranes
2. Maintaining the structural integrity of the cell
3. Playing an important role in blood clotting
4. Providing structural integrity to the insulating sheath that surrounds nerve fibers

Other compound lipids include glycolipids (fatty acids bound with carbohydrate and nitrogen) and water-soluble lipoproteins (protein spheres formed primarily in the liver when a protein molecule joins with either triacylglycerols or phospholipids). Lipoproteins provide the major avenue for transporting lipids in the blood. If blood lipids did not bind to protein, they literally would float to the top like cream in nonhomogenized fresh milk instead of circulating throughout the vascular system.

## High-Density, Low-Density, and Very Low-Density Lipoproteins

Lipoproteins categorize into types according to their size and density and whether they carry cholesterol or triacylglycerol. Figure 1.15 illustrates the general dynamics in the body of cholesterol and lipoproteins, including their transport among the small intestine, liver, and peripheral tissues. Four types of lipoproteins exist on the basis of their gravitational density.

1. Chylomicrons form when emulsified lipid droplets (including long-chain triacylglycerols, phospholipids, and FFAs) leave the intestine and enter the lymphatic vessels. Normally, the liver metabolizes chylomicrons and sends them for storage in adipose tissue. Chylomicrons also transport the fat-soluble vitamins A, D, E, and K.
2. High-density lipoprotein (HDL). Produced in the liver and small intestine, they contain the highest percentage of protein (about $50 \%$ ) and the least total lipid (about 20\%) and cholesterol (about 20\%) of the lipoproteins.
3. Very low-density lipoprotein (VLDL). These are degraded in the liver to produce a low-density lipoprotein (LDL; discussed below). VLDLs, formed in the liver from fats, carbohydrates, alcohol, and cholesterol, contain the highest percentage of lipid (95\%), of which about $60 \%$ consists of triacylglycerol. VLDLs transport triacylglycerols to muscle and adipose tissue. Under the action of lipoprotein lipase, the VLDL molecule becomes a denser LDL molecule because it then


Figure 1.15 General interaction between dietary cholesterol and lipoproteins and their transport among the small intestine, liver, and peripheral tissues.
contains fewer lipids. LDLs and VLDLs have the most lipid and fewest protein components.
4. Low-density lipoprotein. Commonly known as bad cholesterol (in contrast, HDL is known as good cholesterol), this substance normally carries
from 60 to $80 \%$ of the total serum cholesterol and has the greatest affinity for cells of the arterial wall. LDL delivers cholesterol to arterial tissue where the LDL particles are (1) oxidized to alter their physiochemical properties and (2) taken up by macrophages inside the arterial wall to initiate atherosclerotic plaque development. LDL oxidation ultimately contributes to smooth muscle cell proliferation and other unfavorable cellular changes that damage and narrow arteries.

HDL Versus LDL: A Health Perspective. Unlike LDL, HDL protects against heart disease. HDL acts as a scavenger in the reverse transport of cholesterol by removing it from the arterial wall and delivering it to the liver for incorporation into bile and subsequent excretion via the intestinal tract.

The amount of LDL and HDL and their specific ratios (e.g., HDL $\div$ total cholesterol; LDL $\div$ HDL) and subfractions provide more meaningful indicators of coronary artery disease risk than total cholesterol per se. Regular moderateand high-intensity aerobic exercise and abstinence from cigarette smoking increase HDL, lower LDL, and favorably alter the LDL:HDL ratio. ${ }^{44,49,70}$ We discuss these effects more fully in Chapter 31. An online computer program calculates the risk and the appropriate cholesterol levels for adults (www. nhlbi.nih.gov/guidelines/cholesterol/index.htm).

## Derived Lipids

Simple and compound lipids form derived lipids. Cholesterol, the most widely known derived lipid, exists only in animal tissue and from a dietary viewpoint classifies as a lipid. Cholesterol does not contain fatty acids; instead, it shares some of lipids physical and chemical characteristics. Cholesterol, widespread in the plasma membrane of all cells, originates either through the diet (exogenous cholesterol) or through cellular synthesis (endogenous cholesterol). Even with a cholesterol-free diet, endogenous daily cholesterol synthesis varies between 0.5 and 2.0 g . More endogenous cholesterol forms with a diet high in saturated fatty acids and trans-fatty acids, which facilitate LDL cholesterol synthesis in the liver. The liver synthesizes about $70 \%$ of the bodys cholesterol, but other tissuesincluding the walls of the arteries and intestinesalso construct this compound.

## Functions of Cholesterol

Cholesterol participates in many bodily functions; these include building plasma membranes and serving as a precursor in synthesizing vitamin D , adrenal gland hormones, and the sex hormones estrogen, androgen, and progesterone. Cholesterol furnishes a key component for bile (emulsifies lipids during digestion) synthesis and plays a crucial role in forming tissues, organs, and body structures during fetal development.

Egg yolk provides a rich source of cholesterol (average of about 213 mg per egg), as do red meats and organ meats


Figure 1.16 Cholesterol content of representative foods in the diet. (Data from Food Composition Tables, United States Department of Agriculture.)
(liver, kidney, and brains). Shellfish (particularly shrimp) and dairy products (ice cream, cream cheese, butter, and whole milk) contain relatively large amounts of cholesterol. Foods of plant origin contain no cholesterol. Figure 1.16 lists the cholesterol content of different foods.

## Cholesterol and Coronary Heart Disease Risk

High levels of total serum cholesterol and the choles-terol-rich LDL molecule are powerful predictors of increased risk for coronary artery disease. These become particularly potent when combined with other risk factors of cigarette smoking, physical inactivity, excess body fat, and untreated hypertension. Patients with existing heart disease improve coronary blood flow (reducing myocardial ischemia during daily life) within 6 months by aggressively using drug and diet therapy that lower total blood cholesterol and LDL cholesterol. For example, a class of drugs called statins can reduce cholesterol by up to $40 \%$, thus slowing disease progression. ${ }^{2}$

A dietary cholesterol excess in susceptible individuals eventually produces atherosclerosis, a degenerative process that forms cholesterol-rich deposits (plaque) on the inner
lining of the medium and larger arteries, causing them to narrow and eventually close. Reducing saturated fatty acid and cholesterol intake generally lowers serum cholesterol, although for most people the effect remains modest. ${ }^{25,82}$ Similarly, increasing dietary intake of monounsaturated and polyunsaturated fatty acids lowers blood cholesterol, particularly LDL cholesterol. ${ }^{29,66}$ Chapter 31 presents specific recommended values for desirable, borderline, and undesirable plasma lipid and lipoprotein levels.

## RECOMMENDED LIPID INTAKE

Recommendations for dietary lipid intake for physically active individuals generally follow prudent health-related recommendations for the general population. Although dietary lipid currently represents between 34 and $38 \%$ of total caloric intake in the United States, or about $50 \mathrm{~kg}(110 \mathrm{lb})$ of lipid consumed per person each year, current recommendations place intake between 20 and $35 \%$ depending on the type of lipid consumed. Rather than providing a precise number for daily cholesterol intake, the American Heart Association (AHA; www.americanheart.org) encourages Americans to focus more on replacing high-fat foods with fruits, vegetables,
unrefined whole grains, fat-free and low-fat dairy products, fish, poultry, and lean meat. ${ }^{43}$ Other new components of the AHA guidelines include a focus on weight control and addition of two weekly servings of fish high in omega-3 fatty acids. The American Cancer Society (www.cancer.org) advocates a diet that contains only $20 \%$ of total calories from lipid to reduce risk of cancers of the colon and rectum, prostate, endometrium, and perhaps breast. Unfortunately, many patients who suffer a heart attack still fail to follow prudent dietary guidelines one year after an attack. ${ }^{51}$ Only $12.4 \%$ of these men and women met the recommended consumption of vegetables, $7.8 \%$ for fruit, $8 \%$ for cereal fiber, and $5.2 \%$ for trans-fat intake.

The main sources of dietary cholesterol include the same animal food sources rich in saturated fatty acids. Curtailing intake of these foods reduces preformed cholesterol intake and, more importantly, reduces intake of fatty acids known to stimulate endogenous cholesterol synthesis.

## fyi

Reduce Saturated Fat and Cholesterol

| If You Eat <br> This Food | To Reduce Fat, Substitute <br> This Food |
| :--- | :--- |
| Egg | Egg whites or egg substitute <br> Cream cheese <br> Low-fat or fat-free cream <br> cheese; blended cottage <br> cheese or blended low-fat <br> ricotta cheese |
| Cheeses | Part-skim milk cheeses <br> Sour creamLow-fat yogurt, low-fat <br> blended cottage cheese with <br> lemon juice <br> Non-fat milk; evaporated <br> skim milk; non-fat <br> buttermilk |
| Baking chocolate | Unsweetened cocoa powder |

## ROLE OF LIPID IN THE BODY

Four important functions of lipids in the body include:

1. Energy source and reserve
2. Protection of vital organs
3. Thermal insulation
4. Vitamin carrier and hunger suppressor

## Energy Source and Reserve

Fat constitutes the ideal cellular fuel for three reasons:

1. It carries a large quantity of energy per unit weight.
2. It transports and stores easily.
3. It provides a ready source of energy.

Fat provides as much as 80 to $90 \%$ of the energy requirement of a well-nourished individual at rest. One gram of pure lipid contains about $9 \mathrm{kCal}(38 \mathrm{~kJ})$ of energy, more than twice
the energy available to the body from an equal quantity of carbohydrate or protein. Recall that the synthesis of a triacylglycerol molecule from glycerol and three fatty acid molecules produces three water molecules. In contrast, when glycogen forms from glucose, each gram of glycogen stores 2.7 g of water. Fat exists as a relatively water-free, concentrated fuel, whereas glycogen remains hydrated and heavy relative to its energy content.

INTEGRATIVE QUESTION
What benefit derives from storing carbohydrate and lipid within muscle cells and specific tissue depots for selective use under diverse exercise conditions?

Fat and Energy Content of the Body. For young adults, approximately $15 \%$ of the body mass of males and $25 \%$ of that of females consists of fat. Figure 1.17 illustrates the total mass (and energy content) of fat from various sources in an $80-\mathrm{kg}$ man. The potential energy stored in the fat molecules of the adipose tissue translates to about $108,000 \mathrm{kCal}$ ( $12,000 \mathrm{~g}$ body fat $\times 9.0 \mathrm{kCal} \cdot \mathrm{g}^{-1}$ ). A run from San Diego, California, to Seattle, Washington (assuming an energy expenditure of about 100 kCal per mile), would deplete the energy provided from adipose tissue and intramuscular triacylglycerols and a small amount of plasma FFAs. Contrast this with the limited $2000-\mathrm{kCal}$ reserve of stored carbohydrate that would provide energy for only a 20 -mile run. Viewed from a different perspective, the bodys energy reserves from carbohydrate could power high-intensity running for about 1.6 hours, whereas exercise would continue for about 120 hours using the bodys fat reserves! Fat used as a fuel also §pares


Figure 1.17 Distribution of the quantity and energy stored as fat within an average $80-\mathrm{kg}$ man (FFA, free fatty acids).
protein to carry out its important functions of tissue synthesis and repair.

## Protection of Vital Organs and Thermal Insulation

Up to 4\% of the bodys fat protects against trauma to vital organs (e.g., heart, liver, kidneys, spleen, brain, spinal cord). Fat stored just below the skin (subcutaneous fat) provides insulation, permitting individuals to tolerate extremes of cold. ${ }^{74}$ This insulatory layer of fat benefits deep-sea divers, ocean or channel swimmers, or Arctic inhabitants. In contrast, excess body fat hinders temperature regulation during heat stress, most notably during sustained exercise in air, when the bodys heat production can increase 20 times above resting levels. In this case, the insulatory shield from subcutaneous fat retards heat flow from the body.

For large-sized football linemen, excess fat storage provides additional cushioning to protect the participant from the sports normal traumas. Any possible protective benefit must be weighed against the liability imposed by the dead weight of excess fat and its impact on exercise energy expenditure, thermal regulation, and subsequent exercise performance.

## Vitamin Carrier and Hunger Depressor

Consuming approximately 20 g of dietary fat daily provides a sufficient source and transport medium for the four fat-soluble vitamins, A, D, E, and K. Severely reducing lipid intake depresses the bodys level of these vitamins and ultimately leads to vitamin deficiency. Dietary lipid also facilitates absorption of vitamin A precursors from nonlipid plant sources such as carrots and apricots. It takes about 3.5 hours after ingesting lipids for the stomach to empty them.

## FAT DYNAMICS DURING EXERCISE

Intracellular and extracellular fat (FFAs, intramuscular triacylglycerols, and circulating plasma triacylglycerols bound to lipoproteins as VLDL and chylomicrons) supply between 30 and $80 \%$ of the energy for physical activity, depending on nutritional and fitness status and exercise intensity and duration. ${ }^{5,52}$ Increased blood flow through adipose tissue with exercise increases the release of FFAs for delivery to and use by muscle. The quantity of fat used for energy in light and moderate exercise is three times that compared to resting conditions. As exercise becomes more intense (greater percentage of aerobic capacity), adipose tissue release of FFAs fails to increase much above resting levels, leading to a decrease in plasma FFAs. This in turn stimulates increased muscle glycogen use (see Fig. 1.20). ${ }^{67}$ The energy contribution from intramuscular triacylglycerols ranges between 15 and $35 \%$, with endurance-trained athletes catabolizing the largest quantity and a substantial impairment in use among the obese and/or type 2 diabetics. ${ }^{39,41,78}$ Long-term consumption of a high-fat diet induces enzymatic adaptations that enhance fat oxidation during submaximal exercise. ${ }^{47,57}$ Unfortunately, this adaptation does not translate to improved exercise performance.

The major energy for light-to-moderate exercise comes from fatty acids released from triacylglycerol storage sites and delivered to muscle as FFAs and intramuscular triacylglycerols. The start of exercise produces a transient initial drop in plasma FFA concentration because of increased FFA uptake by active muscles. An increased FFA release from adipose tissue follows (with concomitant suppression of triacylglycerol formation) owing to (1) hormonal stimulation by the sympathetic nervous system and (2) a decrease in plasma insulin levels. During moderate-intensity exercise, approximately equal amounts of carbohydrate and fat supply energy. When exercise continues at this level for more than one hour, fat catabolism gradually supplies a greater percentage of energy; this coincides with the progression of glycogen depletion. Carbohydrate availability also influences fat use for energy. With adequate glycogen reserves, carbohydrate becomes the preferred fuel during intense aerobic exercise because of its more rapid rate of catabolism. Toward the end of prolonged exercise (when glycogen reserves become nearly depleted), fat, mainly as circulating FFAs, supplies up to $80 \%$ of the total energy requirement. Figure 1.18 shows this phenomenon first observed in the mid-1930s for a subject who bicycled continuously for

$\square$ FAT $\square$ CHO Figure 1.18 Classic study in 1934 showing the relationship
between respiratory quotient (RQ) and substrate use during long-duration, submaximal exercise. Top. Progressive reduction in RQ at an oxygen consumption of $2.36 \mathrm{~L} \mathrm{~min}^{-1}$ during 6 hours of continuous exercise. Bottom. Percentage of energy derived from carbohydrate and fat. (Modified from Edwards HT, et al. Metabolic rate, blood sugar and utilization of carbohydrate. Am J Physiol 1934;108:203.)


Figure 1.19 Generalized percentage contribution of macronutrient catabolism in relation to oxygen consumption of the leg muscles during prolonged exercise.

6 hours. Carbohydrate combustion (reflected by the RQ [respiratory quotient]; see Chapter 8) steadily declined during exercise, with an associated increase in fat use. Toward the end of exercise, fat breakdown supplied $84 \%$ of the total energy! This classic experiment illustrates fat oxidations important role in providing energy during extended exercise with glycogen depletion.

The increase in fat catabolism during prolonged exercise probably results from a small drop in blood sugar and decrease in insulin (a potent inhibitor of lipolysis), with a corresponding increase in glucagon output by the pancreas. Such responses ultimately reduce glucose catabolism and its potential inhibitory effect on long-chain fatty acid breakdown, further stimulating FFA liberation for energy. Figure 1.19 shows that FFA uptake by active muscle rises during hours 1 and 4 of moderate exercise. In the first hour, fat (including intramuscular fat) supplied about $50 \%$ of the energy; by the third hour, fat contributed up to $70 \%$ of the total energy requirement.

Exercise intensity governs fats contribution to the metabolic mixture. ${ }^{76,80}$ Figure 1.20 illustrates the dynamics of fat use by trained men who exercised between 25 and $85 \%$ of their maximum aerobic metabolism. During light-to-moderate exercise ( $\leq 40 \%$ of maximum), fat provided the main energy source predominantly as plasma FFAs from adipose tissue depots. Increased exercise intensity produced an eventual crossover in the balance of fuel usetotal energy from all sources of fat breakdown remained essentially unchanged. More intense exercise required added energy from blood


Figure 1.20 Steady-state substrate use calculated using three isotopes and indirect calorimetry in trained men performing cycle ergometer exercise at 25,65 , and $85 \%$ of $\mathrm{VO}_{2 \text { max }}$. As exercise intensity increases, absolute use of glucose and muscle glycogen increases, whereas muscle triacylglycerol and plasma FFA use decreases. (From Romijn JA, et al. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am J Physiol 1993;265:E380.)
glucose and muscle glycogen. Total energy from fats during exercise at $85 \%$ of maximum did not differ from exercise at $25 \%$. Such data highlight the major role that carbohydrate, primarily muscle glycogen, plays as a preferential fuel for high-intensity aerobic exercise.

## Exercise Training and Fat Use

Regular aerobic exercise profoundly improves long-chain fatty acid oxidation, particularly from triacylglycerols within active muscle, during mild-to-moderate intensity exercise. ${ }^{8,32,38,79}$ Figure 1.21 illustrates the percentage contribution of various energy substrates during 2 hours of moderateintensity exercise in the trained and untrained state. For a total exercise energy expenditure of about 1000 kCal , intramuscular triacylglycerol combustion supplied $25 \%$ of total energy expenditure before training; this increased to more than $40 \%$ following training. Energy from plasma FFA oxidation decreased from $18 \%$ pretraining to about $15 \%$ posttraining. Biopsy samples revealed a $41 \%$ reduction in muscle glycogen combustion in the trained state. This accounted for the overall decrease in total energy from all carbohydrate fuel sources


Figure 1.21 Percentage of total energy derived from carbohydrate (CHO), intramuscular triacylglycerol (IMTG), and plasma fatty acid (FA) fuel sources during prolonged exercise ( $8.3 \mathrm{kCal} \mathrm{min}^{-1}$ ) before and after endurance training. (From Martin WH III, et al. Effect of endurance training on plasma free fatty acid turnover and oxidation during exercise. Am J Physiol 1993;265:E708.)
( $58 \%$ pretraining to $38 \%$ posttraining). The important point concerns the greater uptake of FFAs and concurrent conservation of glycogen reserves by the trained than by untrained limbs at the same moderate absolute exercise level. Seven factors can produce training-induced increases in fat catabolism in exercise:

1. Facilitated fatty acid mobilization from adipose tissue through increased rate of lipolysis within adipocytes
2. Proliferation of capillaries in trained muscle that increases the total number and density of these microvessels for energy substrate delivery
3. Improved transport of FFAs through the muscle fibers plasma membrane
4. Increased fatty acid transport within the muscle cell, mediated by carnitine and carnitine acyltransferase
5. Increased size and number of mitochondria
6. Increased quantity of enzymes involved in $\beta$-oxidation, citric acid cycle metabolism, and the electrontransport chain within specifically trained muscle fibers
7. Maintenance of cellular integrity and function, which enhances endurance performance independent of conservation of glycogen reserves

Endurance athletes can exercise at a higher absolute submaximal exercise level from an improved capacity for fat oxidation before experiencing the fatiguing effects of
glycogen depletion. However, this adaptation does not sustain the level of aerobic metabolism generated when oxidizing glycogen for energy. Consequently, near-maximal sustained aerobic effort in well-nourished endurance athletes still requires almost total reliance on oxidation of stored glycogen for optimal performance. ${ }^{5}$

## INTEGRATIVE QUESTION

Explain why a high level of daily physical activity requires regular carbohydrate intake. What two nonexercise benefits occur from consuming a diet rich in unrefined, complex carbohydrates?

## Summary

1. Lipids contain carbon, hydrogen, and oxygen atoms, but with a higher ratio of hydrogen to oxygen. The lipid stearin has the formula $\mathrm{C}_{57} \mathrm{H}_{110} \mathrm{O}_{6}$. Lipid molecules consist of 1 glycerol molecule and 3 fatty acid molecules.
2. Lipids, synthesized by plants and animals, classify into one of three groups: simple lipids (glycerol plus three fatty acids), compound lipids (phospholipids, glycolipids, and lipoproteins) composed of simple lipids combined with other chemicals, and derived lipids such as cholesterol, synthesized from simple and compound lipids.
3. Saturated fatty acids contain as many hydrogen atoms as chemically possible; saturated describes this molecule with respect to hydrogen. Saturated fatty acids exist primarily in animal meat, egg yolk, dairy fats, and cheese. A large saturated fatty acid intake elevates blood cholesterol concentration and promotes coronary heart disease.
4. Unsaturated fatty acids contain fewer hydrogen atoms attached to the carbon chain. Unlike saturated fatty acids, double bonds connect carbon atoms; these fatty acids are either monounsaturated or polyunsaturated with respect to hydrogen. Increasing the diets proportion of unsaturated fatty acids protects against coronary heart disease.
5. Lowering blood cholesterol (especially that carried by LDL cholesterol) provides significant heart disease protection.
6. Dietary lipid currently provides about $36 \%$ of total energy intake. Prudent recommendations suggest a level of $30 \%$ or less for dietary lipid, of which 70 to $80 \%$ should consist of unsaturated fatty acids.
7. Lipids provide the largest nutrient store of potential energy for biologic work. They also protect vital organs, provide insulation from the cold, and transport the four fat-soluble vitamins A, D, E, and K.
8. Fat contributes 50 to $70 \%$ of the energy requirement during light- and moderate-intensity exercise. Stored fat (intramuscular and derived from
adipocytes) plays an increasingly important role during prolonged exercise. Fatty acid molecules (mainly circulating FFAs) provide more than $80 \%$ of the exercise energy requirements.
9. Carbohydrate depletion reduces exercise intensity to a level determined by how well the body mobilizes and oxidizes fatty acids.
10. Aerobic training increases long-chain fatty acid oxidation during mild-to-moderate intensity exercise, primarily fatty acids from triacylglycerols within active muscle.
11. Enhanced fat oxidation with training spares glycogen; this allows trained individuals to exercise at a higher absolute level of submaximal exercise before they experience the fatiguing effects of glycogen depletion.

## Part 3 PROTEINS

## THE NATURE OF PROTEINS

Combinations of linked amino acids form proteins (from the Greek word meaning of prime importance). An averagesized adult contains between 10 and 12 kg of protein, with skeletal muscle containing the largest quantity of 6 to 8 kg or 60 to $75 \%$ of all proteins. Additionally, approximately 210 g of amino acids exist in free form, largely as glutamine, a key amino acid that serves as fuel for immune system cells. Humans typically ingest about 10 to $15 \%$ of their total calories as protein. During digestion, protein hydrolyzes to its amino acid constituents for absorption by the small intestine. The protein content of most adults remains remarkably stable and little amino acid feserves exist in the body. Amino acids not used to synthesize protein or other compounds (e.g., hormones) or not available for energy metabolism provide substrate for gluconeogenesis or convert to triacylglycerol for storage in adipocytes.

Structurally, proteins resemble carbohydrates and lipids because they contain atoms of carbon, oxygen, and hydrogen. Protein molecules also contain about $16 \%$ nitrogen, along with sulfur and occasionally phosphorus, cobalt, and iron. Just as glycogen forms from many simple glucose subunits linked together, the protein molecule polymerizes from its amino acid building-block constituents in numerous complex arrays. Peptide bonds link amino acids in chains that take on diverse forms and chemical combinations; two joined amino acids produce a dipeptide, and linking three amino acids produces a tripeptide. A polypeptide chain contains 50 to more than 1000 amino acids. A combination of more than 50 amino acids forms a protein of which humans can synthesize an array of different kinds. Single cells contain thousands of different protein molecules; some have a linear configuration, some are folded into complex shapes having 3-dimensional properties. In total, approximately 50,000 different protein-containing compounds exist in the body. The


Figure 1.22 Four common features of amino acids.
biochemical functions and properties of each protein depend on the sequence of specific amino acids (this aspect is discussed more fully in the final chapter, On the Horizon).

The 20 different amino acids required by the body each have a positively charged amine group at one end and a negatively charged organic acid group at the other end. The amine group has two hydrogen atoms attached to nitrogen $\left(\mathrm{NH}_{2}\right)$, whereas the organic acid group (technically termed a carboxylic acid group) contains 1 carbon atom, 2 oxygen atoms, and 1 hydrogen atom $(\mathrm{COOH})$. The remainder of the amino acid, referred to as the $\mathbf{R}$ group, or side chain, takes on a variety of forms. The $R$ groups specific structure dictates the amino acids particular characteristics. Figure 1.22 shows the four common features that constitute the general structure of all amino acids. The potential for combining the 20 amino acids produces an almost infinite number of possible proteins, depending on their amino acid combinations. For example, linking just three different amino acids could generate $20^{3}$, or 8000, different proteins.

## KINDS OF PROTEIN

The body cannot synthesize eight amino acids (nine in children and some older adults), so individuals must consume foods that contain them. These make up the essential (or indispensable) amino acidsisoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. In addition, the body synthesizes cystine from methionine and tyrosine from phenylalanine. Infants cannot synthesize histidine, and children have reduced capability for synthesizing
arginine. The body manufactures the remaining nine nonessential amino acids. The term nonessential does not indicate a lack of importance; rather, they are synthesized from other compounds already in the body at a rate that meets demands for normal growth and tissue repair.

Animals and plants manufacture proteins that contain essential amino acids. An amino acid derived from an animal has no health or physiologic advantage over the same amino acid from vegetable origin. Plants synthesize amino acids by incorporating nitrogen from the soil (along with carbon, oxygen, and hydrogen from air and water). In contrast, animals have no broad capability for amino acid synthesis; instead, they consume most of their protein.

Synthesizing a specific protein requires the availability of appropriate amino acids. Complete proteins (sometimes referred to as higher-quality proteins) come from foods that contain all of the essential amino acids in the quantity and correct ratio to maintain nitrogen balance and to allow tissue growth and repair. An incomplete protein lacks one or more essential amino acids. A diet of incomplete protein eventually leads to protein malnutrition, whether or not the food sources contain an adequate amount of energy or protein.

## Protein Sources

Sources of complete protein include eggs, milk, meat, fish, and poultry. Eggs provide the optimal mixture of essential amino acids among all food sources; hence, eggs receive the highest quality rating of 100 for comparison with other foods. Table 1.3 rates some common sources of protein in the diet. Reliance on animal sources for dietary protein accounts for the relatively high cholesterol and saturated fatty acid intake in the major industrialized nations.

High-quality protein foods come from animal sources. Vegetables (lentils, dried beans and peas, nuts, and cereals) remain incomplete in one or more essential amino acids; thus, their proteins have a lower biologic value. Eating a variety of

| TABLE 1.3 | Common Sources of Dietary <br> Protein Rated for Protein <br> Quality |
| :--- | :---: |
| Food | Protein Rating |
| Eggs | 100 |
| Fish | 70 |
| Lean beef | 69 |
| Cows milk | 60 |
| Brown rice | 57 |
| White rice | 56 |
| Soybeans | 57 |
| Brewers hash | 45 |
| Whole-grain wheat | 44 |
| Peanuts | 43 |
| Dry beans | 34 |
| White potato | 34 |

grains, fruits, and vegetables supplies all of the essential amino acids.

## The Vegetarian Approach

True vegetarians, or vegans, consume nutrients from only two sourcesthe plant kingdom and dietary supplements. Vegans constitute less than $1 \%$ of the U.S. population, yet between 5 and $7 \%$ of Americans consider themselves ýlmost vegetarians. Nutritional diversity remains the key for these individuals. For example, a vegan diet contains all the essential amino acids if the recommended intake for protein (see next section) contains $60 \%$ of protein from grain products, $35 \%$ from legumes, and 5\% from green leafy vegetables.

An increasing number of competitive and champion athletes consume diets consisting predominately of nutrients from varied plant sources, including some dairy and meat products. ${ }^{59}$ Vegetarian athletes often encounter difficulty in planning, selecting, and preparing nutritious meals with a proper amino acid mixture from only plant sources, without relying on supplementation. In contrast to diets that rely heavily on animal sources for protein, well-balanced vegetarian and vegetarian-type diets provide abundant carbohydrate so crucial in intense, prolonged training. Such diets contain little or no cholesterol but abundant fiber, and rich fruit and vegetable sources of diverse phytochemicals and antioxidant vitamins. A lactovegetarian diet provides milk and related products such as ice cream, cheese, and yogurt. The lactovegetarian approach minimizes the difficulty of consuming sufficient high-quality protein and increases the intake of calcium, phosphorus, and vitamin $\mathrm{B}_{12}$ (produced by bacteria in the digestive tract of animals). Adding an egg to the diet (ovolactovegetarian diet) ensures high-quality protein intake. Figure 1.23 displays the contribution of various food groups to the protein content of the American diet.


[^15]Figure 1.23 Contribution from the major food sources to the protein content of the typical American diet.

## RECOMMENDED PROTEIN INTAKE

Despite the beliefs of many coaches, trainers, and athletes, little benefit accrues from consuming excessive protein. Muscle mass does not increase simply by eating high-protein foods. The diets of endurance- and resistance-trained athletes often exceed two to three times the recommended intake, usually as meat. This occurs primarily for two reasons:

1. Athletes diets normally emphasize high-protein foods.
2. Caloric intake and energy output of athletes surpass those of sedentary counterparts.

If lean tissue synthesis resulted from all of the extra protein consumed by the typical athlete, then muscle mass would increase tremendously. For example, consuming an extra 100 g of protein $(400 \mathrm{kCal})$ daily would translate to a daily $500-\mathrm{g}$ (1.1-lb) increase in muscle mass. This obviously does not happen. Excessive dietary protein catabolizes directly for energy (following deamination) or recycles as components of other molecules including fat stored in subcutaneous depots. Excessive dietary protein intake can trigger harmful side effects, particularly strained liver and kidney function from elimination of urea and other compounds.

## The RDA: A Liberal Standard

The Recommended Dietary Allowance (RDA) for protein, vitamins, and minerals represents a standard for nutrient intake expressed as a daily average. These guidelines, initially developed in 1943 by the Food and Nutrition Board of the National Research Council/National Academy of Science (www.iom. edu/CMS/3708.aspx), have been revised 11 times. RDA levels represent a liberal yet safe excess to prevent nutritional deficiencies in practically all healthy persons. In the 11th edition (1999), RDA recommendations included 19 nutrients, energy intake, and the Estimated Safe and Adequate Daily Dietary Intakes (ESADDIs) for seven additional vitamins and minerals and three electrolytes. ${ }^{22}$ The ESADDI recommendation for certain essential micronutrients (e.g., vitamins biotin and pantothenic acid and trace elements copper, manganese, fluoride,
selenium, chromium, and molybdenum) required sufficient scientific data to formulate a range of intakes considered adequate and safe, yet insufficient for a precise RDA value. No RDA or ESADDI exists for sodium, potassium, and chlorine; instead, recommendations refer to a minimum requirement for health.

We emphasize that the RDA reflects nutritional needs of a population over a long time period; only laboratory measurements can assess a specific individuals requirement. Malnutrition occurs from cumulative weeks, months, and even years of inadequate nutrient intake. Someone who regularly consumes a diet that contains nutrients below the RDA standards may not become malnourished. The RDA represents a probability statement for adequate nutrition; as nutrient intake falls below the RDA, the statistical probability for malnourishment increases for that person and the probability progressively increases with lower nutrient intake. In Chapter 2, we discuss the Dietary Reference Intakes that represent the current set of standards for recommended intakes of nutrients and other food components. ${ }^{21,75}$

Table 1.4 lists the protein RDAs for adolescent and adult males and females. On average, 0.83 g of protein per kg body mass represents the recommended daily intake. To determine the protein requirement for men and women ages 18 to 65 , multiply body mass in kg by 0.83 . For a $90-\mathrm{kg}$ man, total protein requirement equals $75 \mathrm{~g}(90 \times 0.83)$. The protein RDA holds even for overweight persons; it includes a reserve of about $25 \%$ to account for individual differences in the protein requirement for about $97 \%$ of the population. Generally, the protein RDA (and the quantity of the required essential amino acids) decreases with age. In contrast, the protein RDA for infants and growing children equals 2.0 to 4.0 g per kg body mass. Pregnant women should increase total daily protein intake by 20 g , and nursing mothers should increase their intake by 10 g . A $10 \%$ increase in the calculated protein requirement, particularly for a vegetarian-type diet, accounts for dietary fibers effect in reducing the digestibility of many plant-based protein sources. Stress, disease, and injury usually increase protein requirements.

| Protein Recommended Dietary Allowance (RDA) for Adolescent and Adult Men and Women |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Recommended Amount | Men |  | Women |  |
| Grams of protein per kg body mass | Adolescent 0.9 | $\begin{gathered} \text { Adult } \\ 0.8 \end{gathered}$ | $\begin{gathered} \text { Adolescent } \\ 0.9 \end{gathered}$ | $\begin{gathered} \text { Adult } \\ 0.8 \end{gathered}$ |
| Grams of protein per day based on average body mass ${ }^{a}$ | 59.0 | 56.0 | 50.0 | 44.0 |
| ${ }^{a}$ Average body mass based on a feference man and woman. For adolescents (ages 1418 ), body mass averages $65.8 \mathrm{~kg}(145 \mathrm{lb})$ for males and $55.7 \mathrm{~kg}(123 \mathrm{lb})$ for females. For adult men, average mass equals $70 \mathrm{~kg}(154 \mathrm{lb})$; for adult women, mass averages $56.8 \mathrm{~kg}(125 \mathrm{lb})$. |  |  |  |  |

## IN A PRACTICAL SENSE

## How to Read Food Labels

In 1990, the United States Congress passed the Nutrition Labeling and Education Act, which brought sweeping changes to regulations for food labeling. The act (including 19931998 updates) aimed to help consumers choose more healthful diets and offered an incentive to food companies to improve the nutritional qualities of their products. All foods except those containing only a few nutrients, such as plain coffee, tea, and spices, now provide consistent nutrition information. Leading health and nutrition authorities have
petitioned the FDA (www.FDA.gov) to list the grams of added sugars in a serving of the food and to indicate how this amount compares with intakes recommended by other organizations (food labels now only list total sugars-sugars naturally in food plus those added by processing). Currently, the food label must display the following information prominently and in words an average person can understand (the numbers in this figure on p. 35 relate to the numbered information below):


From the Nutrition Labeling Act of 1990. Federal Register 58(3), 1993. U.S. Government Printing Office, Superintendent of Documents, Washington, DC, and updated November, 2004 (www.cfsan.fda.gov/~dms/foodlab.html). (This site provides a complete description of the new Nutrition Facts label and relevant terms and materials related to the label, including Daily Values [DV].)

## IN A PRACTICAL SENSE

1. Product s common or usual name
2. Name and address of manufacturer, packer, or distributor
3. Net contents for weight, measure, or count
4. All ingredients, listed in descending order of predominance by weight
5. Serving size, number of servings per container, and calorie information
6. Quantities of specified nutrients and food constituents, including total food energy in calories, total fat ( g ), saturated fat ( g ), trans fat ( g ), cholesterol ( mg ), sodium ( mg ), and total carbohydrate including starch, sugar, fiber ( g ), and protein ( g )
7. Descriptive terms of content
8. Approved health claims stated in terms of the total diet

The figure displays the current food label generated as an outgrowth of regulations from the FDA, the United States Department of Agriculture, and the Nutrition Labeling and Education Act of 1990.

## TERMS ON FOOD LABELS

## Common Terms and What They Mean

Free: Nutritionally trivial and unlikely to have physiologic consequences; synonyms include without, no, and zero

High: 20\% or more of the Daily Value (DV) for a given nutrient per serving; synonyms include rich in or excellent in

Less: At least $25 \%$ less of a given nutrient or calories than the comparison food

Low: An amount that allows frequent consumption of the food without exceeding the nutrient s DV

Good source: Product provides between 10 and $19 \%$ of a given nutrient s DV per serving

## Cholesterol Terms

Cholesterol-free: Less than 2 mg per serving and 2 g or less saturated fat per serving

Continued

> Low cholesterol: 20 mg or less of cholesterol per serving and 2 g or less of saturated fat per serving
> Less cholesterol: $25 \%$ or less cholesterol per serving and 2 g or less saturated fat per serving

## Fat Terms

Extra lean: Less than 5 g of fat, 2 g of saturated fat, and 95 mg of cholesterol per serving and per 100 g of meat, poultry, and seafood Fat-free: Less than 0.5 g of fat per serving (no added fat or oil) Lean: Less than 10 g of fat, 4.5 g of saturated fat, and 95 mg of cholesterol per serving and per 100 g of meat, poultry, and seafood Less fat: $25 \%$ or less fat than the comparison food
Low-fat: 3 g or less of fat per serving
Light: 50\% or less fat than comparison food (e.g., 50\% less fat than our regular cookies )

Less saturated fat: $25 \%$ or less saturated fat than the comparison food

## Energy Terms

Calorie-free: Fewer than 5 calories per serving
Light: One-third fewer calories than the comparison food
Low-calorie: 40 calories or fewer per serving
Reduced calorie: At least 25\% fewer calories per serving than the comparison food

## Fiber Terms

High-fiber: 5 g or more of fiber per serving

## Sodium Terms

Sodium-free and salt-free: Less than 5 mg of sodium per serving Low sodium: 140 mg or less of sodium per serving Light: Low-calorie food with $50 \%$ sodium reduction Light in sodium: No more than $50 \%$ of the sodium of the comparison food

Very low sodium: 35 mg or less of sodium per serving.

Do Athletes Require a Larger Protein Intake? Debate has focused on the need for a larger protein requirement for athletes that include still-growing adolescent athletes, athletes involved in resistance-training programs that stimulate muscle growth and endurance-training programs that increase protein breakdown, and athletes subjected to recurring tissue microtrauma like wrestlers and football players. ${ }^{1,35,73}$ We present additional information about protein balance in exercise and training in subsequent sections of this chapter and in the Focus on Research section, page 36.

## ROLE OF PROTEIN IN THE BODY

Blood plasma, visceral tissue, and muscle represent the three major sources of body protein. No feservoirs of this macronutrient exist; all protein contributes to tissue structures or exists as important constituents of metabolic, transport, and hormonal systems. Protein makes up between 12 and $15 \%$ of the body mass, but the protein content of different cells varies considerably. A brain cell, for example, consists of about $10 \%$
protein, while red blood cells and muscle cells include up to $20 \%$ of their total weight as protein. The protein content of skeletal muscle can increase to varying degrees with the systematic application of resistance training.

Amino acids provide the major building blocks for synthesizing tissue. They also incorporate nitrogen into (1) coenzyme electron carriers nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) (see Chapter 5), (2) heme components of hemoglobin and myoglobin compounds, (3) catecholamine hormones epinephrine and norepinephrine, and (4) the serotonin neurotransmitter. Amino acids activate vitamins that play a key role in metabolic and physiologic regulation. Tissue anabolism accounts for about onethird of the protein intake during rapid growth in infancy and childhood. As growth rate declines, so does the percentage of protein retained for anabolic processes.

Proteins serve as primary constituents for plasma membranes and internal cellular material. As the final chapter, On the Horizon, discusses in some detail, the cell nucleus contains the genetically coded nucleic acid material deoxyribonucleic

## FOCUS ON RESEARCH

## Protein and Exercise: How Much Is Enough?


#### Abstract

Tarnopolsky MA, et al. Influence of protein intake and training status on nitrogen balance and lean body mass. J Appl Physiol 1988;64:187.


- The question of how much dietary protein a physically active person requires to support training and optimize improvements continues to intrigue nutritionists and exercise physiologists. In the mid-1800s, initial studies of human protein needs postulated that muscular contraction destroyed a portion of the muscles protein content to provide energy for biologic work. Based on this belief, overzealous entrepreneurs and physical culturists (the early predecessors of health club fitness trainers) recommended highprotein diets to those doing intense physical labor and exercise training.

In some ways, many modern-day athletes who devote considerable time and effort to training with resistance equipment mimic the older beliefs and practices. They too believe that a significant excess of dietary protein is the most important macronutrient to build bigger muscles and increase strength. They believe resistance training in some way damages or tears down a muscles inherent structure. This drain on body protein would require additional dietary protein (above the 0.83 g of protein per kg body mass supplied by the RDA) for tissue resynthesis to a new, larger, and more powerful state. Many endurance athletes believe arduous training increases protein catabolism (and consequently its dietary requirement) to sustain the energy requirements of exercise. To some extent, both lines of reasoning have merit. The relevant question, however, concerns whether the protein RDA provides sufficient reserve should 4 to 6 hours of daily heavy training add demands for protein synthesis and/or catabolism. While the debate continues and sales of protein supplements soar, researchers have attempted to quantify any added protein requirements of intense exercise training.

In one of the earlier attempts to study this problem systematically, Tarnopolsky and colleagues determined the effects of aerobic and resistance training on nitrogen balance in subjects fed a high-protein (HP) or relatively lowerprotein (LP) diet. Subjects were placed into three groups of six men each: sedentary controls ( S ), elite endurance athletes (EA), and competitive body builders (BB). Ten-day measurements during training included nitrogen balance evaluation ( N -Bal; daily dietary nitrogen intake vs. nitrogen excretion) under HP and LP diets. Quantification of total nitrogen excretion required three sequential 24 -hour urine collections, 72-hour fecal collections, and representative samplings of resting and exercise sweat secretion.

The figure shows N -Bal ( g of N per day) related to protein intake for each group that received HP and LP diets. The white horizontal line at the zero point on the $y$ axis represents the condition when nitrogen intake equals the bodys nitrogen requirement. The three lines that intersect the zero point of nitrogen balance theoretically represent a sufficient protein intake: $0.73 \mathrm{~g} \cdot \mathrm{~kg}^{-1} \bullet \mathrm{~d}^{-1}$ for the S group, $0.82 \mathrm{~g} \bullet \mathrm{~kg}^{-1} \bullet \mathrm{~d}^{-1}$ for the BB group, and $1.37 \mathrm{~g} \bullet$ $\mathrm{kg}^{-1} \cdot \mathrm{~d}^{-1}$ for the EA group. These findings showed that endurance exercise training increased net protein catabolism and protein requirement not evident for the BB group. The researchers recommended that body builders could reduce their abnormally high protein intakes, whereas endurance athletes could possibly benefit from increased protein intake above the RDA level.


Positive and negative nitrogen balance plotted in relation to daily protein intake of sedentary men ( $S$ ) and groups of elite athletes undergoing either endurance training ( $E A$ ) or resistance training (BB). Subjects consumed either a high-protein (HP) diet or a relatively lower-protein (LP) diet during the 10-day training period. The white horizontal line at zero nitrogen balance represents the point at which nitrogen intake equals excretion (i.e., nitrogen balance). The point at which each of the three lines crosses the zero line indicates the necessary daily protein intake for the group.
acid (DNA). DNA replicates itself before the cell divides to ensure that each new cell contains identical genetic material. It also provides the instructions or thaster plan for the cellular manufacture of all the bodys proteins via its control over cytoplasmic ribonucleic acid (RNA). Collagenous structural proteins compose the hair, skin, nails, bones, tendons, and ligaments. Globular proteins make up the nearly 2000 different enzymes that speed up chemical reactions and regulate the catabolism of nutrients for energy release. Blood plasma also contains the specialized proteins thrombin, fibrin, and fibrinogen required for blood clotting. Within red blood cells, the oxygen-carrying compound hemoglobin contains the large globin protein molecule. Proteins help to regulate the acid base characteristics of bodily fluids. Buffering neutralizes excess acid metabolites formed during vigorous exercise. The structural proteins actin and myosin play the predominant role in muscle action as they slide past each other as muscle fibers shorten and lengthen during movement.

## DYNAMICS OF PROTEIN METABOLISM

Dietary proteins main contribution supplies amino acids to numerous anabolic processes. In addition, some protein is catabolized for energy. In well-nourished individuals at rest, protein catabolism contributes between 2 and $5 \%$ of the bodys total energy requirement. During catabolism, protein first degrades into its component amino acids. The amino acid molecule then loses its nitrogen (amine group) in the liver (deamination) to form urea $\left(\mathrm{H}_{2} \mathrm{NCONH}_{2}\right)$. The remaining deaminated amino acid then either converts to a new amino acid, converts to carbohydrate or fat, or catabolizes directly for energy. Urea formed in deamination (including some ammonia) leaves the body in solution as urine. Excessive protein catabolism promotes fluid loss because urea must dissolve in water for excretion.

Enzymes in muscle facilitate nitrogen removal from certain amino acids (usually $\alpha$-keto acid or glutamate; Figure 1.24), with nitrogen passed to other compounds in the reversible reactions of transamination. Transamination
occurs when an amine group from a donor amino acid transfers to an acceptor acid to form a new amino acid. A specific transferase enzyme accelerates the transamination reaction, In muscle, transamination incorporates branched-chain amino acids (BCAAs) that generate branched-chain ketoacids (mediated by BCAA transferase). This allows amino acid formation from the nonnitrogen-carrying organic compound pyruvate formed in metabolism. In both deamination and transamination, the resulting carbon skeleton of the nonnitrogenous amino acid residue undergoes further degradation during energy metabolism.

## Fate of Amino Acids After Nitrogen Removal

After deamination, the remaining carbon skeletons of $\alpha$-keto acids such as pyruvate, oxaloacetate, or $\alpha$-ketoglutarate follow one of three diverse biochemical routes:

1. Gluconeogenesis 48 of the 20 amino acids serve as a source for glucose synthesis.
2. Energy source The carbon skeletons oxidize for energy because they form intermediates in citric acid cycle metabolism or related molecules.
3. Fat synthesisAll amino acids provide a potential source of acetyl-CoA and thus furnish substrate to synthesize fatty acids.

Figure 1.25 shows the commonality of the carbon sources from amino acids and the major metabolic paths taken by their deaminated carbon skeletons.

## NITROGEN BALANCE

Nitrogen balance occurs when nitrogen intake (protein) equals nitrogen excretion as follows:

$$
\text { Nitrogen balance }=N_{t}-N_{u}-N_{f}-N_{s}=0
$$

where $N_{t}=$ total nitrogen intake from food; $N_{u}=$ nitrogen in urine; $N_{f}=$ nitrogen in feces; and $N_{s}=$ nitrogen in sweat.


Figure 1.24 Transamination provides for the intramuscular synthesis of amino acids from nonprotein sources. Enzyme action facilitates removal of an amine group from a donor amino acid for transfer to an acceptor, nonnitrogencontaining acid to form a new amino acid.


Figure 1.25 Major metabolic pathways for amino acids following removal of the nitrogen group by deamination or transamination. Upon removal of their amine group, all amino acids form reactive citric acid cycle intermediates or related compounds. Some of the larger amino acid molecules (e.g., leucine, tryptophan, and isoleucine-colored gold, green, and red, respectively) generate carbon-containing compounds that enter metabolic pathways at different sites.

In positive nitrogen balance, nitrogen intake exceeds nitrogen excretion to synthesize new tissues from the additional protein. With proper nutrition, positive nitrogen balance often occurs in (1) growing children, (2) during pregnancy, (3) in recovery from illness, and (4) during resistance-exercise training when muscle cells promote protein synthesis. The body does not develop a protein reserve as it does with fat storage in adipose tissue and storage of carbohydrate as muscle and liver glycogen. Nevertheless, individuals who consume the recommended protein intake have a higher content of muscle and liver protein than individuals fed too little protein. Also, muscle protein can be recruited for energy metabolism. In contrast, proteins in neural and connective tissues remain relatively fixed as cellular constituents and cannot be mobilized for energy without disrupting tissue functions.

Greater nitrogen output than intake, or negative nitrogen balance, indicates protein use for energy and possible encroachment on amino acids primarily from skeletal muscle. Interestingly, a negative nitrogen balance can occur even when protein intake exceeds the recommended standard if the body catabolizes protein from a lack of other energy nutrients. For example, an individual who participates regularly in intense exercise training may consume adequate or excess protein but inadequate energy from carbohydrate or lipid. In this
scenario, protein becomes a primary energy fuel, which creates a negative protein (nitrogen) balance and a loss of lean tissue mass. The protein-sparing role of dietary carbohydrate and lipid previously discussed becomes important during tissue growth periods and the high-energy output and/or tissue synthesis requirements of intense training. A negative nitrogen balance can occur during diabetes, fever, burns, dieting, growth, steroid administration, and recovery from many illnesses. The greatest negative nitrogen balance takes place during starvation.

Although protein breakdown increases only modestly with most modes and intensities of exercise, muscle protein synthesis rises substantially following endurance- and resistance-type exercise. ${ }^{11,63}$ Figure 1.26 shows that muscle protein synthesis (determined from labeled leucine incorporation into muscle) increased between 10 and $80 \%$ within 4 hours following termination of aerobic exercise. It then remained elevated for at least 24 hours. Two factors justify reexamining protein intake recommendations for those involved in intense training:

1. Increased protein breakdown during long-term exercise and protracted training
2. Increased protein synthesis in recovery from exercise


Figure 1.26 Degradation of protein during exercise and stimulation of protein synthesis in recovery from aerobic exercise. Values refer to differences between the exercise group and the control group that received the same diet for each time interval. (From Carraro F, et al. Whole body and plasma protein synthesis in exercise and recovery in human subjects. Am J Physiol 1990;258:E821.)

INTEGRATIVE QUESTION
Discuss whether consuming extra protein above the RDA facilitates muscle enlargement if muscle growth with resistance training occurs primarily from deposition of additional protein within the cell.

## PROTEIN DYNAMICS IN EXERCISE AND TRAINING

Current understanding of protein dynamics in exercise comes from studies that expanded the classic method of determining protein breakdown through urea excretion. For example, release of labeled $\mathrm{CO}_{2}$ from amino acids injected or ingested increases during exercise in proportion to the metabolic rate. ${ }^{82}$ As exercise progresses, the concentration of plasma urea also increases, coupled with a dramatic rise in nitrogen excretion in sweat (often without any change in urinary nitrogen excretion). ${ }^{33,65}$ These observations account for prior conclusions concerning minimal protein breakdown during endurance exercise because the early studies only measured nitrogen in urine. The sweat mechanism serves an important role in excreting nitrogen from protein breakdown during exercise (Fig. 1.27). Nonetheless, urea production may not reflect all aspects of protein breakdown because the oxidation of plasma and intracellular leucine (an essential BCAA) increases during moderate exercise independent of changes in urea production. ${ }^{9,81}$

Figure 1.27 also illustrates that protein use for energy reaches its highest level during exercise in the glycogendepleted state. This emphasizes the important role of carbohydrate as a protein sparer and indicates that carbohydrate availability affects the demand on protein feserves in exercise.


Figure 1.27 Excretion of urea in sweat at rest and during exercise after carbohydrate loading (High CHO) and carbohydrate depletion (Low CHO). The largest use of protein (as reflected by sweat urea) occurs when glycogen reserves are low. (From Lemon PWR, Nagel F. Effects of exercise on protein and amino acid metabolism. Med Sci Sports Exerc 1981;13:141.)

Protein breakdown and gluconeogenesis undoubtedly play a role in endurance exercise (or in frequent training) when glycogen reserves diminish. ${ }^{40}$

Increases in protein catabolism during endurance exercise and intense training often mirror the metabolic mixture in acute starvation. With depleted glycogen reserves, gluconeogenesis from carbon skeletons of amino acids largely sustains the livers glucose output. Augmented protein breakdown reflects the bodys attempt to maintain blood glucose for central nervous system functioning. Athletes in training should consume a high-carbohydrate diet with adequate energy to conserve muscle protein. The increased protein use for energy and depressed protein synthesis during intense exercise may partly explain why individuals who resistance train to build muscle size generally refrain from glycogen-depleting endurance workouts to avoid the potential for muscle teardown.

## Some Modification Required for Recommended Protein Intake

A continuing area of controversy concerns whether the initial increased protein demand when training commences creates a true long-term increase in protein requirement above the RDA. A definitive answer remains elusive, but protein breakdown above the resting level does occur during endurance training and resistance training to a greater degree than previously believed. Increased protein catabolism occurs to a
greater extent when exercising with low carbohydrate reserves and/or low energy or protein intakes. ${ }^{62}$ Unfortunately, research has not pinpointed protein requirements for individuals who train 4 to 6 hours daily by resistance exercise. Their protein needs may average only slightly more than requirements for sedentary individuals (see Focus on Research, p. 36). In addition, despite increased protein use for energy during intense training, adaptations may augment the bodys efficiency in using dietary protein to enhance amino acid balance. Based on the available science, we recommend that athletes who train intensely consume between 1.2 and 1.8 g of protein per kg of body mass daily. Protein intake greater than the 1.8 g value offers no further advantage to athletes with regard to whole-body protein use. ${ }^{28}$ This upper value falls within the range typically consumed by physically active men and women, obviating the need to consume supplementary protein. With adequate protein intake, consuming animal sources of protein does not facilitate muscle strength or size gains with resistance training compared with protein intake from only plant sources. ${ }^{34}$

## INTEGRATIVE QUESTION <br> Outline reasons why exercise physiologists debate the adequacy of the current protein $R D A$ for individuals involved in intense exercise training.

## The Alanine Glucose Cycle

Some tissue proteins do not readily metabolize for energy, yet muscle proteins can provide energy for exercise. ${ }^{12,31}$ For example, alanine indirectly participates in energy metabolism when the exercise energy demand increases; its release from active leg muscle increases proportionately to the severity of exercise. ${ }^{84}$

Active skeletal muscle synthesizes alanine (during transamination) from the glucose intermediate pyruvate (with nitrogen derived in part from the amino acid leucine). The residual carbon fragment from the amino acid that formed alanine oxidizes for energy within skeletal muscle. The newly formed alanine leaves the muscle and enters the liver for deamination. Alanines remaining carbon skeleton converts to glucose via gluconeogenesis and enters the blood for delivery to active muscle. Figure 1.28 summarizes the sequence of the alanine glucose cycle. After 4 hours of continuous light exercise, the livers output of alanine-derived glucose accounts for about $45 \%$ of the livers total glucose release. The alanine glucose cycle generates from 10 to 15\% of the total exercise energy requirement. Regular exercise training enhances the livers synthesis of glucose from the carbon skeletons of noncarbohydrate compounds. ${ }^{72}$ This facilitates blood glucose homeostasis during prolonged exercise.


Figure 1.28 The alanine glucose cycle. Alanine, synthesized in muscle from glucose-derived pyruvate via transamination, enters the blood where the liver converts it to glucose and urea. Glucose release into the blood coincides with its subsequent delivery to the muscle for energy. During exercise, increased production and output of alanine from muscle helps to maintain blood glucose for nervous system and active muscle needs. Exercise training augments hepatic gluconeogenesis.

## Summary

1. Proteins differ chemically from lipids and carbohydrates because they contain nitrogen in addition to sulfur, phosphorus, and iron.
2. Subunit amino acid structures form protein. The body requires 20 different amino acids, each containing an amine group $\left(\mathrm{NH}_{2}\right)$ and an organic acid group (carboxylic acid group; COOH). Amino acids contain a side chain (R group) that determines the amino acids particular chemical characteristics.
3. The number of possible protein structures is enormous because of the tremendous number of combinations of 20 different amino acids.
4. Regular exercise training enhances the livers synthesis of glucose from the carbon skeletons of noncarbohydrate compounds, particularly amino acids.
5. The body cannot synthesize 8 of the required 20 amino acids; these essential amino acids must be consumed in the diet.
6. All animal and plant cells contain protein. Complete (higher-quality) proteins contain all the essential amino acids; incomplete (lower-quality) proteins represent the others. Examples of higherquality, complete proteins include animal proteins in eggs, milk, cheese, meat, fish, and poultry.
7. Physically active people and competitive athletes can usually obtain the required nutrients predominantly from a broad array of plant sources.
8. Proteins provide the building blocks for synthesizing cellular material during anabolic processes. Their amino acids also contribute ๕arbon skeletons for energy metabolism.
9. The Recommended Dietary Allowance (RDA) represents a liberal yet safe level of excess to meet the nutritional needs of practically all healthy persons. For adults, the protein RDA equals 0.83 g per kg of body mass.
10. Depleting carbohydrate reserves increases protein catabolism during exercise. Athletes who regularly train vigorously must maintain optimal levels of muscle and liver glycogen to minimize deterioration in athletic performance and a loss of muscle mass.
11. Protein serves as an energy fuel to a much greater extent than previously believed. This applies particularly to branched-chain amino acids oxidized in skeletal muscle rather than in the liver.
12. Reexamining the current protein RDA seems justified for athletes who engage in intense exercise training. This examination must account for increased protein breakdown during exercise and augmented protein synthesis in recovery. Increasing protein intake to 1.2 to 1.8 g per kg body mass daily seems reasonable.
13. Proteins in neural and connective tissues generally do not participate in energy metabolism. The muscle-derived amino acid alanine plays a key role via gluconeogenesis in supporting carbohydrate availability during prolonged exercise. The alanine glucose cycle accounts for up to $45 \%$ of the livers release of glucose during long-duration exercise.

1, References are available online at

On the Internet
www.glucagon.com
National Heart Lung and Blood Institute, Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) www.nhlbi.nih.gov/guidelines/cholesterol/index.htm
American Heart Association
www.americanheart.org
American Cancer Society www.cancer.org
U.S. Food and Drug Administration www.FDA.gov

## CHAPTER



## Vitamins, Minerals, and Water

## CHAPTER OBJECTIVES

- List one function for each fat- and water-soluble vitamin and potential risks of their consumption in excess
- Discuss how free radicals form in the body, particularly during physical activity, and the mechanisms to defend against oxidative stress
- Explain whether it is prudent to advocate vitamin supplementation above the Recommended Dietary Allowance (RDA) for individuals involved in intense exercise training
- Outline three broad roles of minerals in the body
- Define the terms osteoporosis, exercise-induced anemia, and sodium-induced hypertension
- Describe how regular physical activity affects bone mass and the body s iron stores
> Present a possible explanation for sports anemia
> Outline factors related to the female athlete triad
- Advocate for or against mineral supplementation above the RDA with intense exercise training
> List water $s$ diverse functions in the body
- Quantify the volumes of the body s three water compartments
- List five predisposing factors to hyponatremia with prolonged exercise

The effective regulation of all metabolic processes requires a delicate blending of food nutrients in the watery medium of the cell. The micronutrients-the small quantities of vitamins and minerals—play highly specific roles in facilitating energy transfer and tissue synthesis. The physically active person or competitive athlete need not consume vitamin and mineral supplements provided they obtain proper nutrition from a variety of food sources. Such practices, touted by advertising on radio, TV, and the print media, usually prove physiologically and economically wasteful. Consuming some micronutrients in excess can pose a considerable risk to health and safety.

## Part 1 VITAMINS

## THE NATURE OF VITAMINS

The formal discovery of vitamins revealed they were organic substances required by the body in minute amounts. Vitamins have no particular chemical structure in common and are considered accessory nutrients because they neither supply energy nor contribute substantially to the body s mass. With the exception of vitamin D, the body cannot manufacture vitamins; instead they must be supplied in the diet or through supplementation.

## KINDS OF VITAMINS

Thirteen different vitamins have been isolated, analyzed, classified, synthesized, and assigned RDAs. Vitamins classify as fat soluble-vitamins $A, D, E$, and $K$-or water solublevitamin $C$ and the $B$-complex vitamins: thiamine $\left(B_{1}\right)$, riboflavin $\left(B_{2}\right)$, vitamin $B_{6}$ (pyridoxine), niacin (nicotinic acid), pantothenic acid, biotin, folic acid (folacin or folate, its active form in the body), and cobalamin ( $\mathrm{B}_{12}$ ).

## Fat-Soluble Vitamins

Fat-soluble vitamins dissolve and remain in the body s fatty tissues, obviating the need to ingest them daily. It may take years before unhealthy symptoms emerge that denote a fatsoluble vitamin deficiency. The liver stores vitamins A and D, whereas vitamin E distributes throughout the body s fatty tissues. Vitamin K stores only in small amounts, mainly in the liver. Dietary lipids are the source of fat-soluble vitamins; these vitamins, transported as part of lipoproteins in the lymph, travel to the liver for dispersion to various tissues. Consuming a true fat-free diet would certainly accelerate a fat-soluble vitamin insufficiency.

Fat-soluble vitamins should not be consumed in excess without medical supervision. Toxic reactions to excessive fatsoluble vitamin intake occur at a lower multiple of the RDA compared to water-soluble vitamins. High doses of vitamin A consumed early in pregnancy increase the risk of birth defects in utero. In young children, excessive vitamin A accumulation (called hypervitaminosis A) can cause bulging fontanelle and symptoms resembling those of a brain tumor, papilledema
(swelling of the optic disc), and double vision. Vomiting and drowsiness also are common. In adults, symptoms can include nausea, headache, drowsiness, blurry vision, hair loss, diarrhea, and calcium loss from bones. Regular but excessive vitamin D consumption can cause kidney damage. An overdose from vitamins E and K is rare, and intakes above the recommended level yield no known health benefits.

## Water-Soluble Vitamins

Water-soluble vitamins act largely as coenzymes-small molecules combined with a larger protein compound (apoenzyme) to form an active enzyme that accelerates the interconversion of chemical compounds (see Chapter 5). Coenzymes participate directly in chemical reactions; after the reaction runs its course, coenzymes remain intact and participate in additional reactions. Water-soluble vitamins, similar to their fatsoluble counterparts, consist of carbon, hydrogen, and oxygen atoms. They also contain nitrogen and metal ions including iron, molybdenum, copper, sulfur, and cobalt.

Water-soluble vitamins disperse in bodily fluids without storage in tissues to any appreciable extent. Generally, an excess intake of water-soluble vitamins voids in the urine. Water-soluble vitamins exert their influence for 8 to 14 hours after ingestion; thereafter, their potency decreases. The body is remarkably tolerant when it comes to maintaining a storehouse of the water-soluble vitamins. For example, the halflife (time required to convert one-half of a reactant to a product) of vitamin C is approximately 30 minutes, whereas thiamine s half-life is 9 to 18 days. Figure 2.1 illustrates various food sources for vitamin C and its diverse biologic and biochemical functions. These include serving as an electron donor for eight enzymes and as a chemical reducing agent (antioxidant) in intracellular and extracellular reactions.

## ROLE OF VITAMINS

Figure 2.2 summarizes the major biologic functions of vitamins. Vitamins contain no useful energy for the body; instead they serve as essential links and regulators in metabolic reactions that release energy from food. Vitamins also control tissue synthesis and protect the integrity of the cells plasma membrane. The water-soluble vitamins play important roles in energy metabolism. For example:

Vitamin $B_{1}$ facilitates the conversion of pyruvate to acetyl-coenzyme $\mathrm{A}(\mathrm{CoA})$ in carbohydrate breakdown Niacin and vitamin $B_{2}$ regulate mitochondrial energy metabolism
Vitamins $\mathrm{B}_{6}$ and $\mathrm{B}_{12}$ catalyze protein synthesis Pantothenic acid, part of CoA, participates in the aerobic breakdown of the carbohydrate, fat, and protein macronutrients
Vitamin C acts as a cofactor in enzymatic reactions, as a scavenger of free radicals in antioxidative processes, and as a component in hydroxylation reactions that provide connective tissue stability and wound healing


Biologic and Biochemical Functions


Antioxidant (Reduction of Harmful Free Radicals)
$\downarrow$ Oxidative DNA and/or protein damage
$\downarrow$ Low-density lipoprotein oxidation
$\downarrow$ Lipid peroxidation
$\downarrow$ Oxidants and nitrosamines in gastric juice
$\downarrow$ Extracellular oxidants from neutrophils
$\uparrow$ Endothelium-dependent vasodilation

Vitamin C (L-ascorbic acid) oxidation releases donor electrons in pairs for biochemical reactions. The molecular diagrams show carbon atoms in black, oxygen in red, and hydrogen in white. Arrows indicate an increase ( $\uparrow$ ) or decrease ( $\downarrow$ ) in response.

Figure 2.1 Various food sources for vitamin C and biologic and biochemical functions. (Modified from Levine M, et al. Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415.)

Vitamins participate repeatedly in metabolic reactions without degradation; thus, the vitamin needs of physically active persons do not exceed those of sedentary counterparts.

## INTEGRATIVE QUESTION

If vitamins play such an important role in energy release, should athletes supercharge with vitamin supplements to enhance exercise performance and training responsiveness?

Table 2.1 lists the major bodily functions, dietary sources, and symptoms of a deficiency or excess for the water-soluble and fat-soluble vitamins. Well-balanced meals provide an adequate quantity of all vitamins, regardless of age and physical activity level. Indeed, individuals who expend considerable energy in physical activity generally need not consume special foods or supplements that increase vitamin intake above recommended levels. At high levels of daily physical activity, food intake generally increases to sustain the added exercise energy requirements. Additional food through a variety of nutritious meals proportionately increases vitamin and mineral intakes.


Figure 2.2 Biologic functions of vitamins.

Several exceptions exist concerning the possible need for vitamin supplementation because of difficulty obtaining recommended amounts. First, vitamin C and folic acid in foods usually make up only a small part of most Americans total caloric intake; the availability of such foods also varies by season. Second, different athletic groups have relatively low intakes of vitamins $B_{1}$ and $B_{6}$, two vitamins prevalent in fresh fruit, grains, and uncooked or steamed vegetables. ${ }^{53,163}$ Individuals on meatless diets should consume a small amount of milk, milk products, or eggs because vitamin $\mathrm{B}_{12}$ exists only in foods of animal origin.

## DEFINING NUTRIENT NEEDS

Controversy surrounding the RDAs caused the Food and Nutrition Board of the Institute of Medicine of the National Academies (www.iom.edu/CMS/3788.aspx) and scientific nutrition community to reexamine the usefulness of a single standard for specific nutrients. This process led the National

Academies Institute of Medicine (in cooperation with Canadian scientists) to develop the Dietary Reference Intakes (http://fnic.nal.usda.gov/nal_display/index.php?info_center= 4\&tax_level=3\&tax_subject=256\&topic_id=1342\&level3_id= 5140\&level4_id=0\&level5_id=0\&placement_default=0).

## Dietary Reference Intakes

The Dietary Reference Intakes (DRIs) are the umbrella term that encompasses the array of standardsRDAs, Estimated Average Requirements, Adequate Intakes, and the Tolerable Upper Intake Levelsfor nutrient recommendations in planning and assessing diets for healthy persons.

Recommendations encompass not only daily intakes intended for health maintenance but also upper intake levels that reduce the likelihood of harm from nutrient intake excess. The DRIs differ from their predecessor RDAs by focusing more on promoting health maintenance and risk reduction for nutrientdependent diseases (e.g., heart disease, diabetes, hypertension,

## TABLE 2.1 Food Sources, Major Bodily Functions, and Symptoms of Deficiency or Excess of the Fat-Soluble and Water-Soluble Vitamins for Healthy Adults (19 50 Years)

Vitamin Dietary Sources Major Bodily Functions Deficiency Excess

## Fat-soluble

Vitamin A
(retinol)


Vitamin E (tocopherol)

Vitamin K
(phylloquinone)
Water-solubl

| Vitamin $\mathrm{B}_{1}$ |
| :---: |
| (thiamine) |


| Vitamin $\mathrm{B}_{2}$ |
| :---: |
| (riboflavin) |

Niacin
(nicotinic acid)

Vitamin $B_{6}$ (pyridoxine)

Pantothenic
acid

Folate

Vitamin $B_{12}$ (cobalamin)
Vitamin D
Vitamin E
(tocopherol)
Vitamin K
$\quad$ (phylloquinone)

Water-soluble
Vitamin $B_{1}$
(thiamine)

Vitamin $\mathrm{B}_{2}$ (riboflavin)
 acid
(

Provitamin A ( $\beta$ carotene) widely distributed in green vegetables; retinol present in milk, butter, cheese, fortified margarine

Pork, organ meats, whole grains, nuts, legumes, milk, fruits, and vegetables
Widely distributed in foods; meats, eggs, milk products, wholegrain and enriched cereal products, wheat germ, green leafy vegetables
Liver, lean meats, poultry, grains, legumes, peanuts (can be formed from tryptophan)
Meats, fish, poultry, vegetables, whole grains, cereals, seeds

Widely distributed in foods, meat, fish, poultry, milk products, legumes, whole grains
Legumes, green vegetables, wholewheat products, meats, eggs, milk products, liver
Muscle meats, fish,
eggs, dairy products (absent in plant foods)

Constituent of rhodopsin (visual pigment)
Maintenance of epithelial tissues; role in mucopolysaccharide synthesis

Promotes growth and mineralization of bones
Increases absorption of calcium
Functions as an antioxidant to prevent cell damage
Important in blood clotting (involved in formation of active prothrombin)

Coenzyme (thiamine prophosphate) in reactions involving the removal of carbon dioxide
Constituent of two flavin nucleotide coenzymes involved in energy metabolism (FAD and FMN)

Constituent of two coenzymes in oxidation reduction reactions (NAD and NADP)
Coenzyme (pyridoxal phosphate) involved in amino acid and glycogen metabolism
Constituent of coenzyme A, which plays a central role in energy metabolism

Coenzyme (reduced form) involved in transfer of single-carbon units in nucleic acid and amino acid metabolism
Coenzyme involved in transfer of single-carbon units in nucleic acid metabolism

| Xerophthalmia (keratinization of ocular tissue), night blindness, permanent blindness | Headache, vomiting, peeling of skin, anorexia, swelling of long bones |
| :---: | :---: |
| Rickets (bone deformities) in children Osteomalacia in adults | Vomiting, diarrhea, loss of weight, kidney damage |
| Possible anemia | Relatively nontoxic |
| Conditioned deficiencies associated with severe bleeding; internal hemorrhages | Relatively nontoxic Synthetic forms at high doses may cause jaundice |

Beriberi (peripheral nerve changes, edema, heart failure)

Reddened lips, cracks at mouth corner (cheilosis), eye lesions

Pellagra (skin and gastrointestinal lesions, nervous mental disorders)
Irritability, convulsions, muscular twitching, dermatitis, kidney stones
Fatigue, sleep None reported disturbances, impaired coordination, nausea

Anemia, gastroin- None reported testinal disturbances, diarrhea, red tongue

Permicious anemia, None reported neurologic disorders

Flushing, burning and tingling around neck, face, and hands

## None reported

None reported
None reported

$$
5
$$

| TABLE 2.1 | Food Sources, Major Bodily Functions, and Symptoms of Deficiency or Excess of the Fat-Soluble and Water-Soluble Vitamins for Healthy Adults (19 50 Years) continued |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Vitamin | Dietary Sources | Major Bodily Functions | Deficiency | Excess |
| Biotin | Legumes, vegetables, meats, liver, eggyolk, nuts | Coenzymes required for fat synthesis, amino acid metabolism, and glycogen (animal starch) formation | Fatigue, depression, nausea, dermatitis, muscle pain | None reported |
| Vitamin C (ascorbic acid) | Citrus fruits, tomatoes, green peppers, salad greens | Maintains intercellular matrix of cartilage, bone, and dentine; important in collagen synthesis | Scurvy (degeneration of skin, teeth, blood vessels, epithelial hemorrhages) | Relatively nontoxic Possibility of kidney stones |

osteoporosis, various cancers, and age-related macular degeneration). This contrasts with the traditional criterion of preventing the deficiency diseases scurvy or beriberi. In addition to including values for energy, protein, and the micronutrients, the DRIs also provide values for food components of nutritional importance such as phytochemicals.

Unlike its RDA predecessor, the DRI value also includes recommendations that apply to gender and life stages of growth and development based on age and, when appropriate, pregnancy and lactation. The following definitions apply to the four different sets of values for the intake of nutrients and food components in the DRIs:

1. Estimated Average Requirement (EAR): Average level of daily nutrient intake to meet the requirement of one-half of the healthy individuals in a particular life stage and gender group. The EAR provides a
useful value to determine the prevalence of inadequate nutrient intake by the proportion of the population with intakes below this value.
2. Recommended Dietary Allowance (RDA): The average daily nutrient intake level sufficient to meet the requirement of about $97 \%$ of healthy individuals in a particular life-stage and gender group (Fig. 2.3). For most nutrients, this value represents the EAR plus two standard deviations of the requirement.
3. Adequate Intake (AI): The AI provides an assumed adequate nutritional goal when no RDA exists. It represents a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy persons-used when an RDA cannot be


## Intake Needed to Meet Requirements

Figure 2.3 Theoretical distribution of the number of persons adequately nourished by a given nutrient intake. The recommended dietary allowance (RDA) is set at an intake level that would meet the nutrient needs of $97 \%$ of the population ( 2 standard deviations [sd] above the mean). EAR is the Estimated Average Requirement, which represents a nutrient intake value estimated to meet the requirements of half of the healthy individuals in a gender and life-stage group.

TABLE 2.2 Dietary Reference Intakes (DRIs): Recommended Vitamin Intakes and Tolerable Upper Intake Levels (ULs)

Recommended Intakes for Individuals

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Infants |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 06 mo | 400* | 40* | 5* | 4* | 2.0* | 0.2* | 0.3* | 2* | 0.1* | 65* | 0.4* | 1.7* | 5* | 125* |
| 712 mo | 500* | 50* | 5* | 5* | $2.5 *$ | 0.3* | 0.4* | 4* | 0.3* | 80* | 0.5* | 1.8* | 6* | 150* |
| Children |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13 y | 300 | 15 | 5* | 6 | 30* | 0.5 | 0.5 | 6 | 0.5 | 150 | 0.9 | 2* | 8* | 200* |
| 48 y | 400 | 25 | 5* | 7 | 55* | 0.6 | 0.6 | 8 | 0.6 | 200 | 1.2 | 3* | 12* | 250* |
| Males |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | 600 | 45 | 5* | 11 | 60* | 0.9 | 0.9 | 12 | 1.0 | 300 | 1.8 | 4* | 20* | 375* |
| 1418 y | 900 | 75 | 5* | 15 | 75* | 1.2 | 1.3 | 16 | 1.3 | 400 | 2.4 | 5* | 25* | 550* |
| 1930 y | 900 | 90 | 5* | 15 | 120* | 1.2 | 1.3 | 16 | 1.3 | 400 | 2.4 | 5* | 30* | 550* |
| 3150 y | 900 | 90 | 5* | 15 | 120* | 1.2 | 1.3 | 16 | 1.3 | 400 | 2.4 | 5* | 30* | 550* |
| 5170 y | 900 | 90 | 10* | 15 | 120* | 1.2 | 1.3 | 16 | 1.7 | 400 | $2.4{ }^{h}$ | 5* | 30* | 550* |
| $>70$ y | 900 | 90 | 15* | 15 | 120* | 1.2 | 1.3 | 16 | 1.7 | 400 | $2.4{ }^{h}$ | 5* | 30* | 550* |
| Females |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | 600 | 45 | 5* | 11 | 60* | 0.9 | 0.9 | 12 | 1.0 | 300 | 1.8 | 4* | 20* | 375* |
| 1418 y | 700 | 65 | 5* | 15 | 75* | 1.0 | 1.0 | 14 | 1.2 | $400{ }^{f}$ | 2.4 | 5* | $25^{*}$ | 400* |
| 1930 y | 700 | 75 | 5* | 15 | 90* | 1.1 | 1.1 | 14 | 1.3 | $400{ }^{\text {f }}$ | 2.4 | 5* | 30* | 425* |
| 3150 y | 700 | 75 | 5* | 15 | 90* | 1.1 | 1.1 | 14 | 1.3 | $400{ }^{\text {f }}$ | 2.4 | 5* | 30* | 425* |
| 5170 y | 700 | 75 | 10* | 15 | 90* | 1.1 | 1.1 | 14 | 1.5 | 400 | $2.4{ }^{h}$ | 5* | 30* | 425* |
|  | 700 | 75 | 15* | 15 | 90* | 1.1 | 1.1 | 14 | 1.5 | 400 | $2.4{ }^{h}$ | 5* | 30* | 425* |
| Pregnancy ${ }^{\text {i,j }}$ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | 750 | 80 | 5* | 15 | 75* | 1.4 | 1.4 | 18 | 1.9 | $600{ }^{f}$ | 2.6 | 6* | 30* | 450* |
| 1930 y | 770 | 85 | 5* | 15 | 90* | 1.4 | 1.4 | 18 | 1.9 | $600{ }^{f}$ | 2.6 | 6* | 30* | 450* |
| 3150 y | 770 | 85 | 5* | 15 | 90* | 1.4 | 1.4 | 18 | 1.9 | $600{ }^{f}$ | 2.6 | 6* | 30* | 450* |
| Lactation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | 1200 | 115 | 5* | 19 | 75* | 1.4 | 1.6 | 17 | 2.0 | 500 | 2.8 | 7* | 35* | 550* |
| 1930 y | 1300 | 120 | 5* | 19 | 90* | 1.4 | 1.6 | 17 | 2.0 | 500 | 2.8 | 7* | 35* | 550* |
| 3150 y | 1300 | 120 | 5* | 19 | 90* | 1.4 | 1.6 | 17 | 2.0 | 500 | 2.8 | 7* | 35* | 550* |

Note: This table (taken from the DRI reports, see www.nap.edu) presents Recommended Dietary Allowances (RDAs) in bold type and Adequate Intakes (AIs) in ordinary type followed by an asterisk $\left(^{*}\right.$ ). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all ( 97 to $98 \%$ ) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.
${ }^{a}$ As retinol activity equivalents (RAEs). $1 \mathrm{RAE}=1 \mu \mathrm{~g}$ retinol, $12 \mu \mathrm{~g} \beta$-carotene, $24 \mu \mathrm{~g} \alpha$-carotene, or $24 \mu \mathrm{~g} \beta$-cryptoxanthin. To calculate RAEs from REs of provitamin A carotenoids in foods, divide the REs by 2. For preformed vitamin A in foods or supplements and for provitamin A carotenoids in supplements, 1 RE $=1$ RAE.
${ }^{b}$ Calciferol. $1 \mu \mathrm{~g}$ calciferol $=40 \mathrm{IU}$ vitamin D .
${ }^{\text {I }}$ In the absence of adequate exposure to sunlight.
${ }^{d}$ As $\alpha$-tocopherol. $\alpha$-Tocopherol includes $R R R$ - $\alpha$-tocopherol, the only form of $\alpha$-tocopherol that occurs naturally in foods, and the $2 R$-stereoisometric forms of $\alpha$-tocopherol ( $R R R$-, $R S R$-, $R R S$-, and $R S S$ - $\alpha$-tocopherol) that occur in fortified foods and supplements. It does not include the $2 S$-stereoisomeric forms of $\alpha$-tocopherol (SRR-, $S S R-, S R-$, and $S S S$ - $\alpha$-tocopherol), also found in fortified foods and supplements.
${ }^{e}$ As niacin equivalents (NE). 1 mg of niacin $=60 \mathrm{mg}$ of tryptophan; 06 months = preformed niacin (not NE).
${ }^{f}$ As dietary folate equivalents (DFE). $1 \mathrm{DFE}=1 \mu \mathrm{~g}$ food folate $=0.6 \mu \mathrm{~g}$ of folic acid from fortified food or as a supplement consumed with food $=0.5 \mu \mathrm{~g}$ of a supplement taken on an empty stomach.
${ }^{g}$ Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.
${ }^{h}$ Because 10 to $30 \%$ of older people may malabsorb food-bound $\mathrm{B}_{12}$, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with $B_{12}$ or a supplement containing $B_{12}$.
${ }^{i}$ In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume $400 \mu \mathrm{~g}$ from supplements or fortified foods in addition to intake of food folate from a varied diet.
${ }^{j}$ It is assumed that women will continue consuming $400 \mu \mathrm{~g}$ from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period-the critical time for formation of the neural tube.

## TABLE 2.2 Dietary Reference Intakes (DRIs): Recommended Vitamin Intakes and Tolerable Upper Intake Levels (ULs) continued

Tolerable Upper Intake Levels (UL")

|  |  |  |  |  |  |  |  |  |  | $\begin{aligned} & 0 \\ & \stackrel{0}{0} \\ & \frac{\pi}{0} \\ & \hline \text { 응 } \end{aligned}$ |  |  | - |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Infants |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 06 mo | 600 | $\mathrm{ND}^{f}$ | 25 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| 712 mo | 600 | ND | 25 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Children |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13 y | 600 | 400 | 50 | 200 | ND | ND | ND | 10 | 30 | 300 | ND | ND | ND | 1.0 | ND |
| 48 y | 900 | 650 | 50 | 300 | ND | ND | ND | 15 | 40 | 400 | ND | ND | ND | 1.0 | ND |
| Males, Females |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | 1700 | 1200 | 50 | 600 | ND | ND | ND | 20 | 60 | 600 | ND | ND | ND | 2.0 | ND |
| 1418 y | 2800 | 1800 | 50 | 800 | ND | ND | ND | 30 | 80 | 800 | ND | ND | ND | 3.0 | ND |
| 1970 y | 3000 | 2000 | 50 | 1000 | ND | ND | ND | 35 | 100 | 1000 | ND | ND | ND | 3.5 | ND |
| $>70 \mathrm{y}$ | 3000 | 2000 | 50 | 1000 | ND | ND | ND | 35 | 100 | 1000 | ND | ND | ND | 3.5 | ND |
| $\begin{aligned} & \text { Pregnancy }{ }^{i, j} \leq 18 \mathrm{y} \end{aligned}$ | 2800 | 1800 | 50 | 800 | ND | ND | ND | 30 | 80 | 800 | ND | ND | ND | 3.0 | ND |
| 1950 y | 3000 | 2000 | 50 | 1000 | ND | ND | ND | 35 | 100 | 1000 | ND | ND | ND | 3.5 | ND |
| Lactation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | 2800 | 1800 | 50 | 800 | ND | ND | ND | 30 | 80 | 800 | ND | ND | ND | 3.0 | ND |
| 1950 y | 3000 | 2000 | 50 | 1000 | ND | ND | ND | 35 | 100 | 1000 | ND | ND | ND | 3.5 | ND |

${ }^{a} \mathrm{UL}=$ The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin $\mathrm{B}_{12}$, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.
${ }^{b}$ As preformed vitamin A only.
${ }^{c}$ As $\alpha$-tocopheral; applies to any form of supplemental $\alpha$-tocopheral.
${ }^{d}$ The ULs for vitamin E, niacin, and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two. ${ }^{e} \beta$-carotene supplements are advised only to serve as a provitamin A source for individuals at risk of vitamin A deficiency.
${ }^{f} \mathrm{ND}$, not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.
Sources: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B ${ }_{12}$, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); and Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001). These reports may be accessed via www.nap.edu/catalog/dri Copyright by the National Academy of Sciences. All rights reserved.
determined. Intakes at or above the AI level indicate low risk.
4. Tolerable Upper Intake Level (UL): The highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the specified gender and life-stage group of the general population. As intake increases above the UL, the potential risk of adverse effects increases.

Most individuals can meet the daily requirement for the nutrients examined without need for additional supplementation. The exception is the mineral iron; most pregnant women require supplements to obtain their increased daily requirement. Table 2.2 presents the RDA, AI, and UL values for vitamins.

## Antioxidant Role of Vitamins

Most of the oxygen consumed within the mitochondria during energy metabolism combines with hydrogen to produce water. However, 2 to $5 \%$ of oxygen normally forms the reactive oxygen- and nitrogen-containing free radicals superoxide $\left(\mathrm{O}_{2}\right)$, hydrogen peroxide $\left(\mathrm{H}_{2} \mathrm{O}_{2}\right)$, hydroxyl ( OH ), and nitric oxide ( ONOO ) owing to electron leakage along the electron transport chain. A free radical, a highly unstable, chemically reactive molecule or molecular fragment, contains at least one unpaired electron in its outer orbital or valence shell. These are the same free radicals produced by external heat and ionizing radiation and carried in cigarette smoke, environmental pollutants, and even some medications. Once formed, free radicals interact with other compounds to create
new free radical molecules. The new molecules frequently damage the electron-dense cellular components DNA and lipid-rich cell membranes. By contrast, paired electrons represent a far more stable state.

Fortunately, cells possess enzymatic and nonenzymatic mechanisms that work in concert to immediately counter potential oxidative damage from a chemical and enzymatic mutagenic challenge. Antioxidants scavenge the oxygen radicals or chemically eradicate them by reducing oxidized compounds. For example, when $\mathrm{O}_{2}^{-}$forms, the enzyme superoxide dismutase catalyzes its dismutation to form hydrogen peroxide. This enzyme catalyzes the reaction of two identical molecules to produce two molecules in different states of oxidation as follows:

$$
\mathrm{O}_{2}^{-}+\mathrm{O}_{2}^{-} \xrightarrow[\text { superoxide dismutase }]{2 \mathrm{H}^{+}} \mathrm{H}_{2} \mathrm{O}_{2}+\mathrm{O}_{2}
$$

The hydrogen peroxide produced in this reaction breaks down further to water and oxygen in a reaction catalyzed by the widely distributed enzyme catalase as follows:

$$
2 \mathrm{H}_{2} \mathrm{O}_{2} \quad \text { catalase } \quad \rightarrow 2 \mathrm{H}_{2} \mathrm{O}+\mathrm{O}_{2}
$$

## Protection from Disease

An accumulation of free radicals increases the potential for cellular damage (oxidative stress) to biologically important substances through processes that add oxygen to cellular components. These substances include DNA, proteins, and lipid-containing structures, particularly the polyunsaturated fatty acid rich bilayer membrane that isolates the cell from noxious toxins and carcinogens. Also, oxidative stress likely acts as a key regulator of cell signaling pathways that increase protein breakdown and muscle atrophy during prolonged periods of physical inactivity. ${ }^{147}$ During unchecked oxidative stress, the plasma membrane s fatty acids deteriorate through a chain-reaction series of events termed lipid peroxidation. These reactions incorporate abnormal amounts of oxygen into lipids and increase the vulnerability of the cell and its constituents. Free radicals facilitate peroxidation of lowdensity lipoprotein (LDL) cholesterol, thus leading to cytotoxicity and enhanced coronary artery plaque formation. ${ }^{18,190}$ Oxidative stress ultimately increases the likelihood of cellular deterioration associated with advanced aging, many diseases, and a general decline in central nervous system and immune functions.


The body has no way to stop oxygen reduction and free radical production, but it does provide an elaborate natural defense against their damaging effects. This defense includes the antioxidant scavenger enzymes catalase, glutathione peroxidase, superoxide dismutase, and metal-binding proteins (metalloenzyme). ${ }^{93}$ In addition, the nutritive, nonenzymatic reducing agents selenium and vitamins $\mathrm{A}, \mathrm{C}$, and E and the vitamin A precursor $\beta$-carotene serve important protective functions. ${ }^{19,60,62,84,189}$ These antioxidant chemicals protect the plasma membrane by reacting with and removing free radicals, thus quenching the chain reaction; they also blunt the damaging effects to cellular constituents of high serum homocysteine levels. ${ }^{132}$ A diet with appropriate antioxidant vitamins and other chemoprotective agents (in the foods consumed) may reduce cardiovascular disease, stroke, diabetes, osteoporosis, cataracts, premature aging, and diverse cancers including those of the breast, distal colon, prostate, pancreas, ovary, and endometrium. ${ }^{52,85,131,154,210}$

One model for heart disease protection proposes that the antioxidant vitamins inhibit LDL cholesterol oxidation and its subsequent uptake into foam cells embedded in the arterial wall. This oxidative-modification hypothesis posits that the mild oxidation of LDL cholesterol-similar to butter turning rancid-contributes to the plaque-forming, artery-clogging process of atherosclerosis. ${ }^{43,114,188}$

Nutritional guidelines focus more on the consumption of a broad array of foods rather than on supplements containing isolated chemicals within these foods. The current recommendations increase the consumption of fruits, vegetables, and whole grains, and include lean meat or meat substitutes and low-fat dairy foods to provide health benefits and reduce risk of early mortality. Disease protection from diet links to the myriad of accessory nutrients and substances within the vita-min-containing foods in a healthful diet. ${ }^{83}$

The National Cancer Institute (www.cancer.gov/) encourages consumption of five or more servings (nine recommended for men) of fruits and vegetables daily, whereas the USDA s Dietary Guidelines recommend two to four servings of fruits and three to five servings of vegetables daily. Rich dietary sources of antioxidants include:
$\boldsymbol{\beta}$-carotene: pigmented compounds, or carotenoids, that give color to yellow, orange, and green, leafy vegetables: carrots; dark-green leafy vegetables such as spinach, broccoli, turnips, and beet and collard greens; sweet potatoes; winter squash; apricots; cantaloupe; mangos; papaya
Vitamin C: citrus fruits and juices, cabbage, broccoli, turnip greens, cantaloupe, tomatoes, strawberries, apples with skin
Vitamin E: vegetable oils, wheat germ, whole-grain bread and cereals, dried beans, green leafy vegetables

The Latest About Vitamins and Health:
Conclusions Not So Simple Anymore
Routinely consuming vitamin and mineral supplements is a practice almost as ubiquitous as drinking
water on a daily basis. But times are now changing, and a paradigm shift may be underway in how the public perceives the long-term health benefits of popular and highly advertised micronutrient supplements. First, recent studies played down the usefulness of some vitamins and mineral supplements for cancer prevention. ${ }^{\text {b,c,d }}$

In addition, a large clinical trial presented at the American Association for Cancer Research (www.aacr.org) meetings in Washington, DC in November 2008 verified these findings. For 14,641 male physicians age 50 and older who consumed vitamin E (400 IU units every other day) and vitamin C ( 500 mg daily) for up to 10 years (a third group consumed a placebo), neither vitamin conferred any reduction on cancer rates, including prostate cancer. The study, terminated before completion, raised serious worries that taking the antioxidant vitamins might inflict more harm than good. Similar results from the same cohort reported no difference among the groups in the incidence of heart attack, stroke, congestive heart failure, angina, or the need for cardiac revascularization. ${ }^{\text {e }}$ This latest study followed disappointing results of consuming antioxidant supplements (vitamins A, E, C, and selenium) on gastrointestinal cancer reduction based on a thorough review of 212,000 subjects enrolled in 20 randomized trials. ${ }^{\text {a }}$
a. Bjelakovic G, et al. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst Rev. 2008 16:CD004183.
b. Chlebowski RT, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst. 2008;100:1581.
c. de Vogel S, et al. Dietary folate, methionine, riboflavin, and vitamin B-6 and risk of sporadic colorectal cancer. J Nutr. 2008;138:2372.
d. Rohan TE, et al. A randomized controlled trial of calcium plus vitamin $D$ supplementation and risk of benign proliferative breast disease. Breast Cancer Res Treat. 2008, Suppl1(Vol 112, Dec).
e. Sesso, HD, et al. Vitamins E and C in the prevention of cardiovascular disease in men. The Physicians Health Study II Randomized Controlled Trial. JAMA. 2008;300:2123.

## EXERCISE, FREE RADICALS, AND ANTIOXIDANTS

The benefits of physical activity are well documented, but the possibility for negative effects remains controversial. Potentially negative effects occur because an elevated aerobic exercise metabolism increases reactive oxygen and nitrogen free radical production. ${ }^{109,142,201}$ At relatively low cellular
levels, free radicals may negatively influence metabolism through signaling mechanisms that maintain cellular balance. ${ }^{111}$ Increased free radicals could possibly overwhelm the body s natural defenses and pose a health risk from increased oxidative stress. Free radicals also play a role in muscle injury and soreness from eccentric muscle actions and unaccustomed exercise (see Chapter 22). Muscle damage of this nature releases muscle enzymes and initiates inflammatory cell infiltration into the damaged tissue.

The opposing position maintains that while free radical production increases during exercise, the body s normal antioxidant defenses are either adequate or concomitantly improve. Improvement occurs as natural enzymatic defenses (e.g., superoxide dismutase and glutathione peroxidase) up-regulate through exercise training adaptations. ${ }^{146,173,203}$ Research supports this latter position because the beneficial effects of regular exercise decrease the incidence of heart disease and various cancers (whose occurrences relate to oxidative stress). Regular exercise training also protects against myocardial injury from lipid peroxidation induced by short-term tissue ischemia followed by reperfusion. ${ }^{41,74,186}$ In humans, free radical production and tissue damage are not directly measured but, rather, inferred from markers of free radical byproducts.

## Increased Metabolism in Exercise and Free-Radical Production

Exercise produces reactive oxygen in at least two ways. The first occurs via an electron leak in the mitochondria, probably at the cytochrome level, to produce superoxide radicals. The second occurs during alterations in blood flow and oxygen supply-underperfusion during intense exercise followed by substantial reperfusion in recovery-which trigger excessive free radical generation. The reintroduction of molecular oxygen in recovery also produces reactive oxygen species that magnify oxidative stress. Some argue that the potential for free-radical damage increases during trauma, stress, and muscle damage and from environmental pollutants, including smog.

The risk of oxidative stress increases with intense exercise. ${ }^{2,148}$ Exhaustive endurance exercise by untrained persons produces oxidative damage in the active muscles. Intense resistance exercise also increases free radical production, indirectly measured by malondialdehyde, the lipid peroxidation byproduct. ${ }^{124}$ Variations in estrogen levels during the menstrual cycle do not affect the mild oxidative stress that accompanies moderate-intensity exercise. ${ }^{29}$ Figure 2.4 illustrates how regular aerobic exercise affects oxidative response and the potential for tissue damage as well as protective adaptive responses.

## Important Questions

Two questions arise about the potential for increased oxidative stress with exercise.

1. Are physically active individuals more prone to freeradical damage?


Figure 2.4 Cascade of events and adaptations produced by regular aerobic exercise that lessen the likelihood of tissue damage from intense physical activity.
2. Are protective agents with antioxidant properties required in increased quantities in the diets of physically active people?

In answer to the first question, the natural antioxidant defenses in well-nourished humans respond adequately to increased physical activity. ${ }^{205} \mathrm{~A}$ single bout of submaximal exercise increases oxidant production, yet antioxidant defenses cope effectively in healthy individuals and trained heart transplant recipients. ${ }^{94}$ Even with multiple bouts of exercise on consecutive days, the various indices of oxidative stress show no impairment of the body s antioxidant system. The answer to the second question remains equivocal. ${ }^{202}$ Some evidence indicates that consuming exogenous antioxidant compounds either slows exercise-induced free radical formation or augments the body s natural defense system. ${ }^{41,93}$ Research also indicates that low levels of vitamin E in the body of men and women age 65 and older associate with subsequent decline in physical function. ${ }^{14}$ It remains undetermined whether vitamin E supplements yield beneficial results.

If antioxidant supplementation proves beneficial, vitamin $E$ may be the most important antioxidant related to exercise. ${ }^{32,89}$ In one study, vitamin E deficient animals began an exercise program with plasma membrane function compromised from


Figure 2.5 Pentane levels before and after 20 minutes of exercise at $100 \% \mathrm{VO}_{2 \max }$ with and without vitamin E supplementation. (Adapted from Pincemail J, et al. Pentane measurement in man as an index of lipoperoxidation.
Bioelectronchem Bioenerg 1987;18:117.)
oxidative damage and reached exhaustion earlier than animals with recommended vitamin E levels. In animals fed a normal diet, vitamin E supplements diminished oxidative damage to skeletal muscle fibers and myocardial tissue caused by exercise. ${ }^{68}$ Figure 2.5 shows that 3 weeks of a daily 200 International Unit (IU) vitamin E supplement dramatically reduced free radical production measured by pentane elimination in men, following maximal exercise. Humans fed a daily antioxidant vitamin mixture of $\beta$-carotene, vitamin $C$, and vitamin $E$ had lower serum and breath markers of lipid peroxidation at rest and following exercise than subjects not receiving supplements. Five months of vitamin E supplementation in racing cyclists reduced markers of oxidative stress induced by extreme endurance exercise. In another experiment using whole-body resistance training, 2 weeks of supplementation with 120 IU of vitamin E daily decreased free radical interaction with cellular membranes and blunted muscle tissue disruption caused by a single bout of intense exercise. ${ }^{124}$ In contrast, 30 days of vitamin E supplementation ( $1200 \mathrm{IU} \cdot \mathrm{d}^{1}$ ) produced a 2.8 -fold increase in serum vitamin E concentration without affecting contraction-induced indices of muscle damage (including postexercise force decrement) or inflammation caused by eccentric muscle actions. ${ }^{16}$ Similarly, a 4-week daily vitamin E supplement of 1000 IU produced no effect on biochemical or ultrastructural indices of muscle damage in experienced runners after a half marathon. ${ }^{39}$ Differences in exercise severity and oxidative stress could account for discrepancies in research findings.

Recommended vitamin E supplementation ranges between 100 and 400 IU per day. Daily supplements of vitamin E containing up to 800 IU probably pose no risk for most persons. Higher amounts have produced internal bleeding by inhibiting vitamin K metabolism, particularly in persons taking anticoagulant medication.

## VITAMIN SUPPLEMENTS: THE COMPETITIVE EXERCISE EDGE?

Figure 2.6 illustrates the progressive increase in money spent on dietary supplements in the United States between 1990 and 2007, with growth rate exceeding $10 \%$ per year. Reports estimate that 158 million Americans currently take dietary supplements, spending an estimated $\$ 18$ billion annually. ${ }^{69,199} \mathrm{Of}$ this total, vitamin mineral pills and powders represent the most common form of supplement consumed by the general public, accounting for $70 \%$ of the total annual supplement sales. More than $50 \%$ of competitive athletes in some sports consume supplements on a regular basis, either to ensure adequate micronutrient intake or to achieve an excess with the hope of enhancing performance and training responsiveness. ${ }^{31,51,101}$ When vitamin mineral deficiencies appear in physically active people, they often occur among these three groups:

1. Vegetarians or groups with low energy intake such as dancers, gymnasts, and weight-class sport athletes who strive to maintain or reduce body weight.
2. Individuals who eliminate one or more food groups from their diet.
3. Individuals who consume large amounts of processed foods and simple sugars with low micronutrient density (e.g., endurance athletes).

Vitamins synthesized in the laboratory are no less effective for bodily functions than vitamins from food sources. When deficiencies exist, vitamin supplements reverse the deficiency symptoms. When vitamin intake achieves recommended levels, supplements do not improve exercise performance.


Figure 2.6 Growth of an industry. Dietary supplement sales have increased tremendously as indicated by the supplement sales figures from 1990 to 2007. In 2006, estimates indicate that over one-half of the United States population used a dietary supplement.

More than 55 years of research data does not provide evidence that consuming vitamin (and mineral) supplements improves exercise performance, the hormonal and metabolic responses to exercise, or ability to train arduously and recover from such training in healthy persons with nutritionally adequate diets. ${ }^{65,194,200,208}$

## integrative question

Respond to an athlete who asks, Is there anything wrong with taking megadoses of vitamin and mineral supplements to ensure Im getting an adequate intake on a daily basis?

## Excess Vitamins Behave As Chemicals

Once the enzyme systems become saturated with specific vitamin cofactors, any excess vitamins taken in megadose function as chemicals (drugs) in the body. A megadose of water-soluble vitamin C, for example, raises serum uric acid levels to precipitate gout in predisposed individuals. At intakes above 1000 mg daily, urinary excretion of oxalate (a breakdown product of vitamin C) increases and accelerates kidney stone formation in susceptible individuals. ${ }^{112}$ Some American blacks, Asians, and Sephardic Jews have a genetic metabolic deficiency that transforms to hemolytic anemia with excessive vitamin C intake. In iron-deficient individuals, consuming megadoses of vitamin $C$ can destroy vitamin $\mathrm{B}_{12}$. In healthy persons, vitamin $C$ supplementation frequently irritates the bowel and causes diarrhea.

Excess vitamin $\mathrm{B}_{6}$ can induce liver disease and nerve damage, while a riboflavin $\left(\mathrm{B}_{2}\right)$ excess can impair vision. A megadose of nicotinic acid (niacin) functions as a potent vasodilator and inhibits fatty acid mobilization during exercise, which could more rapidly deplete glycogen reserves. Folic acid excess in supplement form can trigger an allergic response, producing hives, light-headedness, and breathing difficulties, and can increase breast cancer risk in postmenopausal women. ${ }^{191}$ Possible side effects of vitamin E megadose include headache, fatigue, blurred vision, gastrointestinal disturbances, internal bleeding, muscular weakness, and low blood sugar.

Some Added Protection Against Upper Respiratory Tract Infection. Moderate exercise heightens immune function, whereas prolonged periods of intense physical activity, as in marathon running or a strenuous training session, transiently suppress the body s first line of defense against infectious agents. This increases the risk of upper respiratory tract infection (URTI) within 1 or 2 weeks of the exercise stress. For these individuals, additional vitamin C and E and perhaps carbohydrate ingestion before, during, and following a workout may boost the normal immune mechanisms for combating infection. ${ }^{73,78,92,133,138,144}$

## Vitamins and Exercise Performance

Figure 2.7 illustrates that the water-soluble B-complex and C vitamins play key roles as coenzymes to regulate energyyielding reactions during carbohydrate, fat, and protein catab-
olism. They also contribute to hemoglobin synthesis and red blood cell production. The belief that if a little is good, more must be better has led many coaches, athletes, fitness enthusiasts, and even some scientists to advocate using vitamin supplements above recommended levels. The facts do not support such advice for individuals who consume an adequate diet.

Supplementing with vitamin $\mathrm{B}_{6}$, an essential cofactor in glycogen and amino acid metabolism, did not benefit the metabolic mixture metabolized by women during intense aerobic exercise. In general, athletes status for this vitamin equals reference standards for the population ${ }^{122}$ and does not decrease with strenuous exercise to a level warranting supplementation. ${ }^{161}$ For endurance-trained men, 9 days of vitamin $\mathrm{B}_{6}$ supplementation ( 20 mg per day) provided no ergogenic effect on cycling to exhaustion performed at 70\% of aerobic capacity. ${ }^{206}$

Chronic high-potency, multivitamin mineral supplementation for well-nourished, healthy individuals does not augment aerobic fitness, muscular strength, neuromuscular performance after prolonged running, and general athletic performance. ${ }^{65,176}$ In addition to the B-complex group, no exercise benefits exist for excess vitamins $C$ and $E$ on stamina, circulatory function, or energy metabolism. Short-term daily supplementation with vitamin E (400 IU) produced no effect on normal neuroendocrine and metabolic responses to strenuous exercise or performance time to exhaustion. ${ }^{177}$ Vitamin C status, assessed by serum concentrations and urinary ascorbate levels, in trained athletes does not differ from untrained individuals despite large differences in daily physical activity level. ${ }^{164}$ Other investigators report similar findings for vitamin C and other vitamins. ${ }^{59,73,162}$ Active persons typically increase daily energy intake to match their increased energy requirement; thus, a proportionate increase occurs in micronutrient intake, often in amounts that exceed recommended levels.

## Summary

1. Vitamins, organic compounds that neither supply energy nor contribute to body mass, serve crucial functions in almost all bodily processes. They must be obtained from food or dietary supplementation.
2. Plants synthesize vitamins; animals also produce them from precursor substances known as provitamins.
3. Thirteen known vitamins are classified as either water soluble or fat soluble. The fat-soluble vitamins include A, D, E, and K; vitamin C and the B-complex vitamins constitute the water-soluble vitamins.
4. Excess fat-soluble vitamins accumulate in body tissues and can increase to toxic concentrations. Except in relatively rare instances, excess watersoluble vitamins remain nontoxic and are eventually excreted in the urine.
5. Vitamins regulate metabolism, facilitate energy release, and play key functions in bone and tissue synthesis.
6. Vitamins A, C, E, and the provitamin $\beta$-carotene serve important protective functions as antioxidants.


Figure 2.7 General schema for the role of water-soluble vitamins in carbohydrate, fat, and protein metabolism.

An appropriate intake of these micronutrients reduces the potential for free radical damage (oxidative stress) and may offer protection against heart disease and some types of cancer.
7. The Dietary Reference Intakes (DRIs) differ from their predecessor RDAs by focusing more on
promoting health maintenance and risk reduction for nutrient-dependent diseases rather than the traditional criterion of preventing deficiency diseases.
8. The new DRIs serve as the umbrella term that encompasses the new standards-the RDAs, Estimated Average Requirements, Adequate

Intakes, and Tolerable Upper Intake Levels-for nutrient recommendations in planning and assessing diets for healthy persons. DRI values include recommendations that apply to gender and life stages of growth and development based on age and during pregnancy and lactation.
9. Physical activity elevates metabolism and increases the production of potentially harmful free radicals. The daily diet should contain foods rich in antioxidant vitamins and minerals to lessen oxidative stress.
10. The body s natural antioxidant defenses up-regulate in response to increased physical activity in wellnourished individuals.
11. Vitamin supplementation above the RDA does not improve exercise performance or the potential for intense physical training.

## Part 2 MINERALS

## THE NATURE OF MINERALS

Approximately $4 \%$ of the body s mass consists of 22 mostly metallic elements collectively called minerals. Minerals serve as constituents of enzymes, hormones, and vitamins; they combine with other chemicals (e.g., calcium phosphate in bone, iron in the heme of hemoglobin) or exist singularly (e.g., free calcium and sodium in body fluids).

The minerals essential to life include seven major minerals (required in amounts $>100 \mathrm{mg}$ daily) and 14 minor or trace minerals (required in amounts $<100 \mathrm{mg}$ daily). Trace minerals account for less than 15 g (approximately 0.5 oz ), or $0.02 \%$ of the total body mass. Excess mineral intake serves no useful physiologic purpose and can produce toxic effects. DRIs have been established for many minerals; a diet that supplies these requirements ensures an adequate intake of the remaining minerals.

Most minerals, major or trace, occur freely in naturemainly in the waters of rivers, lakes, and oceans; in topsoil; and beneath the earth s surface. Minerals exist in the root systems of plants and the body structure of animals that consume plants and water containing minerals. Table 2.3 lists the major bodily functions, dietary sources, and symptoms of deficiency or excess for the minerals, and Table 2.4 presents the RDA, UL, and AI values.

## ROLE OF MINERALS IN THE BODY

Minerals serve three broad roles in the body:

1. Provide structure in forming bones and teeth.
2. Help to maintain normal function (e.g., heart rhythm, muscle contractility, neural conductivity, and acid base balance).
3. Regulate metabolism by becoming constituents of enzymes and hormones that modulate cellular activity.

Figure 2.8 lists the minerals that participate in catabolic and anabolic cellular processes. Minerals activate reactions that release energy during carbohydrate, fat, and protein catabolism. They participate in the biosynthesis of nutrients-glycogen from glucose, triacylglycerols from fatty acids and glycerol, and proteins from amino acids. A lack of one or more essential minerals can disrupt the fine balance between catabolism and anabolism. Minerals also form important constituents of hormones. For example, inadequate thyroxine production from iodine insufficiency slows the body s resting metabolism. In extreme cases, this could predispose a person to develop obesity. Synthesis of insulin, the hormone that facilitates glucose uptake by the cells, requires zinc (as do approximately 100 enzymes), whereas chlorine forms the digestive acid hydrochloric acid.

## Mineral Bioavailability

The body varies considerably in its capacity to absorb and use the minerals in food. For example, spinach contains considerable calcium, but only about 5\% becomes bioavailable (absorbed). The same holds true for dietary iron, which the small intestine absorbs with an average efficiency of 5 to $10 \%$. Four factors that affect mineral bioavailability include:

1. Type of food: The small intestine readily absorbs minerals contained in animal products because they do not contain plant binders and dietary fibers that hinder digestion and absorption. With the exception of magnesium, foods from the animal kingdom generally have a high mineral concentration.
2. Mineral mineral interaction: Many minerals have the same molecular weight and thus compete for intestinal absorption. This makes it unwise to consume an excess of any one mineral because it can retard another mineral s absorption.
3. Vitamin mineral interaction: Various vitamins interact with minerals in a manner that affects mineral bioavailability. From a positive perspective, vitamin D facilitates calcium absorption, while vitamin C improves intestinal absorption of iron.
4. Fiber mineral interaction: High fiber intake blunts the absorption of calcium, iron, magnesium, and phosphorus by binding to them so they pass unabsorbed through the digestive tract.
In the sections that follow, we describe specific functions of important minerals related to physical activity.

## CALCIUM

Calcium, the body s most abundant mineral, combines with phosphorus to form bones and teeth. These two minerals represent about $75 \%$ of the bodys total mineral content or about $2.5 \%$ of body mass. In its ionized form (about $1 \%$ of 1200 g of endogenous calcium), calcium functions in muscle stimulation,

TABLE 2.3 The Important Major and Trace Minerals for Healthy Adults (Age 1950 Years) and Their Food Sources, Functions, and the Effects of Deficiencies and Excesses

| Mineral | Dietary Sources | Major Bodily Functions | Deficiency | Excess |
| :---: | :---: | :---: | :---: | :---: |
| Major Calcium | Milk, cheese, dark green vegetables, dried legumes | Bone and tooth formation, blood clotting, nerve transmission | Stunted growth, rickets, osteoporosis, convulsions | Not reported in humans |
| Phosphorus | Milk, cheese, yogurt, meat, poultry, grains, fish | Bone and tooth formation, acidbase balance, helps prevent loss of calcium from bone | Weakness, demineralization | Erosion of jaw (phossy jaw) |
| Potassium | Leafy vegetables, canteloupe, lima beans, potatoes, bananas, milk, meats, coffee, tea | Fluid balance, nerve transmission, acid-base balance | Muscle cramps, irregular cardiac rhythm, mental confusion, loss of appetite; can be life threatening | None if kidneys functon normally; poor kidney function causes potassium buildup and cardiac arrythmias |
| Sulfur | Obtained as part of dietary protein; present in food preservatives | Acid-base balance, liver function | Unlikely to occur with adequate dietary intake | Unknown |
| Sodium | Common salt | Acid-base balance, body water balance, nerve function | Muscle cramps, mental apathy, reduced appetite | Contributes to high blood pressure |
| Chlorine (chloride) | Chloride part of saltcontaining food; some vegetables and fruits | Important part of extracellular fluids | Unlikely to occur with adequate dietary intake | Contributes to high blood pressure |
| Magnesium | Whole grains, green leafy vegetables | Activates enzymes involved in protein synthesis | Growth failure, behavioral disturbances | Diarrhea |
| Trace Iron | Eggs, lean meats, legumes, whole grains, green leafy vegetables | Constituent of hemoglobin and enzymes involved in energy metabolism | Iron deficiency anemia (weakness, reduced resistance to infection) | Siderosis; cirrhosis of liver |
| Fluoride | Drinking water, tea, seafood | May be important in maintenance of bone structure | Higher frequency of tooth decay | Mottling of teeth, increased bone density |
| Zinc | Widely distributed in foods | Constituent of enzymes involved in digestion | Growth failure, small sex glands | Fever, nausea, vomiting, diarrhea |
| Copper | Meats, drinking water | Constituent of enzymes associated with iron metabolism | Anemia, bone changes (rare) | Rare metabolic condition (Wilson s disease) |
| Selenium | Seafood, meats, grains | Functions in close association with vitamin E | Anemia (rare) | Gastrointestinal disorders, lung irritations |
| Iodine (iodide) | Marine fish and shellfish, dairy products, vegetables, iodized salt | Constituent of thyroid hormones | Goiter (enlarged thyroid) | High intake depresses thyroid activity |
| Chromium | Legumes, cereals, organ meats, fats, vegetable oils, meats, whole grains | Constituent of some enzymes; involved in glucose and energy metabolism | Not reported in humans; impaired ability to metabolize glucose | Inhibition of enzymes Occupational exposures: skin and kidney damage |

blood clotting, nerve impulse transmission, activation of several enzymes, synthesis of calcitriol (active form of vitamin D), and transport of fluids across cell membranes. It also may contribute to easing premenstrual syndrome, preventing colon cancer, and optimizing blood pressure regulation, ${ }^{49,123}$ although its role in reducing heart disease risk remains unclear. ${ }^{1,90}$

## Osteoporosis: Calcium, Estrogen, and Exercise

Bone, a dynamic tissue matrix of collagen and minerals, exists in a continual state of flux called remodeling. Most of the adult skeleton is replaced about every 10 years. Bone-destroying
TABLE 2.4 Dietary Reference Intakes (DRIs): Recommended Mineral Intakes and Tolerable Upper Intake Levels (UL ${ }^{\text {a }}$ )
Recommended Mineral Intakes

| Recommended Mineral Intakes |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Life Stage Group | Calcium (mg/d) | Chromium ( $\mu \mathrm{g} / \mathrm{d}$ ) | Copper <br> ( $\mu \mathrm{g} / \mathrm{d}$ ) | Fluoride (mg/d) | lodine ( $\mu \mathrm{g} / \mathrm{d}$ ) | Iron (mg/d) | Magnesium (mg/d) | Manganese (mg/d) | Molybdenum ( $\mu \mathrm{g} / \mathrm{d}$ ) | Phosphorus (mg/d) | Selenium ( $\mu \mathrm{g} / \mathrm{d}$ ) | $\begin{aligned} & \text { Zinc } \\ & (\mathrm{mg} / \mathrm{d}) \end{aligned}$ |
| Infants |  |  |  |  |  |  |  |  |  |  |  |  |
| 06 mo | 210* | 0.2* | 200* | 0.01* | 110* | 0.27* | 30* | 0.003* | 2* | 100* | 15* | 2* |
| 712 mo | 270* | 5.5* | 220* | 0.5* | 130* | 11* | 75* | 0.6* | 3* | 275* | 20* | 3 |
| Children |  |  |  |  |  |  |  |  |  |  |  |  |
| 13 y | 500* | 11* | 340 | 0.7* | 90 | 7 | 80 | 1.2* | 17 | 460 | 20 | 3 |
| 48 y | 800* | 15* | 440 | 1* | 90 | 10 | 130 | 1.5* | 22 | 500 | 30 | 5 |
| Males |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | 1,300 | 25* | 700 | 2* | 120 | 8 | 240 | 1.9* | 34 | 1,250 | 40 | 8 |
| 1418 y | 1,300* | 35* | 890 | 3* | 150 | 11 | 410 | 2.2* | 43 | 1,250 | 55 | 11 |
| 1930 y | 1,000* | 35* | 900 | 4* | 150 | 8 | 400 | 2.3* | 45 | 700 | 55 | 11 |
| 3150 y | 1,000* | 35* | 900 | 4* | 150 | 8 | 420 | 2.3* | 45 | 700 | 55 | 11 |
| 5170 y | 1,200* | 30* | 900 | 4* | 150 | 8 | 420 | 2.3* | 45 | 700 | 55 | 11 |
| $>70$ y | 1,200* | 30* | 900 | 4* | 150 | 8 | 420 | 2.3* | 45 | 700 | 55 | 11 |
| Females |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | 1,300* | 21* | 700 | 2* | 150 | 8 | 240 | 1.6* | 34 | 1,250 | 40 | 8 |
| 1418 y | 1,300* | 24* | 890 | 3* | 150 | 15 | 360 | 1.6* | 43 | 1,250 | 55 | 9 |
| 1930 y | 1,000* | 25* | 900 | 3* | 150 | 18 | 310 | 1.8* | 45 | 700 | 55 | 8 |
| 3150 y | 1,000* | 25* | 900 | 3* | 150 | 18 | 320 | 1.8* | 45 | 700 | 55 | 8 |
| 5170 y | 1,200* | 20* | 900 | 3* | 150 | 8 | 320 | 1.8* | 45 | 700 | 55 | 8 |
| $>70$ y | 1,200* | 20* | 900 | 3* | 150 | 8 | 320 | 1.8* | 45 | 700 | 55 | 8 |
| Pregnancy |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | 1,300* | 29* | 1,000 | 3* | 220 | 27 | 400 | 2.0* | 50 | 1,250 | 60 | 13 |
| 1930 y | 1,000* | 30* | 1,000 | 3* | 220 | 27 | 350 | 2.0* | 50 | 700 | 60 | 11 |
| 3150 y | 1,000* | 30* | 1,000 | 3* | 220 | 27 | 360 | 2.0* | 50 | 700 | 60 | 11 |
| Lactation |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | 1,300* | 44* | 1,300 | 3* | 290 | 10 | 360 | 2.6* | 50 | 1,250 | 70 | 14 |
| 1930 y | 1,000* | 45* | 1,300 | 3* | 290 | 9 | 310 | 2.6* | 50 | 700 | 70 | 12 |
| 3150 y | 1,000* | 45* | 1,300 | 3* | 290 | 9 | 320 | 2.6* | 50 | 700 | 70 | 12 |

[^16]TABLE 2.4 Dietary Reference Intakes (DRIs): Recommended Mineral Intakes and Tolerable Upper Intake Levels (UL ${ }^{\text {a }}$ ) continued

| Tolerable Upper Intake Levels ${ }^{\text {a }}$ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Life Stage Group | Arsenic ${ }^{\text {b }}$ | Boron (mg/d) | Calcium ( $\mathrm{g} / \mathrm{d}$ ) | Chromium | Copper ( $\mu \mathrm{g} / \mathrm{d}$ ) | Fluoride (mg/d) | lodine ( $\mu \mathrm{g} / \mathrm{d}$ ) | $\begin{aligned} & \text { Iron } \\ & (\mathrm{mg} / \mathrm{d}) \end{aligned}$ | Magnesium $(\mathrm{mg} / \mathrm{d})^{c}$ | Manganese (mg/d) | Molybdenum ( $\mu \mathrm{g} / \mathrm{d}$ ) | Nickel (mg/d) | Phosphorus (g/d) | Selenium ( $\mu \mathrm{g} / \mathrm{d}$ ) | Silicon ${ }^{\text {d }}$ | Vanadium (mg/d) ${ }^{e}$ | $\begin{aligned} & \text { Zinc } \\ & (\mathrm{mg} / \mathrm{d}) \end{aligned}$ |
| Infants | ND ${ }^{f}$ | ND | ND | ND | ND | 0.7 | ND | 40 | ND | ND | ND | ND | ND | 45 | ND | ND | 4 |
| $\begin{aligned} & 06 \mathrm{mo} \\ & 7 \quad 12 \mathrm{mo} \end{aligned}$ | ND | ND | ND | ND | ND | 0.9 | ND | 40 | ND | ND | ND | ND | ND | 60 | ND | ND | 5 |
| Children |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13 y | ND | 3 | 2.5 | ND | 1,000 | 1. | 200 | 40 | 65 | 2 | 300 | 0.2 | 3 | 90 | ND | ND | 7 |
| 48 y | ND | 6 | 2.5 | ND | 3,000 | 2.2 | 300 | 40 | 110 | 3 | 600 | 0.3 | 3 | 150 | ND | ND | 12 |
| Males, females |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 913 y | ND | 11 | 2.5 | ND | 5,000 | 10 | 600 | 40 | 350 | 6 | 1,100 | 0.6 | 4 | 280 | ND | ND | 23 |
| 1418 y | ND | 17 | 2.5 | ND | 800 | 10 | 900 | 45 | 350 | 9 | 1,700 | 1.0 | 4 | 400 | ND | ND | 34 |
| 1970 y | ND | 20 | 2.5 | ND | 10,000 | 10 | 1,100 | 45 | 350 | 11 | 2,000 | 1.0 | 4 | 400 | ND | 1.8 | 40 |
| $>70 \mathrm{y}$ | ND | 20 | 2.5 | ND | 10,000 | 10 | 1,100 | 45 | 350 | 11 | 2,000 | 1.0 | 3 | 400 | ND | 1.8 | 40 |
| Pregnancy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | ND | 17 | 2.5 | ND | 8,000 | 10 | 900 | 45 | 350 | 9 | 1,700 | 1.0 | 3.5 | 400 | ND | ND | 34 |
| 1950 y | ND | 20 | 2.5 | ND | 10,000 | 10 | 1,100 | 45 | 350 | 11 | 2,000 | 1.0 | 3.5 | 400 | ND | ND | 40 |
| Lactation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| $\leq 18$ y | ND | 17 | 2.5 | ND | 8,000 | 10 | 900 | 45 | 350 | 9 | 1,700 | 1.0 | 4 | 400 | ND | ND | 34 |
| 1950 y | ND | 20 | 2.5 | ND | 10,000 | 10 | 1,100 | 45 | 350 | 11 | 2,000 | 1.0 | 4 | 400 | ND | ND | 40 |

${ }^{a}$ UL $=$ The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for arsenic, chromium, and silicon. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.
Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.
${ }^{d}$ Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.
${ }^{d}$ Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.
Athough vanadium in food has not been shown to cause adverse effects in humans, there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is based on
adverse effects in laboratory animals and this data could be used to set a UL for adults but not children and adolescents.
${ }^{f} \mathrm{ND}=$ not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels
(Intakes for Calcium, Phosphorous, Magnesium, Vitamin D and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B 6 , Folate, Vitamin B ${ }_{12}$, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); and Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001).
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Figure 2.8 Minerals that function in macronutrient catabolism and anabolism.
cells (osteoclasts), under the influence of parathyroid hormone, cause the breakdown or resorption of bone by enzyme action, while bone-forming osteoblast cells induce bone synthesis. Calcium availability affects the dynamics of bone remodeling. The two broad categories of bone include:

1. Cortical bone: dense, hard outer layer of bone such as the shafts of the long bones of the arms and legs
2. Trabecular bone: spongy, less dense, and relatively weaker bone, most prevalent in the vertebrae and ball of the femur

## fyi <br> Bone Health Diagnostic Criteria Based on Variation (Standard Deviation [sd]) of Observed Bone Density Values Compared to Values for Sex-Matched Young Adult Population <br> Normal <br> Osteopenia <br> Osteoporosis <br> Severe osteoporosis <br> $<1.0 \mathrm{SD}$ below mean <br> 1.0 to 2.5 SD below mean <br> $>2.5$ SD below mean <br> $>2.5$ SD below mean plus one or more fragility fractures

Calcium from food or calcium derived from bone resorption maintains plasma calcium levels. As a general guideline, adolescents and young adults require 1300 mg of calcium daily ( 1000 mg for adults ages 19 to 50 and 1200 mg for those older than 50 ) or the calcium in five $8-\mathrm{oz}$ glasses of milk. Unfortunately, calcium remains one of the most frequent nutrients lacking in the diet of sedentary and physically active individuals, particularly adolescent girls. For a typical adult, daily calcium intake ranges between 500 and 700 mg . Among athletes, female dancers, gymnasts, and endurance competitors are most prone to calcium dietary insufficiency. ${ }^{18,128}$

Inadequate calcium intake or low levels of calciumregulating hormones cause withdrawal of calcium reserves in bone to restore any deficit. Prolonging this restorative imbalance promotes one of two conditions:

1. Osteopenia-from the Greek words osteo, meaning bone, and penia, meaning poverty -a midway condition where bones weaken with increased risk of fractures.
2. Osteoporosis, literally meaning porous bones, with bone density more than 2.5 standard deviations below normal for gender. Osteoporosis develops progressively as bone loses its calcium mass (bone mineral content) and calcium concentration (bone mineral density). This deterioration causes bone to progressively become more porous and brittle (Fig. 2.9). Eventually, the stresses of normal living can cause bone to break, with compression fractures of the spine occurring most frequently.

## fyi

## Risk Factors for Osteoporosis

Advancing age
History of fracture as an adult, regardless of cause
History of fracture in a parent or sibling
Cigarette smoking
Slight build or tendency toward underweight
White or Asian female
Sedentary lifestyle
Early menopause
Eating disorder
High protein intake (particularly animal protein)
Excess sodium intake
Alcohol abuse
Calcium-deficient diet before and after menopause High caffeine intake (equivocal)
Vitamin D deficiency, either through inadequate exposure to sunlight or dietary insufficiency (prevalent in about $40 \%$ of adults)

## INTEGRATIVE QUESTION

Discuss the interactions between physical activity and calcium intake and bone health.

## A Disease of Considerable Prevalence

Osteoporosis is a major health risk for about 28 million Americans, with an estimated 10 million U.S. residents suffering from osteoporosis and another 18 million suffering from low bone mass and at risk for developing the disease. Fifty percent of all women eventually develop osteoporosis. Men are not immune-about 2 million suffer from this disease. Osteoporosis accounts for more than 1.5 million fractures (the clinical manifestation of the disease) yearly, including about 700,000 vertebral fractures, 300,000 hip fractures, 250,000 wrist fractures, and 300,000 fractures at other sites. On average, $24 \%$ of hip fracture patients aged 50 and over die in the year following their fracture.


Figure 2.9 Radiograph of mid-second metacarpal of person with normal mineralization (left) and of patient with severe osteoporosis (right). Under normal conditions, cortical width (arrows) is more than one third of the total width of the metacarpal, whereas osteoporosis produces extreme cortical narrowing. Note the intracortical tunneling that occurs in more aggressive forms of osteoporosis. (From Brant W, Helms C. Fundamentals of diagnostic radiology. 3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2006.)

One of two women and one of eight men over age 50 will experience an osteoporosis-related fracture in their lifetime. Increased susceptibility to osteoporosis among older women coincides with menopause and the marked decrease in estradiol secretion, the most potent naturally occurring human estrogen. Exactly how estrogen exerts its protective effects on bone remains unknown (see p. 65 for estrogen s possible actions). Most men normally produce some estrogen into old age-a major reason why they exhibit a relatively lower prevalence of osteoporosis. A portion of circulating testosterone converts to estradiol, which also promotes positive calcium balance. Osteoporosis risk factors for men include low testosterone levels, cigarette smoking, and steroid use.

## A Progressive Disease

Between 60 and $80 \%$ of an individual s susceptibility to osteoporosis links to genetic factors, while 20 to $40 \%$ remains lifestyle related. The early teens serve as the prime years to maximize bone mass. ${ }^{17,127}$ Adequate intake of calcium and vitamin D (maintains normal blood levels of calcium and bone mineralization) ${ }^{110,193}$ and regular physical activity (with a synergistic effect of both variables on bone mass in children ${ }^{165}$ ) enable women to gain bone mass throughout the third decade of life. Osteoporosis for many women begins early in life because the average teenager consumes suboptimal calcium to
support growing bones. This creates an irreversible deficit that cannot be fully eliminated after achieving skeletal maturity. Calcium imbalance worsens into adulthood, particularly among women with a genetic predisposition. ${ }^{66,115,198}$

## Prevention Through Diet

Figure 2.10A illustrates that a complex interaction among the factors rather than the separate influence of each factor contributes to the variation in bone mass. ${ }^{121,181}$ That portion of bone mass variation attributable to diet may actually reflect how diet interacts with genetic factors, physical activity patterns, body weight, and drug or medication use (e.g., estrogen therapy). Adequate calcium intake throughout life remains the prime defense against bone loss with age. ${ }^{17,95}$ For example, calcium supplementation in postmenarchal girls with suboptimal calcium intake enhanced bone mineral acquisition. ${ }^{166}$ Adolescent girls should consume 1500 mg of calcium daily. Increasing daily calcium intake for middle-aged women, particularly estrogen-deprived women following menopause, to 1200 to 1500 mg improves the body s calcium balance. ${ }^{77,151}$

Good dietary calcium sources include milk and milk products, sardines and canned salmon, kidney beans, and dark green leafy vegetables. Calcium supplements, best absorbed on an empty stomach, can also correct dietary deficiencies regardless of whether the extra calcium comes from fortified foods or commercial supplements. Calcium citrate causes less stomach upset than other supplement forms; it also enhances iron absorption better than calcium gluconate, calcium carbonate, or other commercial products. Adequate availability of vitamin D (currently estimated at 400 IU daily for persons 51 to 70 and 600 IU for those over 70) facilitates calcium uptake. Excessive meat, salt, coffee, and alcohol consumption inhibits absorption. Individuals who live and train (primarily indoors) in northern latitudes, should supplement with 200 IU of vitamin D daily. ${ }^{7}$ Bone matrix formation also depends on vitamin K, prevalent in leafy green and cruciferous vegetables. The RDA for vitamin $K$ is $90 \mu \mathrm{~g}$ for women and $120 \mu \mathrm{~g}$ for men.

## fyi

## Six Principles for Promoting Bone Health Through Exercise

1. Specificity: Exercise provides a local osteogenic effect.
2. Overload: Progressively increasing exercise intensity promotes continued bone deposition.
3. Initial values: Individuals with the smallest total bone mass show the greatest potential for bone deposition.
4. Diminishing returns: As one approaches the biologic ceiling for bone density, further density gains require greater effort.
5. More not necessarily better: Bone cells become desensitized in response to prolonged mechani-cal-loading sessions.
6. Reversibility: Discontinuing exercise overload reverses the positive osteogenic effects gained through appropriate exercise stress.


Figure 2.10 A. Variation in bone mass within the population is likely a function of how the different factors that affect bone mass interact with each other. (Modified from Specker BL. Should there be dietary guidelines for calcium intake? Am J Clin Nutr 2000;71:663.) B. Weight-bearing exercise augments skeleton mass during growth above the genetic baseline. The degree of augmentation depends largely on the amount of mechanical loading on a particular bone. (Modified from Turner CH. Site-specific effects of exercise: importance of interstitial fluid pressure. Bone 1999;24:161.)

Exercise Benefits. Mechanical loading through regular exercise slows the rate of skeletal aging. Regardless of age or gender, children and adults who maintain an active lifestyle have greater bone mass than sedentary counterparts. ${ }^{4,5,76,143,187}$ Benefits of regular exercise on bone mass accretion (and perhaps bone shape and size) are greatest during childhood and adolescence when peak bone mass increases to the greatest extent (Fig. 2.10B). ${ }^{6,105,134}$ These benefits often accrue into the seventh and eighth decades of life. ${ }^{192,204}$ The decline in vigorous exercise with a sedentary lifestyle with aging closely parallels age-related bone mass loss. In this regard, regular moderate physical activity associates with higher values for cortical bone measures ${ }^{172}$ and a substantially lower risk of hip fracture in postmenopausal women. ${ }^{56,167}$

The osteogenic effect of exercise and everyday physical activity is most effective during the growth periods (childhood and adolescence) and may reduce fracture risk later in life. ${ }^{17,91,98}$ Short bouts of intense mechanical loading of bone with dynamic exercise three to five times a week provide a potent stimulus to maintain or increase bone mass. Figure 2.11 illustrates the beneficial effects of resistance exercises and circuit-resistance training or weight-bearing walking, running, dancing, rope skipping, or gymnastics. These exercises generate a considerable impact load and/or intermittent force against the long bones of the body. ${ }^{47,113,212}$ Men and women in strength and power activities have as much or more bone mass than endurance athletes. ${ }^{158}$ Activities with relatively high impact and strain on the skeletal mass (e.g., volleyball, basketball, and gymnastics) induce the greatest increases in bone mass, particularly at weight-bearing sites. ${ }^{9,36,178}$

Bone mineral density and mass relate directly to measures of muscular strength and regional and total lean tissue mass. ${ }^{38,136}$ For example, lumbar spine and proximal femur bone masses of elite teenage weightlifters exceed representative values for fully mature bone of reference adults. ${ }^{34}$ Eccentric exercise training provides a more potent site-specific osteogenic stimulus than concentric muscle training because greater forces usually occur with eccentric muscle loading. ${ }^{75}$ Prior exercise and sports experience offer residual effects on an adult s bone mineral density. Exercise-induced increases in bone mass achieved during teenage and young-adult years remain despite cessation of active competition. ${ }^{102,104}$

Site-Specific Effects. In a normal hormonal milieu, muscle forces acting on specific bones during physical activity (particularly intermittent compression and tension mechanical loading) modify bone metabolism at the point of stress. ${ }^{13,86,99}$ For example, the lower limb bones of older cross-country runners have greater bone mineral content than the bones of less active counterparts. The throwing arm of baseball players also shows greater bone thickness than the less-used, nondominant arm. Likewise, the bone mineral content of the humeral shaft and proximal humerus of the playing arm of tennis players averages 20 to $25 \%$ more than the nondominant arm; side-to-side difference in the arms of nonplayers generally averages only $5 \% .{ }^{104}$ For females, this response is most noticeable in players who begin training before menarche. ${ }^{97}$


Figure 2.11 Bone mineral density expressed as a percentage of sedentary control values at three skeletal sites for runners, swimmers, and weightlifters. (From Drinkwater BL. Physical activity, fitness, and osteoporosis. In: Bouchard C, et al., eds. Physical activity, fitness, and health. Champaign, IL: Human Kinetics, 1994.)

Mechanism for Increase. Prevailing theory considers that dynamic loading creates hydrostatic pressure gradients within a bone s fluid-filled matrix. Fluid movement within this matrix in response to pressure changes from dynamic exercise generates fluid shear stress on bone cells. This initiates a cascade of cellular events to ultimately stimulate the production of bone matrix protein. ${ }^{197}$ Mechanosensitivity of bone and its subsequent buildup of calcium depends on two factors: (1) magnitude of the applied force (strain magnitude) and (2) frequency or number of cycles of application.

Owing to the transient sensitivity of bone cells to mechanical stimuli, shorter, more frequent periods of highfrequency force (mechanical strain) with rest periods interspersed facilitate bone mass accretion. ${ }^{72,108,159}$ As applied force and strain increase, the number of cycles required to initiate bone formation decrease. ${ }^{37}$ Chemicals produced in bone itself also contribute to bone formation. Alterations in bone s geometric configuration to long-term exercise training enhance its mechanical properties. ${ }^{11}$ Figure 2.12 illustrates the anatomic structure and cross-sectional view of a typical long bone and depicts the dynamics of bone growth and remodeling.

## THE FEMALE ATHLETE TRIAD: UNEXPECTED PROBLEM FOR WOMEN WHO TRAIN INTENSELY

A paradox exists between exercise and bone dynamics for athletic premenopausal women, particularly young athletes who have not attained peak bone mass (see Focus on Research ). Women who train intensely and emphasize weight loss often engage in disordered eating behaviors that link to menstrual irregularities, primarily amenorrhea (cessation of menstrual flow). Disordered eating behaviors eventually lead to the
female athlete triad (Fig. 2.13)—energy drain, amenorrhea, and osteoporosis. ${ }^{33,179,216,117}$

The term female triad more accurately describes the syndrome of disorders because it also afflicts physically active women in the general population who do not fit the typical profile of the competitive athlete.

## INTEGRATIVE QUESTION

Why do resistance exercises for the bodys major muscle groups offer unique benefits to bone mass compared with a typical weight-bearing program of brisk walking?

Many young women who play sports likely suffer from at least one of the triad s disorders, particularly disordered eating behaviors and accompanying energy deficit. This malady afflicts 15 to $60 \%$ of female athletes, most prominently those involved in leanness-related sports. ${ }^{103}$ Figure 2.14 illustrates the contributing factors to exercise-related amenorrhea, considered the red flag, or most recognizable symptom for the triad s presence. The prevalence of amenorrhea among athletes in body weight related sports (distance running, gymnastics, ballet, cheerleading, figure skating, and body building) probably ranges between 25 and $65 \%$; no more than $5 \%$ of the general population of women of menstruating age experience this condition.

## INTEGRATIVE QUESTION

Advise a group of high school females about strategies to achieve weight loss to compete successfully and healthfully in competitive gymnastics.


Figure 2.12 Anatomic structure (A) and longitudinal view of a typical long bone, and (B) bone dynamics during growth and continual remodeling.

Bone density relates closely to menstrual regularity and the total number of menstrual cycles. Premature cessation of menstruation removes estrogen s protective effect on bone, making these young women more vulnerable to calcium loss with concomitant decrease in bone mass. ${ }^{28,70,215}$ The most severe menstrual disorders produce the greatest
negative effect on bone mass. ${ }^{27,195}$ Lowered bone density from extended amenorrhea often occurs at multiple sites, including bone areas regularly subjected to increased force and impact loading during exercise. ${ }^{152}$ Concurrently, the problem worsens in individuals undergoing an energy deficit accompanied by low protein, lipid, and energy intakes. ${ }^{217}$


Figure 2.13 The female athlete triad: disordered eating, amenorrhea, and osteoporosis. (From American College of Sports Medicine Position Stand. The female athlete triad. Med Sci Sports Exerc 2007;39:1867.)

In such cases, a poor diet also provides inadequate calcium intake.

Persistent amenorrhea that begins at an early age diminishes the benefits of exercise on bone mass; it also increases the risk of musculoskeletal injuries, particularly repeated stress fractures during exercise. ${ }^{130}$ A 5\% loss in bone mass increases the risk of stress fractures by nearly $40 \%$. Reestablishing normal menses causes some regain in bone mass but not to levels achieved with normal menstruation. Bone mass often remains permanently at suboptimal levels throughout adult lifeleaving the woman at increased risk for osteoporosis and stress fractures, even years following competitive athletic participation. ${ }^{45,125}$ Successful nonpharmacologic treatment of athletic amenorrhea uses a four-phase behavioral approach plus diet and training interventions: ${ }^{46}$

1. Reduce training level by 10 to $20 \%$
2. Gradually increase total energy intake
3. Increase body weight by 2 to $3 \%$
4. Maintain calcium intake at 1500 mg daily

## fyi

## Estrogens Role in Bone Health

Increases intestinal calcium absorption Reduces urinary calcium excretion Inhibits bone resorption
Decreases bone turnover

## PHOSPHORUS

Phosphorus combines with calcium to form hydroxyapatite and calcium phosphate-compounds that give rigidity to bones and teeth. Phosphorus also serves as an essential component of the intracellular mediator cyclic adenosine monophosphate (cAMP) and the intramuscular high-energy compounds adenosine triphosphate (ATP) and phosphocreatine (PCr). Phosphorus combines with lipids to form phospholipid compounds, integral components of the cells bilayer plasma membrane. The phosphorous-containing phosphatase enzymes regulate cellular metabolism; phosphorus also buffers acid end products of energy metabolism. In Chapter 23, we discuss the usefulness of buffering agents for augmenting intense exercise performance. Athletes usually consume adequate phosphorus, with the possible exception of the low-energy diets of many female dancers and gymnasts. ${ }^{18,128}$ Rich dietary sources of phosphorus include meat, fish, poultry, milk products, and cereals.

## MAGNESIUM

Only about $1 \%$ of the body s 20 to 30 g of magnesium is found in blood, with about one-half of the stores present inside cells of tissues and organs and the remainder combined with calcium and phosphorus in bone. About 400 enzymes that regulate metabolic processes contain magnesium. Magnesium plays an important role in glucose metabolism by


Figure 2.14 Contributing factors to the development of exercise-related amenorrhea.
facilitating muscle and liver glycogen formation from bloodborne glucose. It also participates as a cofactor in glucose, fatty acid, and amino acid breakdown during energy metabolism. Magnesium affects lipid and protein synthesis and contributes to optimal neuromuscular functioning. It acts as an electrolyte, which along with potassium and sodium helps to maintain blood pressure.

By regulating deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis and structure, magnesium affects cell growth, reproduction, and plasma membrane integrity. Because of its role as a $\mathrm{Ca}^{+2}$ channel blocker, inadequate magnesium could lead to hypertension and cardiac arrhythmias. Sweating produces only small losses of magnesium.

Conflicting data exist concerning the possible effects of magnesium supplements on exercise performance and the training response. In one study, magnesium supplementation
did not affect quadriceps muscle strength or measures of fatigue in a 6 -week period following a marathon. ${ }^{196}$ Subsequent research showed that 4 weeks of a 212 mg per day magnesium oxide supplement increased resting magnesium levels but not anaerobic or aerobic exercise performance compared with a placebo. ${ }^{57}$ In contrast, other research shows that untrained men and women who supplemented with magnesium increased quadriceps power compared with a placebo treatment during 7 weeks of resistance training. ${ }^{22}$

The magnesium intake of athletes generally attains recommended levels, although female dancers and gymnasts were reported to have relatively low intakes. ${ }^{18,128}$ The magnesium content of refined foods is usually low. Whole-wheat bread, for example, contains twice the magnesium of white bread because processing removes the magnesium-rich germ and bran. In addition, the nation $s$ water supply provides a

## FOCUS ON RESEARCH

## Female Athletes with Osteoporosis


#### Abstract

Drinkwater BL, et al. Menstrual history as a determinant of current bone density in young athletes. JAMA 1990;263:545.


> Research on female athletes has focused on their reduced bone mineral density associated with menstrual dysfunctions (oligomenorrhea, irregular menstrual cycle; amenorrhea, menstrual cessation). Persistent amenorrhea often minimizes the benefits of exercise on bone mass, increasing risk of repeated stress fractures during exercise because osteoporosis develops at an early age.

A pioneering 1984 study by Drinkwater and colleagues linked amenorrhea in 14 female athletes with a statistically significant $13.8 \%$ decrease in spinal bone mineral density compared with age-matched eumenorrheic athletes. The researchers hypothesized that early onset and repeated menstrual dysfunction produced permanent suboptimal bone mass throughout life. The condition increased these women s risk for developing early osteoporosis and stress fractures, even after competitive athletics ceased and normal menstruation resumed.

A subsequent study by Drinkwater (6 years later and presented here), demonstrated that women with regular menstrual cycles maintained higher lumbar bone densities $\left(1.27 \mathrm{~g} \mathrm{~cm}^{2}\right)$ than athletic women with oligomenorrhea/ amenorrhea interspersed with regular cycles $\left(1.18 \mathrm{~g} \mathrm{~cm}^{2}\right)$. Moreover, the density of the lumbar bone region of both groups exceeded that of athletic women who never had regular cycles ( $1.05 \mathrm{~g} \mathrm{~cm}^{2}$ ).

The researchers studied 97 active women aged 18 to 38 years. No woman smoked, and all exercised regularly at least 4 days per week for 45 minutes or longer per session. None of the women used oral contraceptives, and none experienced medical problems with bone metabolism. The following definitions defined current menstrual status: regular (10 to 13 periods per year), oligomenorrheic (3 to 6 periods per year at intervals longer than 36 days), or amenorrheic (no more than 2 periods per year or no period
during the last 6 months). Assays for estradiol and progesterone levels confirmed menstrual status. Menstrual history included one of three categories: always had regular menses (R), had episodes of oligomenorrhea (O), or amenorrhea (A). Two reproductive endocrinologists ranked subjects on a scale from 1 to 9 on their expectations for bone mass for all combinations of reported present and past menstrual patterns. A pattern of always maintaining regular menses ( $R / R$ ) ranked first as the most positive effect on bone. Current amenorrheics who also exhibited previous amenorrhea (A/A) received the lowest rank (ninth) for the physician s expectation of identifying women with the most negative bone pattern.

The main figure displays vertebral bone density versus menstrual history for the 97 women. The plot includes the averages and variability for the menstrual groupings (only means with 5 or more subjects plotted) containing the following numbers of subjects per grouping: $1, \mathrm{R} / \mathrm{R}(n=$ 21); 2, R/O $(n=7) ; 3, \mathrm{O} / \mathrm{R}(n=2) ; 4, \mathrm{O} / \mathrm{O}(n=5) ; 5$, R/A $(n=22) ; 6, \mathrm{~A} / \mathrm{R}(n=9) ; 7, \mathrm{O} / \mathrm{A}(n=10) ; 8, \mathrm{~A} / \mathrm{O}$ $(n=10) ; 9$ A/A $(n=11)$. Statistical analyses revealed significant bone mineral density differences between group 1 and groups 8 and 9 , but no statistically significant differences among groups 2 through 7. Thus, the researchers merged the nine groups into three subgroups: group 1, women who always maintained regular menses (R/R); group 2, women with bouts of oligomenorrhea or amenorrhea interspersed with regular menses and women with current oligomenorrhea ( $\mathrm{R} / \mathrm{O} / \mathrm{A}$ ); and group 3, women with current amenorrhea who experienced previous amenorrhea or oligomenorrhea (O/A). The inset figure relates the three subgroups to bone mineral density. Women who always menstruated regularly had the highest bone density values, women with occasional irregularity averaged $6 \%$ less bone density, and women who never menstruated regularly averaged $17 \%$ less. The third group was younger, weighed less, and experienced menarche at an older age. They also began to train seriously earlier in

Continued on page 68
ready source of magnesium, but the amount varies according to the source. Hard water contains more magnesium than soft water. We do not recommend taking magnesium supplements because these often are mixed with dolomite $\left(\mathrm{CaMg}\left(\mathrm{CO}_{3}\right)_{2}\right.$, an extract from dolomitic limestone and marble), which often contains the toxic elements mercury and lead. Green leafy vegetables, legumes, nuts, bananas, mushrooms, and whole grains provide rich magnesium sources.

## IRON

The body normally contains between 2.5 and 4.0 g (about $1 / 6 \mathrm{oz}$ ) of the trace mineral iron. Seventy to $80 \%$ exists in functionally active compounds, predominantly combined with hemoglobin in red blood cells ( $85 \%$ of functional iron). This iron protein compound increases the blood s oxygencarrying capacity 65 times. Iron serves other important

## FOCUS ON RESEARCH

life, they trained more frequently and for longer durations each day and traversed more miles than women who always maintained regular menses (group 1).

These studies suggest that prolonged oligomenorrhea/ amenorrhea may irreversibly decrease vertebral bone density; the condition becomes exacerbated in women with persistently low body weight.

The work of Drinkwater and colleagues also increased awareness in the research and medical communities about the importance of understanding interactions among bone mineral density and intense physical training, estrogen levels, menstrual dysfunction, low body weight, and suboptimal energy and nutrient intake. The research paved the way for more clinically relevant treatment of female athletes at increased risk of irreversible loss of bone mass.


Relationship between vertebral bone mineral density (BMD) and menstrual history for 97 young women. (Inset) Bone mineral densities in three groups based on menstrual status.
exercise-related functions including its role as a structural component of myoglobin ( $12 \%$ of functional iron), a compound similar to hemoglobin, which aids in oxygen storage and transport within the muscle cell. Small amounts of iron also exist in cytochromes that facilitate cellular energy transfer. About $20 \%$ of the body s iron does not combine in functionally active compounds and exists as hemosiderin and ferritin stored in the liver, spleen, and bone marrow. These stores replenish iron lost from the functional compounds and provide the iron reserve during periods of insufficient dietary iron intake. An iron-binding plasma glycoprotein, transferrin, transports iron from ingested food and damaged red blood cells to tissues in need, particularly the liver, spleen, bone marrow, and skeletal muscles. Plasma levels of transferrin often reflect the adequacy of the current iron intake.

Physically active individuals should consume normal amounts of iron-rich foods in their diet. Persons with inadequate iron intake or with limited rates of iron absorption or high rates of iron loss often develop a reduced concentration of hemoglobin in red blood cells, commonly called iron deficiency anemia, that produces general sluggishness, loss of appetite, pale skin, sore tongue, brittle nails, frontal headaches, dizziness, and reduced capacity to sustain even mild exercise.
Iron therapy normalizes the blood s hemoglobin content and exercise capacity. Table 2.5 gives recommendations for iron intake for children and adults.

## Females: A Population at Risk

Inadequate iron intake frequently occurs among young children, teenagers, and females of childbearing age, including many physically active women. ${ }^{149}$ In the United States, between 10 and $13 \%$ of premenopausal women suffer from low
iron intake and between 3 and 5\% are anemic by conventional diagnostic criteria. ${ }^{50,116}$ In addition, pregnancy can trigger a moderate iron deficiency anemia from the increased iron demand for both mother and fetus.

Iron loss from the 30 to 60 mL of blood generally lost during a menstrual cycle ranges between 15 and 30 mg . This requires an additional 5 mg of dietary iron daily for premenopausal females and increases the average monthly dietary iron requirement by 150 mg for synthesizing red blood cells lost during menstruation. Not surprisingly, 30 to $50 \%$ of American women experience dietary iron insufficiency from menstrual blood loss and limited dietary iron intake. The typical iron intake averages 6 mg of iron per 1000 calories of food consumed, with heme iron providing about $15 \%$ of the total iron.

## TABLE 2.5 Recommended Dietary Allowances for Iron

|  | Age (years) | Iron (mg) |
| :--- | :---: | :---: |
| Children | 110 | 10 |
| Males | 1118 | 12 |
|  | 19 | 10 |
| Females | 1150 | 15 |
|  | 51 | 10 |
|  | Pregnant | $30^{a}$ |
|  | Lactating | $15^{a}$ |

Food and Nutrition Board, National Academy of Sciences National Research Council, Washington, DC. www.iom.edu/CMS/3788.aspx ${ }^{a}$ Generally, this increased requirement cannot be met by ordinary diets; therefore, the use of 30 to 60 mg of supplemental iron is recommended.

## Exercise-Induced Anemia: Fact or Fiction?

Interest in endurance sports, with increased participation by women, has focused research on the influence of intense training on the body s iron status. The term sports anemia frequently describes reduced hemoglobin levels approaching clinical anemia ( $12 \mathrm{~g} \mathrm{dL}^{-1}$ of blood for women and $14 \mathrm{~g} \mathrm{dL}^{-1}$ for men) attributable to exercise training. Some researchers maintain that strenuous training creates an added demand for iron that often exceeds its intake. This would tax iron reserves and eventually lead to depressed hemoglobin synthesis and/or reduction in iron-containing compounds within the cell s energy transfer system. Individuals susceptible to an iron drain could experience reduced exercise capacity because of iron s crucial role in oxygen transport and use.

Intense physical training theoretically creates an augmented iron demand from three sources:

1. Small loss of iron in sweat ${ }^{207}$
2. Loss of hemoglobin in urine from red blood cell destruction with increased temperature, spleen activity, and circulation rates and from jarring of the kidneys and mechanical trauma from feet pounding on the running surface (called foot-strike hemolysis) ${ }^{96}$
3. Gastrointestinal bleeding with distance running unrelated to age, gender, or performance time ${ }^{26,156}$

## Real Anemia or Pseudoanemia?

Apparent suboptimal hemoglobin concentrations and hematocrits occur more frequently among endurance athletes, thus supporting the possibility of an exercise-induced anemia. However, reductions in hemoglobin concentration remain transient, occurring in the early phase of training and then returning toward pretraining values. Figure 2.15 illustrates the general response for hematologic variables for high school female cross-country runners during a competitive season. The decrease in hemoglobin concentration generally parallels the disproportionately large expansion in plasma volume with both endurance and resistance training (see Fig. 13.5). ${ }^{42,67,171}$ Several days of exercise training increase plasma volume by $20 \%$, while total red blood cell volume remains unchanged. Consequently, total hemoglobin (an important factor in endurance performance) remains the same or increases slightly with training, while hemoglobin concentration decreases in the expanding plasma volume. Despite this hemoglobin dilution, aerobic capacity and exercise performance improve with training.

Mechanical destruction of red blood cells occurs with vigorous exercise, along with some loss of iron in sweat. ${ }^{207}$ However, no evidence indicates that these factors strain an athlete s iron reserves and precipitate clinical anemia if iron intake remains at recommended levels. Applying stringent criteria for both anemia and insufficiency of iron reserves makes sports anemia much less prevalent than generally believed. ${ }^{204}$ For male collegiate runners and swimmers, no


High school female runners $\square$ Control group
Figure 2.15 Hemoglobin, red blood cell count, and hematocrit in female high school cross-country runners and a comparison group during the competitive season. (Adapted from Puhl JL, et al. Erythrocyte changes during training in high school women cross-country runners. Res Q Exerc Sport 1981;52:484.)
indications of the early stages of anemia were noted despite large changes in training volume and intensity during the competitive season. ${ }^{145}$ For female athletes, the prevalence of iron deficiency anemia did not differ in comparisons among specific athletic groups or with nonathletic controls. ${ }^{155}$

Factors Affecting Iron Absorption
Increase Iron Absorption
Acid in the stomach
Iron in heme form
High body demand for red blood cells (blood loss, high-altitude exposure, physical training, pregnancy)
Low body iron stores
Presence of mean protein factor (MPF)
Presence of vitamin C in small intestine

## Decrease Iron Absorption

Phytic acid (in dietary fiber)
Oxalic acid
Polyphenols (in tea and coffee)
High body iron stores
Excess of other minerals ( $\mathrm{Zn}, \mathrm{Mg}, \mathrm{Ca}$ ), particularly when taken as supplements Reduction in stomach acid Antacids

## Should Athletes Take an Iron Supplement?

Any increase in iron loss with exercise training (coupled with poor dietary habits) in adolescent and premenopausal women will strain an already limited iron reserve. This does not mean that all individuals in training should supplement with iron or that dietary iron insufficiency or iron loss caused by exercise produces sports anemia. It does suggest the importance of monitoring an athlete s iron status by periodic evaluation of hematologic characteristics and iron reserves, particularly athletes who supplement with iron. ${ }^{119,120}$ Measuring serum ferritin concentration provides useful information about iron reserves; values below $20 \mu \mathrm{~g} \mathrm{~L}^{1}$ for females and $30 \mu \mathrm{~g} \mathrm{~L}^{1}$ for males indicate depleted reserves.

For healthy individuals whose diets contain the recommended iron intake, excess iron either through diet or supplementation does not increase hemoglobin, hematocrit, or other measures of iron status or exercise performance. Potential harm exists from overconsumption or overabsorption of iron (particularly with the widespread use of vitamin C supplements, which facilitate iron absorption). ${ }^{58}$ Iron supplements should not be used indiscriminately. Excessive iron can accumulate to toxic levels and contribute to diabetes, liver disease, and heart and joint damage; it may even promote the growth of latent cancers and infectious organisms. ${ }^{135}$

## Importance of Iron Source

The small intestine absorbs about 10 to $15 \%$ of the total ingested iron, depending on iron status, the form of iron ingested, and the meal s composition. For example, the small intestine usually absorbs 2 to $5 \%$ of iron from plants (trivalent ferric or nonheme elemental iron), whereas iron absorption from animal (divalent ferrous or heme) sources increases to 10 to $35 \%$. The presence of heme iron, which represents
between 35 and $55 \%$ of iron in animal sources, also increases iron absorption from nonheme sources.

The relatively low bioavailability of nonheme iron places women on vegetarian-type diets at risk for developing iron insufficiency. Female vegetarian runners have a poorer iron status than counterparts who consume the same quantity of iron from predominantly animal sources. ${ }^{180}$ Including foods rich in vitamin C in the diet upgrades dietary iron bioavailability (see Fig. 2.1). This occurs because ascorbic acid prevents oxidation of ferrous iron to the ferric form, thus increasing nonheme iron s solubility for absorption at the alkaline pH of the small intestine. The ascorbic acid in one glass of orange juice stimulates a 3-fold increase in nonheme iron absorption from a breakfast. ${ }^{169}$ Heme sources of iron include beef, beef liver, pork, tuna, and clams; oatmeal, dried figs, spinach, beans, and lentils are good nonheme sources. Fiber-rich foods, coffee, and tea contain compounds that interfere with the intestinal absorption of iron (and zinc).

## Functional Anemia

A relatively high prevalence of nonanemic iron depletion exists among athletes in diverse sports as well as in recreationally active women and men. ${ }^{48,71,175}$ Low values for hemoglobin within the normal range often reflect functional anemia or marginal iron deficiency. Depleted iron stores and reduced iron-dependent protein production (e.g., oxidative enzymes) with a relatively normal hemoglobin concentration characterize this condition. Ergogenic effects of iron supplementation on aerobic exercise performance and training responsiveness occur for these iron-deficient athletes. ${ }^{23,24,61,63}$ Physically active but untrained women classified as iron depleted (serum ferritin $<16 \mu \mathrm{~g} \mathrm{~L}^{1}$ ) but not anemic ( $\mathrm{Hb}>12 \mathrm{~g} \mathrm{dL}^{1}$ ) received either iron therapy ( 50 mg ferrous sulfate) or a placebo twice daily for 2 weeks. ${ }^{80}$ All subjects then completed 4 weeks of aerobic training. The iron-supplemented group increased serum ferritin levels with only a small (nonsignificant) increase in hemoglobin concentration. The improvement in $15-\mathrm{km}$ endurance cycling time in the supplemented group was twice that of women who consumed the placebo ( 3.4 vs . 1.6 min faster). Women with low serum ferritin levels but hemoglobin concentrations above $12 \mathrm{~g} \mathrm{dL}^{1}$, although not clinically anemic, might still be functionally anemic and thus benefit from iron supplementation to augment exercise performance. Similarly, iron-depleted but nonanemic women received either a placebo or 20 mg of elemental iron as ferrous sulfate twice daily for 6 weeks. Figure 2.16 shows that the iron supplement attenuated the rate of decrease in maximal force measured sequentially during 8 minutes of dynamic knee extension exercise. ${ }^{25}$

Current recommendations support iron supplementation for nonanemic physically active women with low serum ferritin levels. ${ }^{137}$ Supplementation in this case exerts little effect on hemoglobin concentration and red blood cell volume. Any improved exercise capacity likely occurs from increased muscle oxidative capacity, not the blood s increased oxygen transport capacity.


Figure $\mathbf{2 . 1 6}$ Maximal voluntary static contractions (MVCs) over the first 6 minutes of a progressive fatigue test of dynamic knee extensions before $(\odot)$ and after ( $)$ supplementation with either a placebo or iron. $\mathrm{MVC}_{\text {end }}$ represents the last MVC of the protocol and occurred at different times (average $\approx 8 \mathrm{~min}$ ) for each subject. (From Brutsaert TD, et al. Iron supplementation improves progressive fatigue resistance during dynamic knee extensor exercise in iron-depleted, nonanemic women. Am J Clin Nutr 2003;77:441.)

## SODIUM, POTASSIUM, AND CHLORINE

Sodium, potassium, and chlorine, collectively termed electrolytes, remain dissolved in the body fluids as electrically charged particles, or ions. Sodium and chlorine represent the chief minerals contained in blood plasma and extracellular fluid. Electrolytes modulate fluid exchange within the body s fluid compartments, promoting a constant, well-regulated exchange of nutrients and waste products between the cell and its external fluid environment. Potassium is the chief intracellular mineral.

Table 2.6 lists normal values for serum and sweat electrolyte concentrations and the electrolyte and carbohydrate concentrations of common beverages.

## Optimal Sodium Intake

Aldosterone conserves sodium in the kidneys under conditions of low-to-moderate dietary sodium intake. In contrast, high dietary sodium blunts aldosterone release, with excess
sodium voided in the urine. This maintains sodium balance throughout a wide range of intakes. However, some individuals cannot adequately regulate excessive sodium intake. Abnormal sodium accumulation in bodily fluids increases fluid volume and elevates blood pressure to levels that pose a health risk.

Sodium intake in the United States regularly exceeds the recommended daily level for adults of 2400 mg , or the amount of one generous teaspoon of table salt (sodium makes up about $40 \%$ of salt). The typical Western diet contains about 4500 mg of sodium (8 to 12 g of salt) each day with three quarters from processed food and restaurant meals. This represents 10 times the 500 mg sodium requirement. Common sodium-rich dietary sources include monosodium glutamate (MSG), soy sauce, condiments, canned foods, baking soda, and baking powder.

## Sodium-Induced Hypertension

One first line of defense in treating high blood pressure eliminates excess sodium from the diet. Reducing sodium

TABLE 2.6 Electrolyte Concentrations in Blood Serum and Sweat, and Carbohydrate and Electrolyte Concentrations of Some Popular Beverages

| Substance | $\mathbf{N a}^{+}$ <br> $\left(\mathbf{m E q} \cdot \mathbf{L}^{-\mathbf{1}}\right)^{a}$ | $\mathbf{K}^{+}$ <br> $\left(\mathbf{m E q} \cdot \mathbf{L}^{-\mathbf{1}}\right)$ | $\mathbf{C a}^{++}$ <br> $\left(\mathbf{m E q} \cdot \mathbf{L}^{-\mathbf{1}}\right)$ | $\mathbf{M g}^{++}$ <br> $\left(\mathbf{m E q} \cdot \mathbf{L}^{-\mathbf{1}}\right)$ | $\mathrm{Cl}^{-}$ <br> $\left(\mathbf{m E q} \cdot \mathbf{L}^{-\mathbf{1}}\right)$ | Osmolality <br> $\left(\mathbf{m O s m} \cdot \mathbf{L}^{-\mathbf{1}}\right)^{\boldsymbol{b}}$ | $\mathbf{C H O}$ <br> $\left(\mathbf{g} \cdot \mathbf{L}^{-\mathbf{1}}\right)^{\boldsymbol{c}}$ |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Blood serum | 140 | 4.5 | 2.5 | 1.52 .1 | 110 | 300 | - |
| Sweat | 60 | 80 | 4.5 | 1.5 | 3.3 | 4090 | 170220 |
| Coca Cola | 3.0 | - | - | - | 1.0 | - |  |
| Gatorade | 23.0 | 3.0 | - | - | 14.0 | 650 | 107 |
| Fruit juice | 0.5 | 58.0 | - | - | - | 690 | 62 |
| Pepsi Cola | 1.7 | Trace | - | - | Trace | 568 | 118 |
| Water | Trace | Trace | - | - | Trace | 1020 | 81 |

${ }^{a}$ Milliequivalents per liter.
${ }^{b}$ Milliosmoles per liter.
${ }^{c}$ Grams per liter.
intake can lower blood pressure via reduced plasma volume depending on the person s responsiveness to NaCl intake. ${ }^{106}$ For salt-sensitive individuals ( $30 \%$ of hypertensive adults, $30 \%$ with prehypertension, and nearly $90 \%$ who eventually get hypertension if they live to age 75), reducing dietary sodium to the low end of the recommended range and upgrading the quality of the diet reduces blood pressure (see In a Practical Sense, p. 73). ${ }^{21,185,213}$ If dietary constraints prove ineffective in lowering blood pressure, diuretic drugs that induce water loss often become the next line of defense. Unfortunately, diuretics also produce losses in other minerals, particularly potassium. A potassium-rich diet (e.g., potatoes, bananas, oranges, tomatoes, and meat) should supplement diuretic use.

## MINERALS AND EXERCISE PERFORMANCE

Consuming mineral supplements above recommended levels on a long- or short-term basis does not benefit exercise performance or enhance training responsiveness.

## Mineral Loss in Sweat

Excessive water and electrolyte loss impairs heat tolerance and exercise performance. It also leads to severe dysfunction that culminates in heat cramps, heat exhaustion, or heat stroke. The yearly toll of heat-related deaths during spring and summer football practice provides a tragic illustration of the importance of fluid and electrolyte replacement. An athlete may lose up to 5 kg of water from sweating during practice or an athletic event. This corresponds to about 8.0 g of salt depletion, because each $\mathrm{kg}(1 \mathrm{~L})$ of sweat contains about 1.5 g of salt. Despite this potential for mineral loss, replacement of water lost through sweating becomes the crucial and immediate need.

## INTEGRATIVE QUESTION

Many young girls and women engaged in sports likely suffer from at least one of the disorders of the female athlete triad. Discuss factors related to this syndrome and how a coach might guard against their occurrence.

## Defense Against Mineral Loss

Sweat loss during vigorous exercise triggers a rapid, coordinated release of the hormones vasopressin and aldosterone and the enzyme renin, which reduce sodium and water loss through the kidneys. An increase in sodium conservation occurs even under extreme conditions as running a marathon in warm, humid weather when sweat output can equal 2 L per hour. Adding salt to the fluid or food ingested usually replenishes electrolytes lost in sweat. During a 20-day road race in Hawaii, runners maintained plasma minerals at normal levels when they consumed an unrestricted diet without mineral supplements. ${ }^{44}$ Salt supplements may be beneficial in prolonged exercise in the heat when fluid loss exceeds 4 or 5 kg . This can be achieved by drinking a 0.1 to $0.2 \%$ salt solution (adding 0.3 tsp of table salt per liter of water). ${ }^{3}$ While a mild potassium deficiency can occur with intense exercise during heat stress, maintaining an adequate diet usually ensures optimum potassium levels. ${ }^{35}$ An 8-oz glass of orange or tomato juice replaces almost all of the calcium, potassium, and magnesium lost in $3 \mathrm{~L}(3 \mathrm{~kg})$ of sweat.

## Trace Minerals and Exercise

Strenuous exercise may increase excretion of the following trace elements:

Chromium: required for carbohydrate and lipid catabolism and proper insulin function and protein synthesis

## IN A PRACTICAL SENSE

## Lowering High Blood Pressure with Dietary Intervention: The Dash Diet

Nearly 50 million Americans have hypertension, a condition that if left untreated increases the risk of stroke, heart attack, and kidney failure. Fifty percent of hypertensives actually seek treatment. Only about onehalf of these individuals achieve long-term success. One reason for the lack of compliance concerns possible side effects of readily available antihypertensive medication. For example, fatigue and impotence often discourage patients from maintaining a chronic medication schedule required by pharmacologic treatment of hypertension.

## THE DASH APPROACH

Research using DASH (Dietary Approaches to Stop Hypertension, www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf) shows that this diet lowers blood pressure in some individuals to the same extent as pharmacologic therapy and often more than other lifestyle changes. Two months of the diet reduced systolic pressure by an average of 11.4 mm Hg ; diastolic pressure decreased by 5.5 mm Hg . Every $2-\mathrm{mm} \mathrm{Hg}$ reduction in systolic


Consumer groups and the AMA urge the limitation of salt in foods to combat high blood pressure, prevalent in about $40 \%$ of the U.S. population. Adults now consume 4000 mg of sodium daily, almost double the 2400 mg ( 1 tsp of table salt) recommended. Much of this excess comes from restaurant and processed foods.

## IN A PRACTICAL SENSE

pressure lowers heart disease risk by $5 \%$ and stroke risk by $8 \%$. Further good news emerges from recent research that indicates that the standard DASH diet combined with a daily dietary salt intake of 1500 mg produced even greater blood pressure reductions than those achieved with the DASH diet only.

Table 1 shows the general nature of the DASH diet with its high content of fruits, vegetables, and dairy products, and low-fat composition. In addition, a 24 -year follow-up of women whose diets most closely resembled the DASH plan showed they were $24 \%$ less likely to develop heart disease and $18 \%$ less likely to have a stroke.

## Sample DASH Diet

TABLE 2 shows a sample DASH diet consisting of approximately 2100 calories (kCal). This level of energy intake provides a stable body weight for a typical $70-\mathrm{kg}$ person. More physically active and

Continued
heavier individuals should boost portion size or the number of individual items to maintain weight. Individuals desiring to lose weight or who are lighter and/or sedentary should eat less, but not less than the minimum number of servings for each food group shown below.

Bray GA, et al. A further subgroup analysis of the effect of the DASH diet and three sodium levels on blood pressure: results of the Dash-Sodium Trial. Am J Cardiol 2004; 94:222.
Fung TT, et al. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008;168:713.
Sacks FM, et al. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH): a multicenter controlled feeding study of dietary patterns to lower blood pressure. Ann Epidemiol 1995;108:118.

## TABLE 1 Dietary Approaches to Stop Hypertension (DASH)

| Food Group | Example of One Serving | Servings |
| :--- | :--- | :--- |
| Vegetables | $1 / 2$ cup of cooked or raw chopped vegetables; 1 cup of raw leafy <br> vegetables; or 6 oz of juice | 8 to 12 daily |
| Fruit | 1 medium apple, pear, orange, or banana; $1 / 2$ grapefruit; $1 / 3$ cantaloupe; <br> $1 / 2$ cup of fresh frozen or canned fruit; $1 / 4$ cup of dried fruit; or 6 oz of juice | 8 to 12 daily |
|  | 1 slice of bread; $1 / 2$ cup of cold, dry cereal; $1 / 2$ cup cooked rice or pasta |  |
| Grains | 1 cup of no-fat or low-fat milk or $11 / 2$ oz of low-fat or part-skim cheese | 6 to 12 daily |
| Dairy | $1 / 3$ cup $(1 / 2$ oz) of nuts; 2 T of seeds; or $1 / 2$ cup of cooked beans | 2 to 4 daily |
| Nuts, seeds, and beans | 3 oz serving (roughly the size of a deck of cards) | 4 to 7 weekly |
| Meat, poultry, or fish | 1 tsp vegetable oil, butter, salad dressings, soft margarine | 1 to 2 daily |
| Oil or other fats |  | 2 to 4 daily |

TABLE 2 Sample DASH Diet ( 2100 kCal )

| Food | Amount | Food | Amount |
| :---: | :---: | :---: | :---: |
| Breakfast |  | Dinner |  |
| Orange juice | 6 oz | Herbed baked cod | 3 oz |
| 1\% low-fat milk | 8 oz (used with corn flakes) | Scallion rice | 1 cup [equals 2 servings of grain] |
| Corn flakes | 1 cup (dry) [equals 2 servings | Steamed broccoli | 1/2 cup |
| (1 tsp sugar) | of grains] | Stewed tomatoes | 1/2 cup |
| Banana | 1 medium | $\underset{\text { (raw spinach) }}{\text { Spinach salad }} \quad 1 / 2$ cup |  |
| Whole-wheat bread | 1 slice |  |  |
| Soft margarine | 1 tsp | Cherry tomatoes | 2 |
| Lunch |  | Cucumber | 2 slices |
| Low-fat chicken salad | 3/4 cup | Light Italian salad | 1 Tbsp [equals $1 / 2$ fat serving] |
| Pita bread | 1/2 large | dressing |  |
| Raw vegetable medley Carrot and celery sticks | 34 sticks each | Whole-wheat dinner roll | 1 |
| Radishes | 2 | Soft margarine | 1 tsp |
| Lettuce | 2 leaves | Melon balls | 1/2 cup |
| Part-skim mozzarella | $11 / 2$ slices (1.5 oz) | Snack |  |
| 1\% low-fat milk | 8 oz | Dried apricots | 1 oz (1/4 cup) |
| Fruit cocktail | 1/2 cup | Mixed nuts, unsalted | 1.5 oz (1/3 cup) |
|  |  | Mini-pretzels, unsalted | 1 oz (3/4 cup) |
|  |  | Diet ginger ale | 12 oz [does not count as a serving of any food] |

[^17]Copper: required for red blood cell formation; influences gene expression and serves as a cofactor or prosthetic group for several enzymes Manganese: component of superoxide dismutase in the body s antioxidant defense system Zinc: component of lactate dehydrogenase, carbonic anhydrase, superoxide dismutase, and enzymes related to energy metabolism, cell growth and differentiation, and tissue repair

Urinary losses of zinc and chromium were 1.5 - to 2.0 -fold higher after a 6-mile run compared to a rest day. ${ }^{8}$ Sweat loss of copper and zinc also can attain relatively high levels. Documentation of trace mineral losses with exercise does not necessarily mean athletes should supplement with these micronutrients. For example, short-term zinc supplementation ( $25 \mathrm{mg} \mathrm{d}^{-1}$ ) did not benefit metabolic and endocrine responses or endurance performance during intense exercise by eumenorrheic women. ${ }^{177}$ Collegiate football players who supplemented with $200 \mu \mathrm{~g}$ of chromium (as chromium picolinate) daily for 9 weeks experienced no beneficial changes in body composition and muscular strength during intense weightlifting compared with a control group that received a placebo. ${ }^{30}$ Power and endurance athletes had higher plasma levels of copper and zinc than nontraining controls. ${ }^{160}$ Men and women who train intensely with large sweat production and with marginal nutrition (e.g., wrestlers, endurance runners, ballet dancers, and female gymnasts) should monitor trace mineral intake to prevent an overt deficiency. However, an excessive intake of one mineral may cause a deficiency in the other because iron, zinc, and copper interact with each other and compete for the same carrier during intestinal absorption. For well-nourished athletes, trace mineral supplementation does not enhance exercise performance or overall health.

## Summary

1. Approximately $4 \%$ of body mass consists of 22 elements called minerals distributed in all body tissues and fluids.
2. Minerals occur freely in nature in the waters of rivers, lakes, and oceans, and in soil. The root system of plants absorbs minerals; they eventually incorporate into the tissues of animals that consume plants.
3. Minerals function primarily in metabolism as important parts of enzymes. Minerals provide structure to bones and teeth and serve in synthesizing the biologic macronutrients-glycogen, fat, and protein.
4. A balanced diet generally provides adequate mineral intake, except in some geographic locations lacking a mineral in the soil such as iodine.
5. Osteoporosis has reached epidemic proportions among older individuals, particularly women. Adequate calcium intake and regular weightbearing exercise and/or resistance training provide an effective defense against bone loss at any age.
6. Women who train intensely often do not match energy intake to energy output. This reduces body weight and body fat to a point that adversely affects menstruation, which contributes to bone loss at an early age. Restoration of normal menstruation does not fully restore bone mass.
7. About $40 \%$ of American women of childbearing age suffer from dietary iron insufficiency. This could lead to iron deficiency anemia, which negatively affects aerobic exercise performance and ability to train intensely.
8. For women on vegetarian-type diets, the relatively low bioavailability of nonheme iron increases the risk for developing iron insufficiency. Vitamin C in food or supplement form increases intestinal absorption of nonheme iron.
9. Regular physical activity probably does not drain the body s iron reserves. If it does, females, with the greatest iron requirement and lowest iron intake, increase their risk for anemia. Periodic assessment of the body s iron status should evaluate hematologic characteristics and iron reserves.
10. Excessive sweating during exercise produces a considerable loss of body water and related minerals. These both should be replaced during and following exercise. Sweat loss during exercise usually does not increase the mineral requirement above recommended values.

## Part 3 WATER

## THE BODYS WATER CONTENT

Water makes up from 40 to $70 \%$ of body mass, depending on age, gender, and body composition. Water also constitutes 65 to $75 \%$ of the weight of muscle and about $10 \%$ of the fat mass. Consequently, differences in total body water between individuals largely result from variations in body composition (i.e., differences in lean versus fat tissue). Body fat has a low water content, so individuals with more total fat have a smaller overall percentage of their body weight as water.

Figure 2.17 depicts the fluid compartments of the body, normal daily body water variation, and specific terminology to describe the various states of human hydration. The body contains two fluid compartments. One compartment, intracellular, refers to fluid inside the cells, whereas extracellular includes fluids that flow within the microscopic spaces between cells (interstitial fluid) in addition to lymph, saliva, fluid in the eyes, fluid secreted by glands and the digestive tract, fluid that bathes the spinal cord nerves, and fluid excreted from the skin and kidneys. Blood plasma accounts for nearly $20 \%$ of the extracellular fluid ( 3 to 4 L). Extracellular fluid provides most of the fluid lost through sweating, predominantly from blood plasma. Of the total body water, an average of $62 \%$ ( 26 L of the body s 42 L of water for an average


Figure 2.17 Fluid compartments, average volumes and variability, and hydration terminology. Volumes represent an $80-\mathrm{kg}$ man. Approximately $55 \%$ of the body mass consists of water in striated muscle, skeleton, and adipose tissue. For a man and woman of similar body mass, the woman contains less total water because of her larger ratio of adipose tissue (low water content) to lean body mass (striated muscle and skeleton). (Adapted from Greenleaf JE. Problem: thirst, drinking behavior, and involuntary dehydration. Med Sci Sports Exerc 1992;24:645.)
$80-\mathrm{kg}$ man) represents intracellular water, with $38 \%$ from extracellular sources. These volumes reflect averages from a dynamic exchange of fluid between compartments, particularly in physically active men and women. ${ }^{168}$ Exercise training often increases the percentage of water distributed within the intracellular compartment because muscle mass increases, with its accompanying large water content. In contrast, an acute bout of exercise temporarily shifts fluid from plasma to interstitial and intracellular spaces from the increased hydrostatic (fluid) pressure within the circulatory system.

## Functions of Body Water

Water is a ubiquitous, remarkable nutrient. Without water, death occurs within days. It serves as the body s transport and reactive
medium; diffusion of gases always takes place across watermoistened surfaces. Nutrients and gases travel in aqueous solution; waste products leave the body through the water in urine and feces. Water, in conjunction with various proteins, lubricates joints and cushions a variety of moving organs such as the heart, lungs, intestines, and eyes. Water is noncompressible so it gives structure and form to the body through the turgor it provides for body tissues. Water has tremendous heat-stabilizing qualities because it absorbs considerable heat with only small changes in temperature. This quality, combined with water s high heat of vaporization, maintains a relatively stable body temperature during environmental heat stress and the increased internal heat load generated by exercise. More is presented in Chapter 25 on the dynamics of thermoregulation during heat stress and exercise, particularly water s vital role.

## WATER BALANCE: INTAKE VERSUS OUTPUT

The body s water content remains relatively stable over days, weeks, months, and even years. Figure 2.18 displays the sources of water intake and output.

## Water Intake

A sedentary adult in a thermoneutral environment requires about 2.5 L of water daily. For an active person in a warm, humid environment, the water requirement often increases to between 5 and 10 L daily. Three sources provide this water: (1) foods, (2) liquids, and (3) metabolism.


Figure 2.18 Water balance in the body. Top. Little or no exercise with thermoneutral ambient temperature and humidity. Bottom. Moderate-to-intense exercise in a hot, humid environment.

## Water in Foods

Fruits and vegetables contain considerable water; in contrast, butter, oils, dried meats, and chocolate, cookies, and cakes have a relatively low water content. The following foods exceed $90 \%$ of their weight as water-lettuce, raw strawberries, cucumbers, and watercress, Swiss chard, boiled squash, green peppers, bean sprouts, boiled collards, watermelon and cantaloupe, canned pumpkin, celery, and raw peaches.

## Water from Liquids

The average individual normally consumes 1200 mL , or 41 oz , of water each day. Exercise and thermal stress increase the need for fluid by five or six times this amount. At the extreme, an individual lost 13.6 kg of water weight during a 2-day, 17-hour, 55-mile run across Death Valley, California. ${ }^{157}$ With proper fluid ingestion, including salt supplements, the actual body weight loss amounted to only 1.4 kg . In this example, fluid loss and replenishment represented nearly 4 gallons of liquid!

## Metabolic Water

The breakdown of macronutrient molecules in energy metabolism forms carbon dioxide and water. This metabolic water provides about $14 \%$ of the daily water requirement of a sedentary person. Glucose catabolism liberates 55 g of metabolic water. A larger amount of water also forms from protein $(100 \mathrm{~g})$ and fat $(107 \mathrm{~g})$ catabolism. Additionally, each gram of glycogen joins with 2.7 g of water as its glucose units link together; glycogen liberates this bound water during its breakdown for energy.

## Water Output

Water loss from the body occurs in four ways: (1) in urine, (2) through the skin, (3) as water vapor in expired air, and (4) in feces.

## Water Loss in Urine

The kidneys under normal conditions reabsorb about $99 \%$ of the 140 to 160 L of renal filtrate formed each day. Consequently, the volume of urine excreted daily by the kidneys ranges from 1000 to 1500 mL , or about 1.5 quarts. Elimination of 1 g of solute by the kidneys requires about 15 mL of water. Thus, a portion of water in urine becomes obligated to rid the body of metabolic byproducts such as urea, an end product of protein breakdown. Large quantities of protein used for energy (as occurs with a high-protein diet) may accelerate dehydration during exercise.

## Water Loss Through the Skin

On a daily basis, perhaps 350 mL of water continually seeps from the deeper tissues through the skin to the body s surface as insensible perspiration. Water loss also occurs
through the skin in the form of sweat produced by specialized sweat glands beneath the skin. Evaporation of sweat provides the refrigeration mechanism to cool the body. The body produces 500 to 700 mL of sweat each day under normal thermal and physical activity conditions. This by no means reflects sweating capacity, because a well-acclimatized person produces up to 12 L of sweat (at a rate of 1 L per hour) during prolonged, intense exercise in a hot environment.

## Water Loss as Vapor

Insensible water loss through small water droplets in exhaled air amounts to between 250 and 350 mL per day from the complete moistening of inspired air as it traverses the pulmonary airways. Exercise affects this source of water loss. For physically active persons, the respiratory passages release 2 to 5 mL of water each minute during strenuous exercise, depending on climatic conditions. Ventilatory water loss is least in hot, humid weather and greatest in cold temperatures (inspired air contains little moisture) and at altitude. The latter occurs because inspired air volumes (which require humidification) are considerably larger than at sea level.

## Water Loss in Feces

Intestinal elimination produces between 100 and 200 mL of water loss because water constitutes approximately $70 \%$ of fecal matter. With diarrhea or vomiting, water loss increases up to 5000 mL , a potentially dangerous situation that can create fluid and electrolyte imbalance.

## WATER REQUIREMENT IN EXERCISE

The loss of body water represents the most serious consequence of profuse sweating. The intensity of physical activity, environmental temperature, and humidity determine the amount of water loss through sweating. Sweating also occurs in the water environment during vigorous swimming and water polo. Relative humidity (water content of the ambient air) affects efficiency of the sweating mechanism in temperature regulation. Ambient air completely saturates with water vapor at $100 \%$ relative humidity. This blocks any evaporation of fluid from the skin s surface to the air, minimizing this important avenue for body cooling. Under such conditions, sweat beads on the skin and eventually rolls off without providing a cooling effect. On a dry day, air can hold considerable moisture, and fluid evaporates rapidly from the skin. The sweat mechanism functions at optimal efficiency and body temperature remains regulated within a narrow range. Importantly, fluid loss from the vascular compartment when sweating strains circulatory function, which ultimately impairs exercise capacity and thermoregulation. Monitoring changes in body weight (after urination) conveniently assesses fluid loss during exercise and/or heat stress. Each 0.45 kg ( 1 lb ) of body weight
loss corresponds to $450 \mathrm{~mL}(15 \mathrm{oz})$ of dehydration. Chapters 3 and 25 present a more detailed discussion of fluid replacement with exercise.

## Hyponatremia

The exercise physiology literature confirms the need to consume fluid before, during, and after exercise. In many instances, the recommended beverage remains plain, hypotonic water. Excessive water intake under certain exercise conditions, however, can be counterproductive and produce the potentially serious medical complication of hyponatremia, or water intoxication, first described in the medical literature among athletes in 1985 (Fig. 2.19).

A sustained low plasma sodium concentration creates an osmotic imbalance across the blood brain barrier that allows for rapid water influx into the brain. The resulting swelling of brain tissue produces a cascade of symptoms that range from mild (headache, confusion, malaise, nausea, cramping) to severe (seizures, coma, pulmonary edema, cardiac arrest, and death). ${ }^{10,64}$ In general, mild hyponatremia exists when serum sodium concentration falls below $135 \mathrm{mEq} / \mathrm{L}^{1}$; serum sodium below $125 \mathrm{mEq} / \mathrm{L}^{1}$ triggers severe symptoms. The most conducive conditions for hyponatremia include water overload during ultramarathon-type, continuous exercise lasting 6 to 8 hours, although it may occur with exercise of only 4 hours such as standard marathons. ${ }^{12,79,82,128}$

fyi<br>\section*{Predisposing Factors to Hyponatremia}<br>Prolonged, high-intensity exercise in hot weather<br>Augmented sodium loss associated with sweat production containing high sodium concentration; often occurs in poorly conditioned individuals Beginning physical activity in a sodiumdepleted state because of salt-free or low-sodium diet Use of diuretic medication for hypertension Frequent intake of large quantities of sodiumfree fluid during prolonged exercise

Mild-to-severe hyponatremia has been reported with increasing frequency in ultraendurance athletes competing in hot weather. ${ }^{184}$ For example, nearly $30 \%$ of the athletes competing in the 1984 Ironman Triathlon had symptoms of hyponatremia, most frequently observed late in the race or in recovery. In a large study of more than 18,000 ultraendurance athletes (including triathletes), approximately $9 \%$ of collapsed athletes during or following competition exhibited symptoms of hyponatremia. ${ }^{139}$ The athletes, on average, drank fluids with low sodium chloride content ( $<6.8 \mathrm{mmol} \cdot \mathrm{L}^{1}$ ). The runner with the most severe hyponatremia (serum Na level $=112 \mathrm{mEq} \cdot \mathrm{L}^{1}$ ) excreted more than 7.5 L of dilute urine during the first 17 hours of hospitalization.


Figure 2.19 A. Factors that contribute to the development of hyponatremia. AVP, arginine vasopressin; CFTR, cystic fibrosis transmembrane regulatory gene. B. Physiologic consequences of hyponatremia. CNS, central nervous system. (Modified from Montain SJ, et al. Hyponatremia associated with exercise: risk factors and pathogenesis. Exerc Sport Sci Rev 2001;29:113.)

## INTEGRATIVE QUESTION

In what way would knowledge about hyponatremia modify your recommendations concerning fluid intake prior to, during, and in recovery from long-duration exercise?

Medical personnel monitored participants in the 1996 New Zealand Ironman Triathlon for changes in body mass and blood sodium concentration. ${ }^{182}$ For athletes with clinical evidence of fluid or electrolyte disturbance, body mass declined 2.5 kg versus a decline of 2.9 kg in athletes not
requiring medical care. Hyponatremia accounted for $9 \%$ of medical abnormalities. One athlete with hyponatremia (serum $\mathrm{Na}=130 \mathrm{mEq} \cdot \mathrm{L}^{1}$ ) drank 16 L of fluid during the race and gained 2.5 kg of body mass-consistent with the hypothesis that fluid overload causes hyponatremia. In an ultradistance multisport triathlon (kayak 67 km , cycle 148 km , run 23.8 km ), average body mass of the competitors declined 2.5 kg ( $3 \%$ of initial body mass). ${ }^{183}$ None of the athletes gained weight, and six weighed the same; the one athlete who became hyponatremic (serum $\mathrm{Na}=134 \mathrm{mEq} \cdot \mathrm{L}^{1}$ ) maintained weight and did not seek medical attention. Serum sodium concentration at the end of the race for the 47 athletes averaged $139.3 \mathrm{mEq} \cdot \mathrm{L}^{1}$.

Acclimatization level affects sodium loss. For example, sodium concentration in sweat ranges from 5 to $30 \mathrm{mmol} \cdot \mathrm{L}^{1}$ (115 $690 \mathrm{mg} \cdot \mathrm{L}^{1}$ ) in individuals fully acclimatized to the heat to 40 to $100 \mathrm{mmol} \cdot \mathrm{L}^{1}\left(9202300 \mathrm{mg} \cdot \mathrm{L}^{1}\right)$ in the unacclimatized. In addition, some individuals produce highly concentrated sweat regardless of their degree of acclimatization. Development of hyponatremia involves extreme sodium loss through prolonged sweating, coupled with dilution of existing extracellular sodium (reduced osmolality) from consuming fluids with low or no sodium (Fig. 2.19A). A reduced extracellular solute concentration moves water into the cells (Fig. 2.19B). Water movement of sufficient magnitude congests the lungs, swells brain tissue, and adversely affects central nervous system function.

Several hours of exercise in hot, humid weather often produces a sweating rate of more than 1 L per hour, with sweat sodium concentrations ranging from 20 to $100 \mathrm{mEq} \cdot \mathrm{L}^{1}$. Frequently ingesting large volumes of plain water draws sodium from the extracellular fluid compartment into the unabsorbed intestinal water, further diluting serum sodium concentration. Exercise magnifies the problem because urine production declines during exercise from reduced renal blood flow, which impedes ability to excrete excess water. Competitive athletes, recreational participants, and occupational workers should become aware of the dangers of excessive hydration and that fluid intake should not exceed fluid loss. We recommend the following six steps to reduce overhydration and hyponatremia risk in prolonged exercise:

1. Drink 400 to 600 mL ( 14 to 22 oz ) of fluid 2 to 3 hours before exercise.
2. Drink 150 to 300 mL ( 5 to 10 oz ) of fluid about 30 minutes before exercise.
3. Drink no more than $1000 \mathrm{~mL} \cdot \mathrm{~h}^{-1}$ ( 33 oz ) of plain water spread over 15-minute intervals during or after exercise.
4. Add a small amount of sodium (approximately $1 / 4$ to $1 / 2$ teaspoon per 32 oz ) to the ingested fluid.
5. Do not restrict salt in the diet.
6. Include some glucose in the rehydration drink to facilitate intestinal water uptake via the glucose sodium transport mechanism.

## Summary

1. Water makes up 40 to $70 \%$ of the total body mass. Muscle contains $70 \%$ water by weight; water represents only about $10 \%$ of the weight of body fat.
2. Of the total body water, about $62 \%$ occurs intracellularly (inside the cells) and $38 \%$ extracellularly in the plasma, lymph, and other fluids.
3. The typical average daily water intake of 2.5 L comes from liquid ( 1.2 L ), food $(1.0 \mathrm{~L})$, and metabolic water produced during energy-yielding reactions ( 0.35 L ).
4. Water loss from the body each day in an inactive person occurs from urine ( 1 to 1.5 L ); skin, as insensible perspiration and sweat ( 0.85 L ); water vapor in expired air $(0.35 \mathrm{~L})$; and feces $(0.10 \mathrm{~L})$.
5. Food and oxygen always are supplied in aqueous solution, and waste products leave via a watery medium. Water also helps to provide structure and form to the body and plays a vital role in temperature regulation.
6. Exercise in hot weather increases the body s water requirement. Extreme conditions increase fluid needs five or six times above normal requirements.
7. Excessive sweating combined with consuming large volumes of plain water during prolonged exercise set the stage for hyponatremia or water intoxication. This dangerous condition relates to a significant decrease in serum sodium concentration.

## On the Internet

Institute of Medicine of the National Academies Food and Nutrition Board
www.iom.edu/CMS/3788.aspx
http://fnic.nal.usda.gov/nal_display/index.php?info_center= 4\&tax_level=3\&tax_subject=256\&topic_id=1342\&level3_id= 5140\&level4_id=0\&level5_id=0\&placement_default=0
National Cancer Institute
www.cancer.gov/


## CHAPTER 3

## Optimal Nutrition for Exercise

## CHAPTER OBJECTIVES

> Compare nutrient and energy intakes of the physically active with sedentary counterparts

- Provide recommendations for carbohydrate, lipid, and protein intake for individuals who (1) maintain a physically active lifestyle and (2) those who regularly engage in intense physical training
> Outline the MyPyramid recommendations
- Give examples of the energy intakes of athletes who train for competitive sports
- Advise an athlete concerning timing and composition of the precompetition meal
> Advise endurance athletes about (1) the potential negative effects of consuming a concentrated sugar drink within 30 minutes of competition and (2) the rationale and recommended carbohydrate intake during intense endurance exercise
> Provide three examples of high-, moderate-, and low-glycemic index foods
- Describe the role of the glycemic index in preand postexercise glycogen replenishment
> Outline an optimal glycogen replenishment schedule following high-intensity endurance exercise
- Describe the ideal sports drink and the rationale for its composition
> Give recommendations for fluid and carbohydrate replacement during exercise
- Discuss the controversy concerning high-fat diets for training and endurance performance

An optimal diet supplies required nutrients in adequate amounts for tissue maintenance, repair, and growth, without excess energy intake. Less than optimal fluid, nutrient, and energy intakes profoundly affect thermoregulatory function, substrate availability, exercise capacity, recovery from exercise, and training responsiveness. Dietary recommendations for physically active individuals must account for the energy requirements of a particular activity or sport and its training demands, including individual dietary preferences. No one food or diet exists for optimal health and exercise performance; careful planning and evaluation of food intake must follow sound nutritional guidelines. The physically active person must obtain sufficient energy and macronutrients to replenish liver and muscle glycogen, provide amino acid building blocks for tissue growth and repair, and maintain adequate lipid intake to provide essential fatty acids and fat-soluble vitamins. For the most part, those who exercise regularly to keep fit do not require additional nutrients beyond those in a regular intake of a nutritionally wellbalanced diet.

## NUTRIENT INTAKE AMONG THE PHYSICALLY ACTIVE

Inconsistencies exist among studies that relate diet quality to physical activity level or physical fitness. Part of the discrepancy relates to relatively crude and imprecise self-reported measures of physical activity, unreliable dietary assessments, and/or small sample size. ${ }^{6,36,46,61,64}$ TABLE 3.1 contrasts the nutrient and energy intakes with national dietary recommendations of a large population-based cohort of about 7000 men and 2500 women classified as low, moderate, and high for cardiorespiratory fitness. The four most significant findings indicate the following:

1. A progressively lower body mass index with increasing levels of physical fitness for men and women
2. Remarkably small differences in energy intake related to physical fitness classification for women ( $\leq 94 \mathrm{kCal}$ per day) and men ( $\leq 82 \mathrm{kCal}$ per day); the moderate fitness group for both sexes consumed the fewest calories

TABLE 3.1 Average Values for Nutrient Intake Based on 3-Day Diet Records by Levels of Cardiorespiratory Fitness in 7059 Men and 2453 Women

| Variable | Low Fitness $(N=786)$ | Moderate Fitness $(N=2457)$ | High Fitness $(N=4716)$ |
| :---: | :---: | :---: | :---: |
| Demographic and health data |  |  |  |
| Age (y) | $47.3 \pm 11.1^{a, b}$ | $47.3 \pm 10.3^{c}$ | $48.1 \pm 10.5$ |
| Apparently healthy (\%) | $51.5{ }^{\text {a,b }}$ | $69.1{ }^{\text {c }}$ | 77.0 |
| Current smokers (\%) | $23.4{ }^{\text {a,b }}$ | $15.8{ }^{\text {c }}$ | 7.8 |
| BMI ( $\mathrm{kg} \cdot \mathrm{m}^{-2}$ ) | $30.7 \pm 5.5^{a, b}$ | $27.4 \pm 3.7^{c}$ | $25.1 \pm 2.7$ |
| Nutrient data |  |  |  |
| Energy (kCal) | $2378.6 \pm 718.6^{a}$ | $2296.9 \pm 661.9^{c}$ | $2348.1 \pm 664.3$ |
| $\mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~d}^{-1}$ | $25.0 \pm 8.1^{a}$ | $26.7 \pm 8.4^{c}$ | $29.7 \pm 9.2$ |
| Carbohydrate (\% kCal) | $43.2 \pm 9.4{ }^{\text {b }}$ | $44.6 \pm 9.1^{c}$ | $48.1 \pm 9.7$ |
| Protein (\% kCal) | $18.6 \pm 3.8$ | $18.5 \pm 3.8$ | $18.1 \pm 3.8$ |
| Total fat (\% kCal) | $36.7 \pm 7.2^{b}$ | $35.4 \pm 7.1^{\text {c }}$ | $32.6 \pm 7.5$ |
| SFA (\% kCal) | $11.8 \pm 3.2^{b}$ | $11.3 \pm 3.2^{c}$ | $10.0 \pm 3.2$ |
| MUFA (\% kCal) | $14.5 \pm 3.2^{a, b}$ | $13.8 \pm 3.1^{c}$ | $12.6 \pm 3.3$ |
| PUFA (\% kCal) | $7.4 \pm 2.2^{a, b}$ | $7.5 \pm 2.2$ | $7.4 \pm 2.3$ |
| Cholesterol (mg) | $349.5 \pm 173.2^{b}$ | $314.5 \pm 147.5^{c}$ | $277.8 \pm 138.5$ |
| Fiber (g) | $21.0 \pm 9.5^{b}$ | $22.0 \pm 9.7^{\circ}$ | $26.2 \pm 11.9$ |
| Calcium (mg) | $849.1 \pm 371.8^{a, b}$ | $860.2 \pm 360.2^{c}$ | $924.4 \pm 386.8$ |
| Sodium (mg) | $4317.4 \pm 1365.7$ | $4143.0 \pm 1202.3$ | $4133.2 \pm 1189.4$ |
| Folate (mcg) | $336.4 \pm 165.2^{b}$ | $359.5 \pm 197.0^{c}$ | $428.0 \pm 272.0$ |
| Vitamin $\mathrm{B}_{6}(\mathrm{mg})$ | $2.4 \pm 0.9^{b}$ | $2.4 \pm 0.9^{c}$ | $2.8 \pm 1.1$ |
| Vitamin $\mathrm{B}_{12}(\mathrm{mcg})$ | $6.6 \pm 5.5^{a}$ | $6.8 \pm 6.0$ | $6.6 \pm 5.8$ |
| Vitamin A (RE) | $1372.7 \pm 1007.3^{\text {a,b }}$ | $1530.5 \pm 1170.4^{c}$ | $1766.3 \pm 1476.0$ |
| Vitamin C (mg) | $117.3 \pm 80.4^{b}$ | $129.2 \pm 108.9^{c}$ | $166.0 \pm 173.2$ |
| Vitamin E (AE) | $11.5 \pm 9.1^{b}$ | 12.1. $\pm 8.6^{c}$ | $13.7 \pm 11.4$ |

[^18]3. A progressively higher dietary fiber intake and lower cholesterol intake across fitness categories
4. Men and women with higher fitness levels generally consumed diets that more closely approached dietary recommendations for dietary fiber, percentage energy from total fat, percentage energy from saturated fat, and dietary cholesterol than peers of lower levels of fitness

## INTEGRATIVE QUESTION

In what ways might nutritional and energy intake goals for training differ from the requirements for actual competition?

## Recommended Nutrient Intake

Figure 3.1 illustrates the recommended intakes for protein, lipid, and carbohydrate and the food sources for these macronutrients for a resting daily energy requirement of about 1200 kCal . A total daily energy requirement of 2000 kCal for women and 3000 kCal for men represents the average values for typical young adults. After meeting basic nutrient requirements (as recommended in Fig. 3.1), a variety of food sources based on individual preference with emphasis on unrefined complex carbohydrates can supply the extra energy demands for physical activity.


Figure 3.1 General recommendations for carbohydrate, lipid, and protein components and the general categories of food sources in a balanced diet to meet resting daily energy requirement of about 1200 kCal . Values within bars represent percentage of that groups contribution to the specific macronutrient intake.

## Protein

As discussed in Chapter 1, 0.83 g per kg of body mass represents the Recommended Dietary Allowance (RDA) for protein intake. A person weighing $77 \mathrm{~kg}(170 \mathrm{lb})$ requires about $64 \mathrm{~g}(2.2 \mathrm{oz})$ of protein daily. Even if relatively little protein catabolism occurs through energy metabolism during physical activity (an assumption not entirely correct), this protein recommendation remains adequate for most physically active individuals. Also, the protein intake of the typical North American considerably exceeds protein s RDA. For athletes who train intensely, a protein intake between 1.2 and 1.8 g per kg body mass should meet any added protein-related nutrient demands. This does not necessarily require protein supplementation because an athlete s diet typically exceeds the protein RDA by two to four times.

## INTEGRATIVE QUESTION

In what situations might a protein intake representing twice the RDA still prove inadequate for an individual involved in intense exercise training?

## Lipid

Standards for optimal lipid intake have not been established. The amount of dietary lipid varies widely depending on personal taste, money spent on food, geographic influences, and availability of lipid-rich foods. Lipid furnishes only about $10 \%$ of the energy in the average diet of people living in Asia, whereas in many Western countries it accounts for 40 to $45 \%$ of the total energy intake. To promote good health, lipid intake should not exceed $30 \%$ of the diet s energy content. Of this, at least $70 \%$ should be unsaturated fatty acids. For those who consume a Mediterranean-type diet (see p. 89), rich in mono- and polyunsaturated fatty acids, a somewhat higher total fat percentage of 35 to $40 \%$ remains reasonable.

## High-Fat Versus Low-Fat Diets for Exercise Training and Performance

High-Fat Diets. Debate centers on the wisdom of maintaining a higher-fat diet (higher than average) during training or prior to endurance competition. ${ }^{89,106,117}$ Adaptations to high-fat diets have consistently shown a shift in substrate use toward higher fat oxidation during rest and exercise. ${ }^{8,50,108}$ Proponents of high-fat diets argue that a prolonged increased dietary fat intake stimulates fat burning and augments capacity to mobilize and catabolize fat during intense aerobic exercise. Any fatburning enhancement could theoretically conserve glycogen reserves and/or contribute to improved endurance capacity under conditions of low glycogen reserves. ${ }^{41}$ To investigate possible benefits, endurance capacity was compared in two groups of 10 young men matched for aerobic capacity and fed either a high-carbohydrate diet $(65 \% \mathrm{kCal}$ from carbohydrate)

## IN A PRACTICAL SENSE

## Nutrition to Prevent Chronic Athletic Fatigue


#### Abstract

Endurance runners, swimmers, cross-country skiers, and cyclists frequently experience chronic fatigue as successive days of hard training become progressively more difficult. Normal exercise performance deteriorates because the individual experiences increasing difficulty recovering from each training session. The overtraining syndrome (see Chapter 21) also relates to frequent infections, general malaise, and loss of interest in sustaining high-level training. Injuries occur more frequently in the overtrained, stale state.


requires at least 1 to 2 days of rest or lighter exercise combined with a high carbohydrate intake to reestablish preexercise muscle glycogen levels after exhaustive training or competition. Unduly heavy exercise performed regularly requires an upward adjustment of daily carbohydrate intake to optimize glycogen resynthesis and high-quality training. The table below provides nutritional recommendations to reduce the likelihood of athletic fatigue or staleness.

## DEPLETED CARBOHYDRATE PLAYS A ROLE

Gradually depleting carbohydrate reserves with repeated strenuous training most likely contributes to the overtraining syndrome. It

## Practical Nutritional Guidelines to Prevent Chronic Fatigue

1. Consume easily digested, high-carbohydrate drinks or solid foods 1 to 4 h before training or competition. Consume about 1 g carbohydrate/kg body mass 1 h before exercise and up to 5 g carbohydrate/kg body mass if the feeding occurs 4 h prior to exercise. For example, a $70-\mathrm{kg}$ swimmer could drink 350 mL ( 12 oz ) of a $20 \%$ carbohydrate beverage 1 h before exercise or eat 14 energy bars, each containing 25 g carbohydrate, spread over the 4 -h period before exercise.
2. Consume a readily digested, high-carbohydrate liquid or solid food containing 0.351 .5 g carbohydrate $/ \mathrm{kg}$ body mass $/ \mathrm{h}$ immediately after exercise and for the first 4 h after exercise. Thus, a 70-kg swimmer could drink $100450 \mathrm{~mL}(3.616 \mathrm{oz}$ ) of a $25 \%$ carbohydrate beverage or 1 to 4 energy bars, each containing 25 g of carbohydrate immediately after exercise and every hour thereafter for 4 h .
3. Consume a 15 to $25 \%$ carbohydrate drink or a solid, high-carbohydrate supplement with each meal. For example, reduce consumption of normal foods by 250 kCal and consume a high-carbohydrate beverage or solid food containing 250 kCal of carbohydrate with each meal.
4. Stabilize body weight during all phases of training by matching energy consumption to training senergy demands. This also helps to maintain body glycogen reserves.

From Sherman WJ, Maglischo EW. Minimizing chronic athletic fatigue among swimmers: special emphasis on nutrition. Sports Science Exchange. Gatorade Sports Science Institute. 1991;35(4).
or high-fat diet ( $62 \% \mathrm{kCal}$ from lipid) for 7 weeks. Each group trained for 60 to 70 minutes at 50 to $85 \%$ of aerobic capacity, 3 days a week during weeks 1 through 3 and 4 days a week during weeks 4 through 7 . Following 7 weeks of training, the group consuming the high-fat diet switched to the highcarbohydrate diet. Figure 3.2 displays the performance of both groups. The results for endurance were clear-the group consuming the high-carbohydrate diet performed considerably longer after training for 7 weeks than the group consuming the high-fat diet ( 102.4 min vs. 65.2 min ). When the high-fat diet group switched to the high-carbohydrate diet during week 8 of the experiment, only a small improvement in endurance of 11.5 minutes occurred. Consequently, total overall improvement in endurance over the 8 -week period reached $115 \%$ for the high-fat diet group, and endurance for the group receiving the high-carbohydrate diet while training improved by $194 \%$ ! The inset table shows daily intakes of energy and nutrients prior to the experimental treatment (habitual diet) and during the 7 -week experimental diet. The authors concluded that the high-fat diet produced suboptimal adaptations in endurance performance, which did not become fully remedied by switching
to a high-carbohydrate diet. Subsequent research from the same laboratory failed to demonstrate any endurance-enhancing effect of a high-fat diet containing only moderate carbohydrate ( $15 \%$ total calories) in rats, regardless of their current training status. For sedentary humans, maintaining a low or high dietary fat intake for 4 weeks produced no differences in maximal or submaximal aerobic exercise performance. ${ }^{73}$

A high-fat diet may stimulate adaptive responses that augment fat use, but reliable research has yet to demonstrate consistent exercise or training benefits from a diet high in fat. Compromised training capacity and symptoms of lethargy, increased fatigue, and higher ratings of perceived exertion usually accompany exercise when subsisting on a high-fat diet. ${ }^{90,108}$ One must carefully consider recommending a diet consisting of $60 \%$ of total calories from lipid from the standpoint of potential detrimental health risks. This concern may prove unwarranted for athletes with high daily levels of energy expenditure. Increasing the percentage of total lipid calories in the diet to $50 \%$ for physically active individuals who maintain a stable body weight and body composition does not compromise selected heart disease risk factors,


Figure 3.2 Effects of a high-carbohydrate (CHO) versus a high-fat diet on endurance performance. The group consuming the high-fat diet for 7 weeks switched to the high CHO diet during week 8 . The endurance test consisted of pedaling a bicycle ergometer at the desired rate. (From Helge JW, et al. Interaction of training and diet on metabolism and endurance during exercise in man. J Physiol 1996;492:293.)
including plasma lipoprotein profiles. ${ }^{8,58}$ Considered in total, available research does not support the popular notion that reducing carbohydrate while increasing fat intake above a 30\% level produces a more optimal metabolic zone for endurance performance. ${ }^{82,95,105}$

Low-Fat Diets. Restricting dietary fat below recommended levels can impair exercise performance. ${ }^{40,105}$ For example, a diet of $20 \%$ lipid produced poorer endurance performance scores than a diet of identical caloric value containing about $40 \%$ lipid. ${ }^{70}$ A low-fat diet also blunts the normal rise in plasma testosterone following an acute bout of resistance exercise. ${ }^{109}$ If additional research verifies these findings, and if changes in the hormonal milieu actually diminish training responsiveness and tissue synthesis, a low-fat intake may be contraindicated for optimal resistance training responses. Consuming low-fat diets during strenuous training creates difficulty in increasing carbohydrate and protein intake enough to furnish energy to maintain body weight and muscle mass.

## Carbohydrate

The negative end of the nutrition continuum includes lowcalorie semistarvation diets and other potentially harmful high-fat, low-carbohydrate diets, liquid-protein diets, or single-food centered diets. Such extremes threaten good health, exercise performance, and attainment of optimum body composition. A low-carbohydrate diet rapidly compro-
mises glycogen reserves for vigorous physical activity or regular training. Excluding sufficient carbohydrate energy from the diet causes an individual to train in a state of relative glycogen depletion; this may eventually produce staleness that can hinder exercise performance.

The prominence of dietary carbohydrates varies widely throughout the world depending on availability and relative cost of lipid-rich and protein-rich foods. Carbohydrate-rich unrefined grains, starchy roots, and dried peas and beans usually cost less relative to their energy value. In the Far East, carbohydrates (rice) contribute $80 \%$ of the total energy intake, whereas in the United States only about 40 to $50 \%$ of total energy comes from carbohydrates. No hazard to health exists when subsisting chiefly on a variety of fiber-rich complex unrefined carbohydrates, with adequate intake of essential amino acids, fatty acids, minerals, and vitamins.

Muscle glycogen becomes the prime energy contributor during exercise with inadequate oxygen supply to active muscles. In addition to its anaerobic energy role, muscle glycogen and blood glucose provide substantial energy during intense aerobic exercise. Considering the bodys limited glycogen reserves, the diet of physically active individuals should contain at least 55 to $60 \%$ of calories as carbohydrates, predominantly starches from fiber-rich, unprocessed grains, fruits, and vegetables. For many competitive athletes (e.g., swimmers, rowers, and speed skaters), the importance of maintaining a relatively high daily carbohydrate intake relates more to the considerable energy demands of training than to the shortterm demands of competition.

## FOCUS ON RESEARCH

## Potential Effect of Diet on Health Status

## Connor WE, et al. The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. Am J Clin Nutr 1978;31:1131.

$>$ The Tarahumara Indians compose a group of about 50,000 farmers who inhabit the rugged Sierra Madre Occidental Mountains in the north-central state of Chihuahua, Mexico. These individuals, renowned for their endurance capacity, reportedly run distances of up to 200 miles in the competitive sport of kickball that lasts 2 days.

Conner and colleagues assessed the diet, blood lipid status, and blood pressure of these 20th-century Spartans. Measurements of 523 Tarahumaras over a 3-year period included plasma cholesterol and triacylglycerol, lipoprotein fractions, body stature and mass, triceps skinfold, resting blood pressure, and nutrient intake by dietary history and observation of food intake. The most striking findings included extremely low values for total cholesterol, LDLand VLDL-cholesterol, blood pressure, skinfold thickness, and dietary lipid intake. The average blood cholesterol levels ( $136 \mathrm{mg} \cdot \mathrm{dL}^{1}$ for men; $117 \mathrm{mg} \cdot \mathrm{dL}^{1}$ for women; and $116 \mathrm{mg} \cdot \mathrm{dL}^{1}$ for children) contrast sharply with typical U.S. values of more than $200 \mathrm{mg} \cdot \mathrm{dL}^{1}$.

The low plasma cholesterol of the Tarahumaras largely relates to their unique dietary patterns. Their diet averaged a low cholesterol intake of $71 \mathrm{mg} \cdot \mathrm{d}^{1}$ (typical U.S. cholesterol intake ranges from 500 to $700 \mathrm{mg} \cdot \mathrm{d}^{1}$ ). Additionally, lipid intake averaged only $11 \%$ of total energy intake, compared with nearly $40 \%$ for the U.S. diet. Corn and beans accounted for $95 \%$ of total lipid consumption, mainly from polyunsaturated and monounsaturated fatty acids. Saturated fat constituted only $2 \%$ of total calories, compared with $15 \%$ in the United States. Thus, the healthful polyunsaturated-to-saturated fat ratio exceeded 2.0, compared with only 0.35 for the U.S. diet.

Simple sugars provided only 5\% of total energy intake, compared with $25 \%$ for the typical North American diet. No obesity or hypertension occurred in the Tarahumara. Vegetable sources provided more than $96 \%$ of all dietary protein, while protein intake ranged from 79 to $96 \mathrm{~g} \cdot \mathrm{~d}^{1}$ and accounted for 236 to $1221 \%$ of the total essential amino acid requirements based on the U.S. RDA. The Tarahumaras high level of physical activity coincided with favorable blood lipid and blood pressure profiles and other low coronary risk factors. Overall, the results illustrated that diet and increased physical activity linked to the group s relatively good health status.


Dietary and blood lipid variables for the Tarahumara Indians of Mexico. Plasma cholesterol, triacylglycerol, and LDL-Chol in mg per dL . Chol Intake is cholesterol intake in mg per day. Lipid intake (Lipid \%) and saturated fat intake (Saturated Fat) expressed as percentage of total caloric intake; $P / S$ Ratio represents ratio of polyunsaturated to saturated fatty acid intake; Refined CHO is the percentage of total calories from refined sugar; Salt is salt intake in g per day; SBP and DBP represent systolic and diastolic blood pressure in mm Hg .


Figure 3.3 Changes in muscle glycogen concentration (mean response) for six male subjects before and after each 10-mile ( $16.1-\mathrm{km}$ ) run performed on 3 successive days. Muscle glycogen measured 5 days after the last run is referred to as 5 th day post. (From Costill DL, et al. Muscle glycogen utilization during prolonged exercise on successive days. J Appl Physiol 1971;31:834.)

## Carbohydrate Needs in Intense Training

Athletes training for endurance running, ocean swimming, cross-country skiing, or cycling frequently experience a state of chronic fatigue when successive days of hard training become progressively more difficult. This condition of staleness often relates to the gradual depletion of the body s glycogen reserves, even though the diet contains the typical percentage of carbohydrate. Figure 3.3 shows that three successive days of running 16.1 km ( 10 miles) nearly depletes the glycogen in the thigh muscle. This occurred even though the runners diet contained 40 to $60 \%$ carbohydrates. By the third day, the quantity of glycogen used during the run averaged considerably lower than on the first day. Presumably, the body s fat reserves supplied the predominant energy for exercise on day 3. Unmistakably, a person who performs unduly strenuous exercise on a regular basis must adjust daily carbohydrate intake upward to permit optimal glycogen resynthesis to maintain high-quality training. The need for optimal replenishment of depleted glycogen reserves provides nutritional justification to gradually reduce or taper exercise intensity several days prior to competition. ${ }^{97}$

Carbohydrate intake recommendations for physically active individuals assume that daily energy intake balances daily energy expenditure. Unless this condition exists, even consuming a relatively large percentage of carbohydrate calories will not adequately replenish this important energy macronutrient. General recommendations for carbohydrate intake range between 6 and 10 g per kg of body mass per day. This amount varies with an individual s daily energy expenditure and type of exercise performed. Glycogen synthesis depends on carbohydrate intake. This means individuals who train
intensely should consume 10 g of carbohydrate per kg of body mass each day to induce protein sparing and ensure adequate glycogen reserves. The daily carbohydrate intake for a small $46-\mathrm{kg}$ ( $100-\mathrm{lb}$ ) athlete who expends about 2800 kCal per day should average 450 g or 1800 kCal . A $68-\mathrm{kg}$ ( $150-\mathrm{lb}$ ) athlete should consume 675 g of carbohydrate $(2700 \mathrm{kCal})$ daily to sustain an energy requirement averaging 4200 kCal . In both examples, carbohydrates exceed the minimum recommendation of 55 to $60 \%$ to represent $65 \%$ of total energy intake. This relatively high level of carbohydrate intake better maintains physical performance and mood state over the course of training. ${ }^{1}$ Even with a high-carbohydrate diet, complete glycogen replenishment does not occur rapidly following prolonged effort, particularly in type I (slow-twitch) muscle fibers.

## IQ

## INTEGRATIVE QUESTION

From a nutritional perspective, how can a reduced total volume of daily training (taper) improve training responsiveness and competitive performance?

## MyPyramid: THE ESSENTIALS OF GOOD NUTRITION

Key principles of good eating include variety, balance, and moderation. The typical pattern of food intake in the United States increases the risk for obesity, marginal micronutrient intakes, low high-density lipoprotein (HDL) and high lowdensity lipoprotein (LDL) cholesterol, type 2 diabetes, and elevated levels of homocysteine. ${ }^{27,54,45,48,79}$

In April 2005, the U.S. government unveiled its latest attempt to personalize the approach of Americans to choose a healthier lifestyle that balances nutrition and exercise. The new color-coded food pyramid (Fig. 3.4A), termed MyPyramid, offers a fresh look and a complementary Web site (www. mypyramid.gov) to provide personalized and supplementary materials on food intake guidance (e.g., the recommended number of cups of vegetables) based on age, sex, and level of daily exercise. The pyramid is based on the 2005 Dietary Guidelines for Americans published by the Department of Health and Human Services and the Department of Agriculture (www.healthierus.gov/dietaryguidelines/). It provides a series of vertical color bands of varying widths with the combined bands for fruits (red band) and vegetables (green band) occupying the greatest width, followed by grains, and with the narrowest bands occupied by fats, oils, meats, and sugars. A personalized pyramid is obtained by logging on to the Web site. Note the addition of a figure walking up the left side of the pyramid to emphasize at least 30 minutes of moderate-tovigorous daily physical activity. The Guidelines are formulated for the general population but also provide a sound framework for meal planning for physically active individuals. The principle message advises consuming a varied but balanced diet. Importance is placed on a diet rich in fruits and vegetables,
cereals and whole grains, nonfat and low-fat dairy products, legumes, nuts, fish, poultry, and lean meats. ${ }^{4,18,48,103}$

Figure 3.4B and C present modifications of the basic pyramid. These apply to individuals whose diet consists largely of foods from the plant kingdom (Near-Vegetarian Diet Pyramid) or fruits, nuts, vegetables, fish, beans, and all manner of grains, with dietary fat composed mostly of monounsaturated fatty acids with mild ethanol consumption (Mediterranean Diet Pyramid). A Mediterranean-style diet protects individuals at high risk of death from heart disease. ${ }^{23}$ Its high content of monounsaturated fatty acids (generally olive oil with its associated phytochemicals ${ }^{88}$ ) helps delay age-related memory loss, cancer, and overall mortality rate in healthy, elderly people. ${ }^{57,85,99}$ The dietary focus of all three pyramids also reduces risk for ischemic stroke ${ }^{51,52}$ and enhances the benefits of cholesterol-lowering drugs. ${ }^{53}$

## INTEGRATIVE QUESTION

How would you advise a high school soccer team with individuals from diverse ethnic backgrounds with unique food intake patterns about sound nutrition?

## Nutritional Guidelines for the General Population

| Population Goals | Major Guidelines |
| :--- | :--- |
| Overall healthy eating pattern | Consume a varied diet that includes foods from each of the major food groups with an emphasis on <br> fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean <br> meats. <br> Monitor portion size and number to ensure adequate, not excess, intake. |
| Appropriate body weight | Match energy intake to energy needs. <br> Whi $\leq 25^{a}$ |
| (physical activity). |  |
| Limit foods with a high sugar content, and those with a high caloric density. |  |

Modified from Krauss RM, et. al. AHA dietary guidelines revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association, Circulation 2000;102:2284.
${ }^{a} B M I$, body mass index $\left(\mathrm{kg} \cdot \mathrm{m}^{-2}\right)$.

Recommended protein intake ranges between 10 and $35 \%$ of calories, which remains consistent with prior recommendations. For the first time, age-based recommendations are provided for all of the essential amino acids contained in dietary protein. Table 3.2 presents an example of the macronu-
trient composition for a $2500-\mathrm{kCal}$ diet based on the new guidelines (www.10m.edu/CMS/3788.aspx).

The panel s recommendations for intake of dietary fiber were discussed in Chapter 1. Particularly important is the consumption of water-soluble fibers (pectin from fruits and oat
MyPyramid


| GRAINS Make half your grains whole | VEGETABLES <br> Vary your veggies | FRUITS <br> Focus on fruits | MILK <br> Get your calcium-rich foods | MEAT \& BEANS Go lean with protein |
| :---: | :---: | :---: | :---: | :---: |
| Any food made from wheat, rice, oats, cornmeal, barley, or another cereal grain is a grain product <br> Bread, pasta, oatmeal, breakfast cereals, tortillas, and grits are examples of grain products | Eat more dark-green veggies like broccoli, spinach, and other dark leafy greens Eat more orange vegetables like carrots and sweet potatoes <br> Eat more dry beans and peas like pinto beans, kidney beans, and lentils | Eat a variety of fruit Choose fresh, frozen, canned, or dried fruit <br> Go easy on fruit juices | Go low-fat or fat-free when you choose milk, yogurt, and other milk products <br> If you don't or can't consume milk, choose lactose-free products or other calcium sources such as fortified foods and beverages | Choose low-fat or lean meats and poultry <br> Bake it, broil it, or grill it <br> Vary your protein routine choose more fish, beans, peas, nuts, and seeds |

For a 2000-Calorie diet you need the amounts below from each food group. To find the amounts right for you, go to www.MyPyramid.gov.

$$
\text { Eat } 3 \text { oz. every day Eat } 2 \frac{1}{2} \text { cups every day } \quad \text { Eat } 2 \text { cups every day } \quad \begin{gathered}
\text { Drink } 3 \text { cups every day; } \\
\text { for kids aged } 2 \text { to } 8 \text {, it' } 2
\end{gathered} \quad \text { Eat } 5 \frac{1}{2} \text { oz. every day }
$$

## B <br> Mediterranean Diet Pyramid

## C Near-Vegetarian Diet Pyramid



Figure 3.4 A. MyPyramid: A more comprehensive and personalized guide to sound nutrition. B. Mediterranean Diet Pyramid. C. Near-Vegetarian Diet Pyramid.

| TABLE 3.2 | Macronutrient Composition <br> of a 2500-kCal Diet Based on <br> Recommendations of the <br> Institute of Medicine |  |  |
| :--- | :---: | :---: | :---: |
|  | Composition of 2500-kCal Intake |  |  |
|  | Carbohydrate | Lipid | Protein |
| Percentage | 60 | 15 | 25 |
| kCal | 1500 | 375 | 625 |
| Grams | 375 | 94 | 69 |
| Ounces | 13.2 | 3.3 | 2.4 |

and rice bran); these lower plasma cholesterol and reduce the risk of overeating.

## EXERCISE AND FOOD INTAKE

Balancing energy intake with energy expenditure represents a primary goal for the physically active individual of normal body weight. Energy balance not only optimizes physical performance but helps to maintain lean body mass, training responsiveness, and immune and reproductive function. The level of physical activity represents the most important factor that impacts daily energy expenditure.

Figure 3.5 illustrates that average energy intakes for males and females in the United States peak between ages 16 and 29 years and then decline for succeeding age groups. A similar pattern occurs for both males and females, although males report higher daily energy intakes than females at all ages. Between ages 20 and 29 years, women consume on average $35 \%$ fewer kCal than men on a daily basis $(3025 \mathrm{kCal}$ vs. 1957 kCal ). Thereafter, the gender difference in energy intake becomes smaller; at age 70 years, women consume about $25 \%$ fewer kCal than men.

## Physical Activity Makes a Difference

Individuals who engage regularly in moderate-to-intense physical activity eventually increase daily energy intake to match higher energy expenditure levels. Lumber workers, who expend approximately 4500 kCal daily, unconsciously adjust energy intake to closely balance energy output. Consequently, body mass remains stable despite a seemingly large food intake. The daily food intake of athletes in the 1936 Olympics reportedly averaged more than 7000 kCal , or roughly three times the average daily intake. These oft-quoted energy values justify what many believe to be an enormous food requirement of athletes in training. These figures probably depict inflated estimates because objective dietary data do not appear in the original report. Distance runners who train upward of 100 miles weekly ( $6-$ min mile pace at 15 kCal per min ) probably do not expend more than 800 to 1300 extra


Figure 3.5 Average daily energy intake for males and females by age in the U.S. population during the years 1988 to 1990 . Multiply by 0.239 to convert kJ to kCal . (From Briefel RR, et al. Total energy intake of the U.S. population: the third National Health and Nutrition Examination Survey, 1988 1991. Am J Clin Nutr 1995;62(suppl):1072S.)
kCal each day above their normal energy requirements to balance the increased energy expenditure. Figure 3.6 presents energy intake data from a large sample of elite male and female endurance, strength, and team sport athletes in the Netherlands. Daily energy intake for males ranged between 2900 and 5900 kCal , whereas female competitors consumed between 1600 and 3200 kCal . Daily energy intake generally did not exceed 4000 kCal for men and 3000 kCal for women (except for the large energy intakes of athletes at extremes of performance and training). For male and female recruits of the U.S. Marine Corps, daily energy expenditures averaged 6142 kCal for the men and 4732 kCal for the women during a 54-hour training exercise. ${ }^{14}$

To complement these observations, daily energy expenditure of elite female swimmers increased to 5593 kCal during high-volume training. ${ }^{98}$ This value represents the highest level of sustained daily energy expenditure reported for female athletes, yet energy intake did not increase to match training demands. It averaged only 3136 kCal implying a negative energy balance of $43 \%$. A negative energy balance in the transition from moderate to intense training can ultimately compromise an athlete s full potential to train and compete.

## Tour de France and Other Endurance Activities

Figure 3.7 outlines the variation in daily energy expenditure for a male competitor during the Tour de France professional cycling race. In this grueling sporting event, energy expenditure averaged 6500 kCal daily for nearly 3 weeks. Large variation occurred depending on activity level for a particular

Daily Energy Expenditure (kCal)


Figure 3.6 Daily energy intake ( kCal ) of elite male and female endurance, strength, and team sport athletes. (Modified from van Erp-Baart AMJ, et al. Nationwide survey on nutritional habits in elite athletes. Int J Sports Med 1989;10:53.)
day; the daily energy expenditure decreased to about 3000 kCal on a rest day and increased to 9000 kCal cycling over a mountain pass. By combining liquid nutrition with normal meals, this cyclist nearly matched daily energy expenditure with energy intake.

Other sport and training activities also require extreme energy output and correspondingly high energy intake, sometimes in excess of 1000 kCal per hour in elite marathoners. Daily energy requirements of world class cross-country skiers during 1 week of intense training averaged 3740 to 4860 kCal for women and 6120 to 8570 kCal for men. ${ }^{84}$ The values for
women agree with the average 3957 kCal daily energy expenditure over a 14-day training period reported for seven elite lightweight female rowers. ${ }^{44}$ In another study, the doubly labeled water technique (see Chapter 8) evaluated the energy balance for two men who pulled sledges with starting weights of 222 kg ( $10 \mathrm{~h} \cdot \mathrm{~d}^{1}$ for 95 days) for 2300 km across Antarctica. ${ }^{92}$ During a 10 -day period, one man averaged a daily energy expenditure of $10,654 \mathrm{kCal}$, while his counterpart averaged an extraordinary output of $11,634 \mathrm{kCal}$. These values approach the $13,975-\mathrm{kCal}$ theoretical daily energy expenditure ceiling attained by ultra long-distance runners. ${ }^{15}$

## Ultraendurance Running Competition

Energy balance was studied during a $1000-\mathrm{km}$ (approximately 600-mile) race from Sidney to Melbourne, Australia. The Greek ultramarathon champion Kouros completed the race in 5 days, 5 hours, and 7 minutes, finishing 24 hours and 40 minutes ahead of the next competitor. Table 3.3 provides relevant features of race conditions, distance covered, average daily speed, and rest and sleep patterns. Kouros did not sleep during the first 2 days of competition. He covered 463 km ( 287.8 miles) at an average speed of $11.4 \mathrm{~km} \cdot \mathrm{~h}{ }^{1}$ during day 1 and $8.3 \mathrm{~km} \cdot \mathrm{~h}^{1}$ on day 2 . During the remaining days, he took frequent rest periods including periodic breaks for short naps. Weather ranged from spring to winter conditions ( 30 to 8 C ) and terrain varied. The bottom of Table 3.3 lists the pertinent details of food and water intake.

The near equivalence between Kouros estimated total energy intake ( $55,970 \mathrm{kCal}$ ) and energy expenditure $(59,079 \mathrm{kCal})$ represents a remarkable aspect of energy balance homeostasis to extremes of physical activity. Of the total energy intake, carbohydrates represented $95.3 \%$, lipids $3 \%$, with the remaining $1.7 \%$ from proteins. Protein intake from food averaged considerably below recommended levels, but Kouros did take protein supplements in tablet. The unusually large daily energy intake, which ranged from 8,600 to $13,770 \mathrm{kCal}$, came from Greek sweets (baklava, cookies, and doughnuts), some chocolate, dried fruit and nuts, various fruit juices, and fresh fruits. Every 30 minutes after the first 6 hours of running, Kouros replaced sweets and fruit with a small biscuit soaked in honey or jam. He consumed a small amount of roasted chicken on day 4 and drank coffee every morning. He took a $500-\mathrm{mg}$ vitamin $C$ supplement every 12 hours and a protein tablet twice daily.

Kouros exceptional achievement exemplifies a highly conditioned athlete s exquisite regulatory control for energy balance during this most demanding exercise. He performed at a pace that required an energy metabolism averaging $49 \%$ of aerobic capacity during the first 2 days of competition and $38 \%$ for days 3 through 5 . He also finished the competition without compromising overall health (no muscular injuries or thermoregulatory problems, and body mass remained unchanged); reported difficulties included a severe bout of constipation during the run and frequent urination that persisted for several days postrace.


Figure 3.7 Daily energy expenditure (yellow circles) and energy intake (red circles) for a cyclist during the Tour de France competition. For 3 weeks in July, nearly 200 cyclists ride over and around the perimeter of France, covering 2405 miles, more than 100 miles daily (only 1 day of rest), at an average speed of 24.4 mph . Note the extremely high energy expenditure values and ability to achieve energy balance with liquid nutrition plus normal meals. $P$, stage; $R$, rest day. (Modified from Saris WHM, et al. Adequacy of vitamin supply under maximal sustained workloads; the Tour de France. In: Walter P, et al., eds. Elevated dosages of vitamins. Toronto: Huber Publishers, 1989.)

Another case study of a 37-year-old male ultramarathoner further demonstrates the tremendous capacity for prolonged, high daily energy expenditure. The doubly labeled water technique (discussed in Chapter 8) evaluated energy expenditure during a 2 -week period of a $14,500-\mathrm{km}$ run around Australia in 6.5 months (average $7090 \mathrm{~km} \cdot \mathrm{~d}^{1}$ ) with no days for rest. ${ }^{43}$ Daily energy expenditure over the measurement period averaged 6321 kCal ; daily water turnover equaled 6.1 L . The athlete ran about the same distance each day over the study period as in the entire race period. As such, these data likely represent energy dynamics for the entire run.

## Extreme Ultraendurance Sports

The Iditasport ultramarathon consists of a choice of one race event from among the following options: run 120 km , snowshoe 120 km , bicycle 259 km , cross-country ski 250 km , or snowshoe, ski, and bicycle 250 km . Begun in 1983 as a single-event (Iditaski), a parallel competition emerged in 1987 consisting of long-distance cycling (Iditabike). In 1991, the two races merged along with foot, snowshoe, and triathlon events. The triathlon was discontinued in 1997, and the lengths of all other races changed to 160 km . The competition
begins in late February, and the athletes traverse varied terrain, mostly in the wilderness over frozen rivers and lakes; wooded, rolling hills; and packed snow trails. On any given day, racers can experience extremes in weather conditions, ranging from calm, balmy 30 F to harsh 40 F with blizzard conditions. During the 48 -hour time limit for the event, racers carry a minimum of 15 pounds of survival gear; this includes a sleeping bag rated to 20 F , insulated sleeping pad, bivy sack or tent, stove and 8 ounces of fuel with fire starter (matches or lighter), pot to melt snow, insulated water containers to carry 2 quarts of water, headlamp or flashlight, and a minimum of 1 day s supply of emergency food. The supplies are carried in a backpack or pulled by sled (weighing from 15 to 30 lb ).

Researchers estimated the total energy and macronutrient requirements for 14 participants ( 13 males, 1 female) in the 1995 race with 49 entrants (Fig. 3.8). The bikers consumed the most total calories ( 8458 kCal ), $74.1 \%$ as carbohydrate, $9.4 \%$ as protein, and $16.5 \%$ as fat. A comparison study between 19971998 Iditasport athletes and their 1995 counterparts showed only small differences in energy and nutrient contents except for higher intakes of carbohydrate (78.5\%) and less fat ( $14.5 \%$ ) and protein ( $7.3 \%$ ) for skiers. The

authors concluded that even though the length of the events differed in 19941996 and 1997 1998, few differences existed in the energy content and macronutrient percentages of the diets among the four categories of competitors from the two time periods.

## High-Risk Sports for Marginal Nutrition

Gymnasts, ballet dancers, ice dancers, and weight-class athletes in boxing, wrestling, rowing, and judo engage in arduous training. Owing to the nature of their sport, these athletes continually strive to maintain a lean, light body mass dictated by either esthetic or weight-class considerations. Energy intake often intentionally falls short of energy expenditure, and a relative state of malnutrition develops. ${ }^{94}$

Nutritional supplementation for these athletes may prove beneficial as suggested by the data in Figure 3.9 for daily nutrient intake (\% of RDA) of 97 competitive female gymnasts aged 11 to 14 years. Twenty-three percent of the girls consumed less than 1500 kCal daily, and more than $40 \%$ consumed less than two thirds of the RDA for vitamins E and folic acid and the minerals iron, magnesium, calcium, and zinc. Clearly, many of these adolescent gymnasts needed to upgrade the nutritional quality of their diets or consider supplementation.

## Strategy to Eat More Yet Weigh Less

Physically active individuals generally consume more calories per kg of body mass than sedentary counterparts. The extra energy required for exercise accounts for the larger caloric


Figure 3.8 Energy and macronutrient content of the diets of Iditasport competitors. Multiply kCal value by 4.182 to convert to kJ. (Data for 1995 from Case D, et al. Dietary intakes of participants in the Iditasport ultra-marathon. Alaska Med 1995;37:20. Data reported in the text for 19971998 from Stuempfle K, et al. Dietary factors of participants in the 19941998 Iditasport ultramarathon. Med Sci Sports Exerc 1999;31:S80.)
intake. Paradoxically, the most active men and women, who eat more on a daily basis, weigh less than those who exercise at a lower total caloric expenditure. Regular exercise allows a person to eat more yet weigh less while maintaining a lower percentage of body fat despite the age-related tendency toward weight gain in middle age. ${ }^{9}$ Physically active persons maintain a lighter and leaner body and a healthier heart disease risk profile, despite increased intake of food. Table 3.4 presents a sample model for food intake for active athletes and an example of a $2500-\mathrm{kCal}$ menu with 350 g of carbohydrates. Chapter 30 discusses the important role of exercise for weight control in more detail.


Figure 3.9 Average daily nutrient intake for 97 adolescent female gymnasts ( 11 to 14 y ) related to recommended values. The RDA on the $y$ axis (top) reflects only protein, while energy, CHO, and lipid reflect recommended values. Percentage of gymnasts consuming less than two thirds of the RDA for micronutrients (bottom). Mean age, 13.1 years; mean stature, 152.4 cm (60 in.); mean body mass, 43.1 kg ( 94.8 lb ). (Modified from Loosli AR, Benson J. Nutritional intake in adolescent athletes. Sports Med 1990;37:1143.)

## PRECOMPETITION MEAL

Athletes often compete in the morning following an overnight fast. As pointed out in Chapter 1, significant depletion occurs in the bodys carbohydrate reserves over an 8- to 12 -hour period without eating. This occurs even if the person previously follows appropriate dietary recommendations. Consequently, precompetition nutrition takes on considerable importance. The precompetition meal should provide adequate carbohydrate energy and ensures optimal hydration. Fasting before competition or training makes no sense physiologically because it rapidly depletes liver and muscle glycogen and impairs

## TABLE 3.4 Sample Training Diet ${ }^{a}$

| Body Weight | $\begin{gathered} 110 \mathrm{lb} \\ (50 \mathrm{~kg}) \end{gathered}$ | $\begin{gathered} 132 \mathrm{lb} \\ (60 \mathrm{~kg}) \end{gathered}$ | $\begin{gathered} 154 \mathrm{lb} \\ (70 \mathrm{~kg}) \end{gathered}$ | $\begin{gathered} 176 \mathrm{lb} \\ (80 \mathrm{~kg}) \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
| Total kCal | $2500^{\text {b }}$ | 3000 | 3500 | 4000 |
| Milk group ( 90 kCal) Skim milk, 1 cup Plain, low-fat yogurt, 1 cup | 4 | 4 | 4 | 4 |
| Meat group ( $55 \mathbf{7 5} \mathbf{~ k C a l}$ ) <br> Cooked, lean meat (fish, poultry), 1 oz Egg, 1 <br> Peanut butter, 1 Tbsp <br> Low-fat cheese, 1 oz <br> Cottage cheese, $1 / 4$ cup | 5 | 5 | 6 | 6 |
| Fruits | 7 | 9 | 10 | 12 |
| Vegetables | 3 | 5 | 6 | 7 |
| Grains | 16 | 18 | 20 | 24 |
| Lipids | 5 | 6 | 8 | 10 |

Sample high-carbohydrate 2500 -kCal menu ( 350 g )

| Breakfast | Lunch | Dinner | Snack 1 | Snack 2 |
| :--- | :--- | :--- | :--- | :--- |
| 1 cup bran cereal | 3 oz lean roast beef | Chicken stir-fry: | 3 cups popcorn | 8 oz apple cider |
| 8 oz low-fat milk | 1 hard roll | 3 oz chicken |  |  |
| 1 English muffin | 2 tsp mayonnaise or | mustard, lettuce and | cup diced <br>  <br>  <br> tomato | 2 vegetables |
| 1 tsp margarine | 2 cup rice |  |  |  |
| 4 oz orange juice | $1 / 2$ cup cole slaw | 1 cup orange and |  |  |
|  | 2 gresh plums | grapefruit sections |  |  |
|  | 8 oz seltzer water with lemon | 1 cup vanilla yogurt |  |  |
|  |  |  |  |  |

${ }^{a}$ An active athlete requires approximately 50 kCal of food per kg ( 23 kcal per lb ) of body mass each day to provide enough calories for optimal athletic performance. A training diet ideally consists of approximately $60 \%$ carbohydrates, 15 to $20 \%$ proteins, and less than $25 \%$ lipids.
${ }^{6}$ Numbers below total kCal values are recommended number of daily servings.
Modified from Carbohydrates and Athletic Performance. Sports Science Exchange, vol. 7. Chicago: Gatorade Sports Science Institute, 1988.
exercise performance. If a person trains or competes in the afternoon, breakfast becomes the important meal to optimize glycogen reserves. For late afternoon training or competition, lunch becomes the important source for topping off glycogen stores. Consider the following three factors when individualizing the precompetition meal plan:

## 1. Athlete s food preference

2. Psychological set of competition
3. Digestibility of foods

As a general rule, on competition day exclude foods high in lipid and protein because they digest slowly and remain in the digestive tract longer than foods containing similar energy content as carbohydrate. Precompetition meal timing also deserves consideration. The increased stress and tension that usually accompany competition reduce blood flow to the digestive tract to produce depressed intestinal absorption. It takes 3 to 4 hours to digest, absorb, and store a carbohydrate-rich, precompetition meal as muscle and liver glycogen. Extending the
time for eating beyond this period may negatively affect glycogen replenishment and subsequent endurance exercise. ${ }^{63}$

## Making a ChoiceProtein or Carbohydrate?

The following five reasons justify modifying or even abolishing the high-protein precompetition meal in favor of one high in carbohydrates:

1. Dietary carbohydrates replenish liver and muscle glycogen depletion from the overnight fast.
2. Carbohydrate digestion and absorption are more rapid than either protein or lipid, allowing carbohydrate to provide energy faster and reduce the feeling of fullness after a meal.
3. A high-protein meal elevates resting metabolism more than a high-carbohydrate meal because of protein s greater energy requirements for digestion, absorption, and assimilation. This additional thermic effect could
strain the body s heat-dissipating mechanisms and impair exercise performance in hot weather.
4. Protein catabolism for energy facilitates dehydration during exercise because the byproducts of amino acid breakdown require water for urinary excretion. About 50 mL of water accompanies the excretion of one gram of urea.
5. Carbohydrate, not protein, represents the main energy nutrient for short-term anaerobic activity and high-intensity aerobic exercise.

The ideal precompetition meal maximizes muscle and liver glycogen storage and provides glucose for intestinal absorption during exercise. The meal should accomplish the following three goals:

1. Contain 150 to 300 g of carbohydrate ( 3 to 5 g per kg body mass in either solid or liquid form)
2. Be consumed 3 to 4 hours before exercising
3. Contain relatively little fat and fiber to facilitate gastric emptying and minimize gastrointestinal distress

The benefits of proper precompetition feeding occur only if the athlete maintains a nutritionally sound diet throughout training. Preexercise feedings cannot correct existing nutritional deficiencies or inadequate nutrient intake during the weeks before competition. Chapter 23 discusses how endurance athletes can augment precompetition glycogen storage in conjunction with specific exercise/diet modifications using carbohydrate-loading techniques.

## INTEGRATIVE QUESTION

Outline how to eat well to establish a physically active and healthy lifestyle.

## Liquid and Prepackaged Bars, Powders, and Meals

Commercially prepared nutrition bars, powders, and liquid meals offer an alternative approach in precompetition feeding or as supplemental feedings during periods of competition. These supplements also effectively enhance energy and nutrient intake in training when energy output exceeds energy intake from lack of interest or mismanaged feedings.

## Liquid Meals

Liquid meals provide high carbohydrate content but contain enough lipid and protein to contribute to satiety. They also supply the person with fluid because they exist in liquid form. The liquid meal digests rapidly, leaving essentially no residue in the intestinal tract. Liquid meals prove particularly effective during daylong swimming and track meets, or during tennis, soccer, and basketball tournaments. In these situations,
the person usually has little time for (or interest in) food. Liquid meals offer a practical approach to supplementing caloric intake during the high-energy output phase of training. Athletes can also use liquid nutrition if they have difficulty maintaining body weight, and as a ready source of calories to gain weight.

## Nutrition Bars

Nutrition bars (also called energy bars, protein bars, and diet bars ) contain a relatively high protein content that ranges between 10 and 90 g per bar. The typical $60-\mathrm{g}$ bar contains 25 g ( 100 kCal ) of carbohydrate (equal amounts of starch and sugar), 15 g ( 60 kCal ) of protein, and $5 \mathrm{~g}(45 \mathrm{kCal})$ of lipid ( 3 g or 27 kCal of saturated fat), with the remaining weight as water. Thus, $49 \%$ of the bar s total 205 calories are from carbohydrates, $29 \%$ from protein, and $22 \%$ from lipid. Nutrition bars often include vitamins and minerals ( 30 to $50 \%$ of recommended values), and some contain dietary supplements such as $\beta$-hydroxy- $\beta$-methylbutyrate (HMB). In addition to the above, most energy bars contain at least 10 to 25 added ingredients including, but not limited to: Fruit C2 max carbohydrate blend (organic evaporated cane juice syrup); dried fruit blend (strawberries, cranberries, sugar, rice flour); fruit paste (sugar, mixed fruit juice concentrate from pear, pineapple, apple and peach, apple juice concentrate, apple powder, glycerin, water, pectin, locust bean gum); malodextrin; dextrose; fructose; milk protein isolate; oats; canola oil; citric acid; natural flavor; beet juice color; soy lecithin; salt; almond butter; soy protein isolate; peanut flour (taken from www.powerbar.com/Products/Energize/). These bars must be labeled as dietary supplements rather than as foods.

The composition of nutrition bars generally varies with their purpose. For example, so-called energy bars contain a greater proportion of carbohydrates, whereas diet or weight loss bars are lower in carbohydrate content and higher in protein, usually in the form of whey protein. Mealreplacement bars have the largest energy content (240 to 900 kCal ) with proportionately more of the three macronutrients. Protein bars simply contain a larger amount of protein. Although nutrition bars provide a relatively easy way to obtain important nutrients, they should not totally substitute for normal food intake. They lack the broad array of plant fibers and phytochemicals found in food and contain a relatively high level of saturated fatty acids. As an added warning, these bars sell as dietary supplements so they need not receive independent assessment by the FDA or other federal or state agency to validate the labeling claims for their macronutrient content and composition.

## Nutrition Powders and Drinks

A high protein content between 10 and 50 g per serving represents a unique aspect of nutrition powders and drinks. They also contain added vitamins, minerals, and other dietary supplement ingredients. The powders come in canisters or packets that readily mix with water (or other liquid), while the drinks come
premixed in cans. These products often serve as an alternative to nutrition bars; they are marketed as meal replacements, dieting aids, energy boosters, or concentrated protein sources.

The composition of nutrition powders and drinks varies considerably from nutrition bars. Most nutrition bars contain at least 15 g of carbohydrates to provide texture and taste, whereas powders and drinks contain little carbohydrate. This accounts for the relatively high protein content of powders and drinks. Nutrition powders and drinks generally contain fewer calories per serving than bars, but this can vary for a powder, depending on the liquid used for mixing. When mixed in water, a powdered nutrient supplement can exceed the recommended protein intake percentage and fall below recommended lipid and carbohydrate percentages.

Athletes in training should not use powders and drinks to substitute for regular food because of their relatively high protein content and lack of the broad array of plant fibers and phytochemicals in a well-balanced diet. As with nutrition bars, neither the FDA nor other federal or state agency makes an independent assessment about the validity of labeling claims for nutrient content and composition.

## CARBOHYDRATE FEEDINGS PRIOR TO, DURING, AND IN RECOVERY FROM EXERCISE

Intense aerobic exercise for 1 hour decreases liver glycogen by about $55 \%$, whereas a 2-hour strenuous workout almost depletes the glycogen content of the liver and active muscle fibers. Even supermaximal, repetitive 1- to 5-minute bouts of exercise interspersed with brief rest intervals (e.g., soccer, ice hockey, field hockey, European handball, and tennis) dramatically lower liver and muscle glycogen. The vulnerability of the body s glycogen stores during strenuous exercise has focused research on the potential benefits of carbohydrate feedings immediately before and during exercise. Scientists also study ways to optimize glycogen replenishment in the postexercise recovery period.

## Prior to Exercise

Confusion exists regarding the potential endurance benefits of preexercise ingestion of simple sugars. Some researchers argue that consuming rapidly absorbed high-glycemic carbohydrates within 1 hour before exercising accelerates glycogen depletion. This negatively affects endurance performance by the following two mechanisms:

1. A rapid rise in blood sugar triggers an overshoot in insulin release. An excess of insulin causes a relative hypoglycemia (also called rebound hypoglycemia, or reactive hypoglycemia). Significant blood sugar reduction impairs central nervous system function during exercise.
2. A large insulin release facilitates the influx of glucose into muscle, which disproportionately increases
glycogen catabolism in exercise. At the same time, high insulin levels inhibit lipolysis, which reduces fatty acid mobilization from adipose tissue.
Augmented carbohydrate breakdown and depressed fat mobilization contribute to premature glycogen depletion and early fatigue.

Research in the late 1970s showed that drinking a highly concentrated sugar solution before exercise precipitated early fatigue in endurance activities. When young men and women consumed a $300-\mathrm{mL}$ solution containing 75 g of glucose 30 minutes before cycling exercise, endurance was $19 \%$ less than in similar trials preceded by 300 mL of plain water or a liquid meal of protein, lipid, and carbohydrate. ${ }^{28}$ Paradoxically, the concentrated sugar drink depleted muscle glycogen reserves prematurely compared with drinking plain water. The researchers hypothesized that the dramatic rise in blood sugar within 5 to 10 minutes after consuming the concentrated pre-event sugar drink caused the pancreas to oversecrete insulin (accentuated hyperinsulinemia). This, in turn, triggered rebound hypoglycemia as glucose moved rapidly into muscle. ${ }^{38,115}$ At the same time, insulin inhibited mobilization and use of fat for energy (lipolysis suppression). ${ }^{86}$ Consequently, intramuscular glycogen catabolized to a much greater extent, causing early glycogen depletion and fatigue compared with control conditions. Subsequent research has not corroborated these negative effects of concentrated preexercise sugar feedings on endurance. ${ }^{3,26,86}$ The discrepancy in research findings has no clear explanation. One way to eliminate any potential for negative effects of preexercise simple sugars is to ingest them at least 60 minutes before exercising. ${ }^{34}$ This provides sufficient time to reestablish hormonal balance before exercise begins.

## Debate Concerning Fructose

The small intestine absorbs fructose more slowly than either glucose or sucrose to cause a minimal insulin response with essentially no decline in blood glucose. ${ }^{21}$ The theoretical rationale for fructose use appears plausible, but its exercise benefits remain inconclusive. From a practical standpoint, gastrointestinal distress (vomiting and diarrhea) often accompanies high-fructose beverage consumption, which itself negatively affects exercise performance. After absorption, the liver must first convert the fructose to glucose; this further limits the rapidity of fructose availability as an energy source.

## During Exercise

Physical and mental performance improves with carbohydrate supplementation during exercise. ${ }^{1,104,110,113}$ The addition of protein to the carbohydrate-containing beverage (4:1 ratio of carbohydrate to protein) may delay fatigue and reduce muscle damage compared with supplementation during exercise with carbohydrate only. ${ }^{47,80}$ When a person consumes carbohydrates during endurance exercise, the carbohydrate form exerts little negative effect on hormonal response, exercise metabolism, or endurance performance. ${ }^{12}$ The reason is straightforward:

Increased levels of sympathetic nervous system hormones (catecholamines) released during exercise inhibit insulin release. Concurrently, exercise increases muscles absorption of glucose, so any exogenous glucose moves into the cells with a lower insulin requirement.

Ingested carbohydrate provides a readily available energy nutrient for active muscles during intense exercise. Consuming about 60 g of liquid or solid carbohydrates each hour during exercise benefits high-intensity, long-duration $(\geq 1 \mathrm{~h})$ aerobic exercise and repetitive short bouts of nearmaximal effort. ${ }^{13,50,65}$ Supplemental carbohydrate during protracted intermittent exercise to fatigue also facilitates skill performance such as improved stroke quality during the final stages of prolonged tennis play. Supplementation also blunts the depression of neuromuscular functions associated with prolonged exercise, possibly as a consequence of protecting muscle membrane excitability. ${ }^{91}$ Ingestion of multiple transportable carbohydrates may further enhance endurance performance. ${ }^{22}$ Ingesting glucose plus fructose improved timed-trial cycling performance by $8 \%$ compared with glu-cose-only feedings. Combined glucose, fructose, and sucrose mixtures ingested at a high rate (about 1.8 to $2.4 \mathrm{~g} \cdot \min { }^{1}$ ) produced 20 to $55 \%$ higher exogenous carbohydrate oxidation rates peaking as high as $1.7 \mathrm{~g} \cdot \mathrm{~min}{ }^{1}$ (with reduced oxidation of endogenous carbohydrate) compared with ingestion of an isocaloric amount of glucose. ${ }^{49,77}$

Exogenous carbohydrate intake during intense exercise provides the following three benefits:

1. Spares muscle glycogen, particularly in the type I, slow-twitch muscle fibers, because the ingested glucose powers exercise. ${ }^{100} 102$
2. Maintains a more optimal blood glucose level. This lowers the rating of perceived exertion; elevates plasma insulin; lowers cortisol and growth hormone levels; prevents headache, lightheadedness, and nausea; and attenuates other symptoms of central nervous system distress and diminished muscular performance. ${ }^{10,67,68}$
3. Blood glucose maintenance supplies muscles with glucose when glycogen reserves deplete in the later stages of prolonged exercise. ${ }^{17,37}$

Carbohydrate feedings during exercise at 60 to $80 \%$ of aerobic capacity postpone fatigue by 15 to 30 minutes. ${ }^{20}$ This effect contributes to enhanced performance in endurance competition because well-nourished athletes without supplementation usually fatigue within 2 hours. A single concentrated carbohydrate feeding about 30 minutes before anticipated fatigue (about 2 hours into exercise) proves as effective as periodic carbohydrate ingestion throughout exercise. This later feeding restores the blood glucose level (Fig. 3.10), which delays fatigue by increasing carbohydrate availability to active muscles.

The greatest benefits from carbohydrate feedings emerge during prolonged exercise at about $75 \%$ of aerobic capacity. ${ }^{17}$ Fat provides the primary energy fuel in light-to-moderate


## Glucose polymer $\square$ Placebo

Figure 3.10 Average plasma glucose concentration during prolonged high-intensity aerobic exercise when subjects consumed a placebo or glucose polymer ( 3 g per kg body mass in a $50 \%$ solution). (Modified from Coggan AR, Coyle EF. Metabolism and performance following carbohydrate ingestion late in exercise. Med Sci Sports Exerc 1989;21:59.)
exercise below $50 \%$ of maximum; at this intensity, glycogen reserves do not decrease to a level that limits endurance. ${ }^{2}$ Repeated feedings of carbohydrate in solid form ( 43 g sucrose with 400 mL water) at the beginning and at 1,2 , and 3 hours of exercise maintain blood glucose and slow glycogen depletion during 4 hours of cycling. Glycogen conservation not only extends endurance but also enhances sprint performance to exhaustion at the end of exercise. ${ }^{76,87,93}$ These findings demonstrate that carbohydrate feeding during prolonged, high-intensity exercise either conserves muscle glycogen for later use or maintains blood glucose for use as exercise progresses and muscle glycogen depletes, or both. The end result is as follows: (1) improved endurance at a high steady pace or during intense intermittent exercise and (2) augmented sprint capacity toward the end of prolonged physical efforts. In a marathon run, a sustained high-energy output and final sprint to the finish contribute greatly to a winning performance.

## Replenishing Glycogen Reserves: Refueling for the Next Bout of Intense Training or Competition

All carbohydrates and carbohydrate-containing foods do not digest and absorb at similar rates. Plant starch composed primarily of amylose is a resistant carbohydrate because of its relatively slow hydrolysis rate. Conversely, starch with a relatively high amylopectin content digests more rapidly. The glycemic index provides a relative measure of the increase in
blood glucose concentration in the 2 hours after ingestion of a food containing 50 g of carbohydrate compared with a standard for carbohydrate (usually white bread or glucose) with an assigned value of $100 .{ }^{29}$ Ingesting 50 g of a food with a glycemic index of 45 raises blood glucose concentrations to levels that reach $45 \%$ of the value for 50 g of glucose. The glycemic index is a function of glucose appearance in the systemic circulation (Fig. 3.11) and its uptake by peripheral tissues, which is influenced by the properties of the carbohy-drate-containing food. For example, the food s amylose-toamylopectin ratio and its fiber and fat content influence intestinal glucose absorption, whereas the protein content of the food may augment insulin release to facilitate tissue glucose uptake. ${ }^{81}$ Figure 3.12 presents a sample from the more than 600 foods classified by their glycemic index. This includes high- and low-glycemic index meals of similar calorie and macronutrient composition (see top inset tables).

The glycemic index should not be viewed as an unwavering standard because variability exists among individuals in their response to consuming a specific carbohydrate- containing food. Also, a high-glycemic index rating does not necessarily indicate poor nutritional quality. ${ }^{71,114}$ For example, carrots, brown rice, and corn all have relatively high-glycemic index values yet contain rich quantities of health-protective micronutrients, phytochemicals, and dietary fibers. A food with a mod-erate- to high-glycemic index rating offers more benefit for rapid replenishment of carbohydrate following prolonged exercise than one rated low, ${ }^{19,111}$ even if the replenishment meal contains a small amount of lipid and protein. ${ }^{11}$

Optimal glycogen replenishment benefits individuals involved in regular intense training, tournament competition


Figure 3.11 General response of intestinal glucose absorption following feeding of foods with either (A) low or (B) high glycemic index. Arrows indicate absorption of glucose from the areas of the small intestine.
with qualifying rounds, or events scheduled with only 1 or 2 days for recuperation. An intense bout of resistance training also reduces muscle glycogen reserves. For athletes, acute weight loss by energy restriction without dehydration impairs anaerobic exercise capacity. ${ }^{74}$ Even without full glycogen replenishment, some restoration in recovery provides beneficial effects in the next exercise bout. For example, consuming carbohydrate for only 4 hours in recovery from a glycogendepleting exercise bout improves capacity in subsequent exercise compared with performance when no carbohydrate is eaten in the 4-hour recovery.

## INTEGRATIVE QUESTION

Explain why foods with different glycemic index values dictate the nutritional recommendations for immediate preexercise versus immediate postexercise feedings.

Glycogen depletion of previously exercised muscle augments the resynthesis of glycogen during recovery. ${ }^{116}$ In addition, endurance-trained individuals restore more muscle glycogen than untrained counterparts. ${ }^{42}$ Consuming food after exercising facilitates glucose transport into muscle cells for three reasons:

1. Enhanced hormonal milieu, particularly higher insulin and lower catecholamine levels
2. Increased tissue sensitivity to insulin and intracellular glucose transporter proteins (e.g., GLUT 1 and GLUT 4, members of a family of facilitative monosaccharide transporters that mediate much of glucose transport activity; see Chapter 20)
3. Increased activity of a specific form of the glycogenstoring enzyme glycogen synthase

## Practical Recommendations

Consuming carbohydrate-rich, high-glycemic foods immediately following intense training or competition speeds glycogen replenishment. The addition of protein to the carbohydrate supplement early in recovery can enhance the magnitude of glycogen resynthesis. ${ }^{5}$ One strategy is to consume about 50 to 75 g ( 2 to 3 oz ) of high- to moderateglycemic carbohydrates every 2 hours until reaching 500 to 700 g ( 7 to 10 g per kg of body mass) or until eating a large, high-carbohydrate meal. If immediately ingesting carbohydrate after exercise proves impractical, an alternative strategy entails eating meals that contain 2.5 g of high-glycemic carbohydrate per kg body mass at $2,4,6,8$, and 22 hours postexercise. This replenishes glycogen to levels similar to those with the same protocol begun immediately postexercise. ${ }^{69}$ Legumes, fructose, and milk products have a slow rate of digestion and/or intestinal absorption and should be avoided. Glycogen resynthesis occurs more rapidly if the person remains inactive during the recovery period. ${ }^{16}$



Figure 3.12 Categorization for glycemic index (GI) of common food sources of carbohydrates. The inset table presents high- and low-glycemic index diets that contain the same amounts of energy and macronutrients and derive 50\% of energy from carbohydrate (CHO) and 30\% of energy from lipid. (Diets from Brand-Miller J, Foster-Powell K. Nutr Today 1999;34:64.)

## Glycogen Replenishment Takes Time

Optimal carbohydrate intake replenishes glycogen stores at about 5 to $7 \%$ per hour. Even under the best of circumstances, it takes at least 20 hours to reestablish glycogen stores following glycogen-depleting exercise. Postexercise
consumption of high-glycemic carbohydrates also may speed recovery by facilitating removal of free ammonia that forms at an increased rate during strenuous exercise. Consuming glucose enhances glutamine and alanine synthesis in skeletal muscle; these compounds provide the primary vehicle to transport ammonia out of muscle tissue. ${ }^{33}$

## Cellular Uptake of Glucose

Normal blood glucose concentration (euglycemia) approximates 5 mM , equivalent to 90 mg of glucose per dL $(100 \mathrm{~mL})$ of blood. Following a meal, blood glucose can rise above the hyperglycemic level to about $9 \mathrm{mM}\left(162 \mathrm{mg} \cdot \mathrm{dL}^{-1}\right)$. A decrease in blood glucose concentration well below normal to $2.5 \mathrm{mM}\left(<45 \mathrm{mg} \cdot \mathrm{dL}^{1}\right)$ classifies as hypoglycemia and can occur during starvation or extremes of prolonged exercise.

Glucose entry into red blood cells, brain cells, and kidney and liver cells depends on the maintenance of a positive concentration gradient of glucose across the cell membrane (termed unregulated glucose transport). In contrast, skeletal and heart muscle and adipose tissue require glucose transport via regulated uptake with insulin and GLUT 4, the predominant intracellular glucose transporter protein as the regulating compounds. ${ }^{62}$ Active skeletal muscle can increase the uptake of glucose from the blood, independent of the effect of insulin. This effect persists into the early postexercise period and helps to replenish glycogen stores. Maintaining adequate blood glucose levels during exercise and in recovery decreases possible negative effects from a low blood glucose concentration.

## The Glycemic Index and Preexercise Feedings

The ideal meal immediately before exercising should provide a source of carbohydrate to sustain blood glucose and muscle metabolism while minimizing any increase in insulin release caused by the meal. Maintaining a relatively normal plasma insulin level should theoretically preserve blood glucose availability, optimize fat mobilization and catabolism, and at the same time spare liver and muscle glycogen reserves.

Use the glycemic index to formulate the immediate preexercise feeding. ${ }^{24,26,112}$ Consuming simple sugars (concentrated high-glycemic carbohydrates) immediately before exercising could cause blood sugar to rise rapidly (glycemic response), triggering an excessive insulin release (insulinemic response). In contrast, consuming low-glycemic, carbohy-drate-rich foods (starch with high amylose content or moder-ate-glycemic carbohydrate with high dietary fiber content) in the immediate 45 - to 60 -minute preexercise period allows a slower rate of glucose absorption (less insulinemic response). This strategy would eliminate the insulin surge, while a steady supply of slow-release glucose remains available from the digestive tract throughout exercise. This effect should prove beneficial during prolonged, high-intensity exercise (such as ocean swimming), where it often becomes impractical to consume carbohydrate during the activity.

Several studies support the wisdom of consuming lowglycemic carbohydrates (starch with high amylose content or moderate-glycemic carbohydrates with high fiber content) 45 to 60 minutes prior to exercise to allow for a slower rate of glucose absorption and reduce the potential for a rebound glycemic response. For trained cyclists who performed highintensity aerobic exercise, a preexercise low-glycemic meal
of lentils extended endurance compared with feedings of glucose or a high-glycemic meal of potatoes of equivalent carbohydrate content. ${ }^{96}$ A moderate-glycemic index breakfast cereal with added dietary fiber eaten 45 minutes before moderately intense exercise increased time to fatigue by $16 \%$ over control conditions or a high-glycemic meal without fiber. ${ }^{55}$

Maintaining relatively high plasma glucose levels during prolonged exercise following a preexercise meal of low-glycemic carbohydrate also enhances subsequent performance at maximal effort (Fig. 3.13). Ten trained cyclists consumed either a low-glycemic or high-glycemic meal 30 minutes before bicycling for 2 hours at $70 \% \mathrm{VO}_{2 \max }$ followed by bicycling to exhaustion at $100 \% \mathrm{VO}_{2 \text { max }} \cdot{ }^{21}$ The low-glycemic meal produced lower plasma insulin levels after 20 minutes of exercise. After 2 hours, carbohydrate oxidation and plasma glucose levels remained higher, with ratings of perceived exertion lower than under the high-glycemic conditions. Thereafter, time to exhaustion exercising at $\mathrm{VO}_{2 \max }$ averaged $59 \%$ longer than the highglycemic maximal effort. Some research does not support the wisdom of preexercise low-glycemic feedings to enhance endurance performance. ${ }^{36,35,111}$ Further study of the topic seems warranted.

INTEGRATIVE QUESTION
Advise an endurance athlete whose pre-event nutrition consists of a fast-food hamburger and high-protein shake consumed 1 hour before competition.

## GLUCOSE FEEDINGS, ELECTROLYTES, AND WATER UPTAKE

As we discuss in Chapter 25, ingesting fluid before and during exercise minimizes the detrimental effects of dehydration on cardiovascular dynamics, temperature regulation, and exercise performance. Adding carbohydrate to an oral rehydration solution provides additional glucose energy. Determining the optimal fluid/carbohydrate mixture and volume becomes important to minimize fatigue and prevent dehydration. Concern centers on the dual observations that (1) a large fluid volume intake impairs carbohydrate uptake, whereas (2) a concentrated sugar solution impairs fluid replenishment.

## Important Considerations

The rate the stomach empties affects fluid and nutrient absorption by the small intestine. Figure 3.14 shows the important factors that influence gastric emptying. Little negative effect of exercise on gastric emptying occurs up to an intensity of about $75 \%$ of maximum, after which the emptying rate slows. ${ }^{60}$ A major factor to speed gastric emptying (and compensate for any inhibitory effects of the beverages carbohydrate content) involves maintaining a relatively high fluid

$a_{\text {The glycemic index ( } \mathrm{GI} \text { ) of mixed meals is expressed as the weighted }}$ mean of the GI values of each of the component foods, with the weighting based on the percentage of the total meal carbohydrate provided by each food.

C Mean dietary composition of meals $a$

|  | High GI Meal <br> $(\mathrm{HGI})$ | Low GI Meal <br> $(\mathrm{LGI})$ |
| :--- | :---: | :---: |
| Available CHO (g) | 113 | 113 |
| Protein (g) | 18 | 33 |
| Fat (g) | 6 | 9 |
| Dietary fiber (g) | 5 | 57 |
| Total energy | 2418 | 2782 |
| $\mathrm{~kJ} /$ meal | 578 | 665 |
| $\mathrm{kCal} / \mathrm{meal}$ |  |  |

a Data from United States Department of Agriculture, Home and Garden Bulletin, No. 72. Nutritive Value of Foods. Washington, D.C., U.S. Government Printing Office. 1988.

Figure 3.13 (A) All-out cycling time to exhaustion (after 2 h high-intensity exercise) for control (CON), moderately highglycemic index meal (HGI), and low-glycemic index meal (LGI) trials. Values represent the average cycling times for 10 trained cyclists. *Indicates LGI significantly longer than HGI and CON. Inset boxes indicate (B) calculation of mixed-meal glycemic index and (C) average dietary composition of the meals. (From DeMarco HM, et al. Preexercise carbohydrate meals: application of glycemic index. Med Sci Sports Exerc 1999;31:164.)
volume in the stomach. Consuming 400 to 600 mL of fluid immediately before exercise optimizes the beneficial effect of increased stomach volume on fluid and nutrient passage into the intestine. Then, regularly drinking 150 to 250 mL of fluid at 15-minute intervals throughout exercise continually replenishes fluid passed into the intestine. ${ }^{25,56,59,66}$ This protocol produces a fluid delivery rate of about 1 L per hour, a volume sufficient to meet the fluid needs of most endurance athletes. Moderate hypohydration of up to $4 \%$ body mass does not impair the gastric emptying rate. ${ }^{78}$ Fluid temperature does not exert a major effect during exercise, but highly carbonated beverages retard gastric emptying. ${ }^{72}$ Beverages containing alcohol or caffeine induce a diuretic effect (alcohol most pronounced) that facilitates water loss from the kidneys, making them inappropriate for fluid replacement.

## Particles in Solution

Gastric emptying slows when ingested fluids contain a high concentration of particles in solution (osmolality) or possess high caloric content. ${ }^{7,78,107}$ The negative effect of concentrated sugar solutions on gastric emptying diminishes (and plasma volume remains unaltered) when the drink contains a short-chain glucose polymer (maltodextrin) rather than simple sugars. Short-chain polymers (3 to 20 glucose units) derived from cornstarch breakdown reduce the number of particles in solution. Fewer particles facilitate water movement from the stomach for intestinal absorption. Adding small amounts of glucose and sodium (glucose the more important factor) to the oral rehydration solution exerts little negative effect on gastric emptying. ${ }^{30,39}$ Glucose plus sodium actually facilitates fluid uptake by the intestinal lumen because of the rapid, active cotransport of glucose sodium across the intestinal mucosa. Absorption of these particles stimulates water s passive uptake by osmotic action. ${ }^{31,59}$ Extra glucose uptake also helps to preserve blood glucose. The additional glucose then spares muscle and liver glycogen and/or maintains blood glucose should glycogen reserves decrease as prolonged exercise continues.

Adding sodium to a fluid aids in maintaining plasma sodium concentrations. Extra sodium benefits the ultraendurance athlete at risk for hyponatremia because of a large sweat sodium loss coupled with the intake of copious amounts of plain water (see Chapter 2). Maintaining plasma osmolality by adding sodium to the rehydration beverage also reduces urine output and sustains the sodium-dependent osmotic drive to drink (see Chapter 25). ${ }^{75}$ A normal plasma and extracellular fluid osmolality promotes continued fluid intake and fluid retention during recovery.

## fyi <br> Recommendations for Fluid and Carbohydrate Replenishment During Exercise

Monitor dehydration rate from changes in body weight; require urination before postexercise body weight measurement for precise determination of the body s total fluid loss. Each pound of weight loss corresponds to $450 \mathrm{~mL}(15 \mathrm{oz})$ of dehydration.

Drink fluids at the same rate as their estimated depletion (or at least drink at a rate close to $80 \%$ of sweating rate) during prolonged exercise that increases cardiovascular stress, metabolic heat load, and dehydration.
Achieve carbohydrate ( 30 to $60 \mathrm{~g} \cdot \mathrm{~h}{ }^{1}$ ) and fluid requirements by drinking a 4 to $8 \%$ carbohydrate beverage each hour ( 625 to 1250 mL ; average 250 mL every 15 min ).

## Recommended Oral Rehydration Beverage

A 5 to 8\% carbohydrate electrolyte beverage consumed during exercise in the heat contributes to temperature regulation and fluid balance as effectively as plain water. As an added bonus, the drink provides intestinal energy delivery of approximately $5.0 \mathrm{kCal} \cdot \mathrm{min}^{1}$; this helps to maintain glucose metabolism and glycogen reserves in prolonged exercise. ${ }^{35,83}$ Consuming this solution in recovery from prolonged exercise in a warm environment also improves endurance capacity for subsequent exercise. To determine a drink s percentage carbohydrate, divide the carbohydrate content (g) by the fluid volume ( mL ) and multiply by 100 . For example, 80 g of carbohydrate in $1 \mathrm{~L}(1000 \mathrm{~mL})$ of water represents an $8 \%$ solution. Effective fluid absorption during prolonged exercise occurs over a wide range of osmolalities. For example, total fluid absorption of carbohydrate electrolyte beverages with
osmolalities of 197 (hypotonic), 295 (isotonic), and 414 (hypertonic) mOsm per liter of $\mathrm{H}_{2} \mathrm{O}$ did not differ from the absorption rate of a plain water placebo. ${ }^{32}$

Do not confuse the conventional fluid replacement beverage with more-concentrated carbohydrate beverages designed to provide significant carbohydrate without concern for rapid fluid replenishment. These products, composed of 20 to $25 \%$ carbohydrates (largely as maltodextrins to prevent excessive sweetness), are good carbohydrate sources during recovery from heavy training or competition.

Environmental and exercise conditions interact to influence the rehydration solution s optimal composition. Fluid replenishment becomes crucial to health and safety when intense aerobic effort performed under high thermal stress lasts 30 to 60 minutes. The individual should consume a more dilute carbohydrate electrolyte solution ( $5 \%$ carbohydrate). In cooler weather, when dehydration does not pose a problem, a more-concentrated $15 \%$ carbohydrate beverage would suffice. Little difference exists among liquid glucose, sucrose, or starch as the ingested carbohydrate fuel source during exercise. Fructose is undesirable because of its potential to cause gastrointestinal distress. Furthermore, fructose absorption by the gut does not involve the active cotransport process required for glucose sodium. This makes fructose absorption relatively slow and promotes less fluid uptake than an equivalent amount of glucose. The optimal carbohydrate replacement rate during intense aerobic exercise ranges from 30 to 60 g (about 1 to 2 oz ) per hour.


Figure 3.14 Major factors that affect gastric emptying (stomach) and fluid absorption (small intestine).


Figure 3.15 Volume of fluid to ingest each hour to obtain the noted amount of carbohydrate $\left(\mathrm{g} \cdot \mathrm{h}^{1}\right.$ ). (Modified from Coyle EF, Montain SJ. Benefits of fluid replacement with carbohydrate during exercise. Med Sci Sports Exerc 1992;24:S324.)

## fyi <br> The Ideal Oral Rehydration Beverage <br> Tastes good <br> Absorbs rapidly <br> Causes little or no gastrointestinal distress Maintains extracellular fluid volume and osmolality <br> Offers the potential to enhance exercise performance

Figure 3.15 presents a general guideline for fluid intake each hour during exercise for a given amount of carbohydrate replenishment. A tradeoff exists between how much carbohydrate to consume versus gastric emptying. The stomach still empties up to 1700 mL of water per hour even when drinking an $8 \%$ carbohydrate solution. Approximately 1000 mL (about 1 qt ) of fluid consumed each hour probably represents the optimal volume to offset dehydration because larger fluid volumes often produce gastrointestinal discomfort.

## Summary

1. A balanced diet with as few as 1200 kCal provides the vitamin, mineral, and protein requirements of athletes and other individuals who train regularly.
2. The recommended protein intake of 0.83 g per kg body mass represents a liberal requirement believed adequate for nearly all persons regardless of physical activity level.
3. A protein intake between 1.2 and 1.8 g per kg of body mass should adequately meet the possibility of added protein needed during intense exercise training. Athletes generally consume two to four times
the protein RDA because their greater caloric intake usually provides proportionately more protein.
4. No precise recommendations exist for daily lipid and carbohydrate intake. Prudent advice recommends no more than $30 \%$ of daily calories from lipids; of this amount, most should be unsaturated fatty acids. For physically active persons, unrefined polysaccharides should provide $60 \%$ or more of the daily calories ( 400 to 600 g on a daily basis).
5. A high-fat diet stimulates adaptative responses that augment fat catabolism. Reliable research has not demonstrated consistent exercise or training benefits from this dietary modification.
6. Successive days of hard training gradually deplete the body s liver and muscle glycogen reserves and could lead to training staleness (making continued training more difficult).
7. MyPyramid provides a comprehensive and personalized approach for Americans to choose a healthier lifestyle that balances sound nutrition and regular exercise.
8. Intensity of daily physical activity largely determines energy intake requirements. The daily caloric needs of athletes in strenuous sports do not consistently exceed 4000 kCal .
9. The precompetition meal should include foods high in carbohydrates and relatively low in lipids and proteins. Three hours provides sufficient time to digest and absorb the precompetition meal.
10. Commercially prepared liquid meals offer wellbalanced nutritive value, contribute to fluid need, absorb rapidly and leave little residue in the digestive tract.
11. Carbohydrate-containing rehydration solutions consumed during exercise enhance high-intensity
endurance performance by maintaining blood glucose concentration.
12. Glucose supplied via the blood can spare existing glycogen in active muscles during exercise and/or serve as reserve blood glucose for later use should muscle glycogen become depleted.
13. The glycemic index provides a relative measure of blood glucose increase after consuming a specific carbohydrate food. For rapid carbohydrate replenishment after exercise, individuals should consume 50 to 75 g of moderate- to high-glycemic index, car-bohydrate-containing foods each hour.
14. Glycogen stores replenish at a rate of about 5 to $7 \%$ per hour with optimal carbohydrate intake. It takes about 20 hours for full liver and muscle glycogen replenishment following a glycogen-depleting exercise bout.
15. Foods with a low glycemic index digest and absorb at a relatively slow rate to provide a steady supply of slow-release glucose during prolonged exercise.
16. Consuming 400 to 600 mL of fluid immediately before exercise followed by regular fluid ingestion during exercise ( 250 mL every 15 minutes)
optimizes gastric emptying by maintaining a relatively large fluid volume in the stomach.
17. The ideal oral rehydration solution to maintain fluid balance during exercise and heat stress contains between 5 and $8 \%$ carbohydrates.
18. Adding a moderate amount of sodium to fluid stabilizes plasma sodium concentrations to minimize risk for hyponatremia. Added sodium in the rehydration beverage also reduces urine production and sustains the sodium-dependent osmotic drive to drink.

1, References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

USDA s MyPyramid
www.mypyramid.gov
Dietary Guidelines for Americans 2005
www.healthierus.gov/dietaryguidelines/
PowerBar
www.powerbar.com

## SECTION



## OVERVIEW

Biochemical reactions that do not consume oxygen generate considerable energy for short durations. The rapid generation of energy remains crucial in maintaining a high standard of performance in sprint activities and other bursts of all-out exercise. In comparison, longer-duration, less intense exercise extracts energy more slowly from food through reactions that require oxygen. For greatest effectiveness, training the various physiologic systems requires an understanding of three important factors:

1. How the body generates energy to sustain exercise
2. The sources that provide energy

## 3. The energy requirements of diverse physical activities

This section presents a broad overview of how cells extract chemical energy bound within the food molecules and use it to power all forms of biologic work. We emphasize the importance of the food nutrients and processes of energy transfer to sustain physiologic function during light, moderate, and strenuous exercise.

# Interview with Dr. John O. Holloszy 



Education: BS (Oregon State College, Salem, OR); MD (Washington University School of Medicine, St. Louis, MO); postgraduate training (NIH Special Research Fellow, Department of Biological Chemistry, Washington University School of Medicine, St. Louis, MO)
Current Affiliation: Professor of Internal Medicine; Chief, Division of Geriatrics and Gerontology, and Director, Section of Applied Physiology, Washington University School of Medicine, St. Louis, MO

Honors and Awards: See Appendix E, available online at http://thepoint.lww.com/mkk7e

Research Focus: The biological adaptations to exercise
Memorable Publication: Holloszy JO. Biochemical adaptations in muscle. J Biol Chem 1967;242:2278.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

Over the past 25 years, John O. Holloszy has been the most important individual responsible for the development of cellular exercise research. His contributions have advanced knowledge in glucose transport, substrate provision, skeletal muscle metabolism, biochemical adaptations
induced by training, fiber type responses, blood lipids, the aging process, and rehabilitation. His innovative work, which has been applied to health-related aspects of exercise, has spawned a wealth of research inquiries by other investigators. He was the first to introduce postdoctoral training to exercise science. Our valued colleague, whose work has always exemplified quality, has fused exercise science with other disciplines.

## What first inspired you to enter the exercise

 science field? What made you decide to pursue your advanced degree and/or line of research?$>$ After completing medical school and four years of training in Internal Medicine and Endocrinology and Metabolism, I worked for two years as a Lt. Commander in the U.S. Public Health Service. Because of my interest in the prevention of coronary heart disease through diet and exercise, I was stationed at the Physical Fitness Research Laboratory at the University of Illinois.

At the time, Dr. Tom Cureton, Director of the Laboratory and pioneer in the area of endurance exercise training, conducted a year-round, daily exercise program, staffed by his graduate students, for university faculty and other individuals in the community. Most of the participants were middle-aged men, and I was tasked with obtaining information on the physiological
and metabolic effects induced by the exercise program. With the help of some of Dr. Curetons students and junior faculty, particularly James S. Skinner, who used this research for his doctoral dissertation, I conducted a series of studies on the effect of a 6-month exercise program on body composition, blood lipids, and cardiovascular function.

This was my first experience with the effects of endurance training. I became fascinated with the remarkable improvements in endurance and exercise capacity that developed rapidly in response to training. I was also impressed by the decrease in body fat, reduction in serum triglycerides, and improvement in cardiovascular function. I had become convinced by the epidemiological evidence that obesity, ischemic heart disease, and type 2 diabetes were largely diseases of exercise deficiency. But, at the time, there was little research being done on the effects of exercise and research on the biological effects of exercise
was a low priority, generally viewed as unimportant and not prestigious. Therefore, because I had become extremely interested in the biological mechanisms responsible for the adaptive responses to exercise at the cellular level, and because I thought that exercise deficiency had become the country s number one health problem, I decided to devote my career to research on the effects of exercise. My goals were to (1) elucidate the biological mechanisms underlying the improvements in performance and metabolism induced by exercise training; (2) evaluate the roles of exercise in the maintenance of health, treatment of disease, and prevention of loss of independence with advancing age; and, in the process, (3) bring research on the biology of exercise into the scientific mainstream.

## Who were the most influential people in your career, and why?

- The only person who had a major influence on my career was Dr. Hiro Narahara, my mentor during my two years of postdoctoral research training in biochemistry. Like many physicians who come to basic research relatively late in their careers, I tended to be sloppy in laboratory work. Hiro forced me to become careful and accurate in my technical work, although, because of a lack of natural aptitude, I never did become a skilled bench researcher. My other mentors generally tried to dissuade me from devoting my research career to the biology of exercise because they thought that I would ruin my academic career by working in what was at the time a lowprestige area of science.


## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> The most interesting and enjoyable aspects of my involvement in science have been the excitement and intellectual stimulation that comes from making new discoveries.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

> Although it is difficult to single out, the most meaningful contribution that I have made to exercise science-the one that has probably had the greatest impact-is the discovery that endurance training induces an increase in muscle mitochondria. The importance of this finding is that it plays a major role in explaining how endurance training improves endurance and alters the metabolic response to exercise.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

$>$ A career in research in any area of biology can be extremely exciting and rewarding. This is particularly true of exercise science, a field in which there are still so many interesting, unanswered questions. However, biological research is extremely competitive in terms of coming up with novel, important ideas, obtaining research funding, keeping current with new methodology, and getting papers published. I would, therefore, strongly discourage students from pursuing a research career if they are not (1) highly intelligent, able to think independently and originally, with the ability to identify important problems and devise approaches for solving them; (2) highly motivated; (3) persevering and not easily discouraged; and (4) able to write well. There is probably nothing more discouraging than having to struggle for support and advancement, yet to be unsuccessful in one s chosen profession, but the chance for both is extremely high in biological research. A sensible approach for individuals who have an interest in exercise science but are not sure that they can succeed in a research career is to get a professional degree (MD, DO, PT, RN, RD, etc.), preferably along with a PhD. This way, one can remain associated with the research area and yet still be assured of making a good living.


What interests have you pursued outside of your professional career?
> My interests unrelated to my professional career include literature, particularly historical novels, opera; and gourmet food.

Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 20 years?

- The most discouraging aspect of working in the field of exercise science is that, despite the now rather general perception that exercise is necessary for maintenance of health and functional capacity, the majority of people in North America
are sedentary. Therefore, it seems likely to me that the major emphasis during the next 20 years will be (1) from a practical aspect, trying to get people to exercise, and (2) from a basic research perspective, trying to find pharmacological and other approaches that induce some of the same health benefits as exercise.


## You have the opportunity to give a last lecture. Describe its primary focus. <br> - The adaptive response of muscle mitochondria to endurance exercise.



## CHAPTER 4

## Energy Value of Food

## CHAPTER OBJECTIVES

$>$ Describe the method to directly determine the energy content of the macronutrients
> Discuss three factors that influence the difference between a foods gross energy value and its net physiologic energy value
> Define heat of combustion, digestive efficiency, and Atwater general factors
> Compute the energy content of a meal from its macronutrient composition

## MEASUREMENT OF FOOD ENERGY

## The Calorie as a Measurement Unit

For food energy, 1 calorie expresses the quantity of heat needed to raise the temperature of $1 \mathrm{~kg}(1 \mathrm{~L})$ of water 1 C (specifically from 14.5 to 15.5 C ). Thus, a kilogram calorie or kilocalorie (kCal) more accurately defines the calorific value of food and is used in most applications related to food and human energy transfer. For example, if a particular food contains 400 kCal , then releasing the potential energy trapped within this food s chemical structure increases the temperature of 400 L of water 1 C . Different foods contain different amounts of potential energy. One-half cup of peanut butter with a caloric value of 759 kCal contains the equivalent heat energy to increase the temperature 1 C for 759 L of water.

A corresponding unit of heat using Fahrenheit degrees is the British thermal unit, or BTU. One BTU represents the quantity of heat required to raise the temperature of 1 pound (weight) of water 1 F from 63 to 64 F . A clear distinction exists between temperature and heat. Temperature reflects a quantitative measure of an object $s$ hotness or coldness. Heat describes energy transfer or exchange from one object (body or system) to another.

Electrical, mechanical, and heat energy are basically the same and can be changed, one form into another. Using the terminology of the Syst me International d Unit s (International System of Units or SI units), this energy is measured in units of joules (J), named after English physicist James Prescott Joule (1818 1889) whose work formed the basis of the first law of thermodynamics, the law of conservation of energy. One J is the work done, or energy expended, when one Newton ( N ) of force acts through a distance of one meter along the direction of force; in other words, $1 \mathrm{~J}=1$ Newtonmeter (Nm). The J, or more properly in nutritional science kilojoule ( $\mathbf{k J}$ : equals $\mathbf{1 0 0 0} \mathbf{J}$ ), represents the standard international unit to express food energy. To convert kCal to $\mathbf{k J}$, multiply the kCal value by 4.184 (sometimes rounded to 4.19 ). The kJ value for one-half cup of peanut butter, for example,


Conversion between calories and joules. The blue rectangle on the left, labeled heat, corresponds to 1.0 calorie (cal; lowercase c) of heat energy. The blue rectangle labeled work on the right corresponds to 4.184 J; the smaller purple rectangle corresponds to 1.0 J . The areas of the two large rectangles are equal, indicating that 1 cal of heat and 4.184 J of work are equivalent in terms of energy. In terms of everyday life, one joule is equivalent to one-hundredth of the energy in a single drop of beer.


Figure 4.1 A bomb calorimeter directly measures the energy value of food.
equals $759 \mathrm{kCal} \times 4.184$, or 3176 kJ . The megajoule (MJ) equals 1000 kJ ; its use avoids unmanageably large numbers. The following conversions apply: $1000 \mathrm{cal}=1 \mathrm{kCal}=4184 \mathrm{~J}$, or $0.004184 \mathrm{~kJ} ; 1 \mathrm{BTU}=778 \mathrm{ft}-\mathrm{lb}=252 \mathrm{cal}=1055 \mathrm{~J}$. Appendix A (available online at http://thepoint.lww.com/ mkk7e) lists metric system transpositions and conversion constants commonly used in exercise physiology.

## Gross Energy Value of Foods

Food and nutrition laboratories use bomb calorimeters similar to the one illustrated in Figure 4.1 to measure the total or gross energy value of various food macronutrients. Bomb calorimeters operate on the principle of direct calorimetry by measuring the heat liberated as the food completely burns.

Food is placed within a sealed chamber charged with oxygen at high pressure. An electrical current moving through the fuse at the tip ignites the food oxygen mixture. As the food burns, a water jacket surrounding the bomb absorbs the heat energy liberated. The calorimeter remains fully insulated from the ambient environment so the increase in water temperature directly reflects the heat released during a food $s$ oxidation (burning).

Heat of combustion refers to the heat liberated by oxidizing a specific food; it represents the food s total energy value. For example, a teaspoon of margarine releases 100 kCal of heat energy when burned completely in a bomb calorimeter. This
equals the energy required to raise $1.0 \mathrm{~kg}(2.2 \mathrm{lb})$ of ice water to the boiling point. The oxidation pathways of an intact organism and the bomb calorimeter differ, yet the quantity of energy liberated remains the same in the complete breakdown of a food.

## Heat of Combustion: Lipid

The heat of combustion for lipid varies with the structural composition of the triacylglycerol molecule s fatty acids. One $g$ of either beef or pork fat yields 9.50 kCal , whereas oxidizing 1 g of butterfat liberates 9.27 kCal . The average caloric value for 1 g of lipid in meat, fish, and eggs equals 9.50 kCal . In dairy products, the calorific equivalent amounts to 9.25 kCal per gram and in vegetables and fruits 9.30 kCal . The average heat of combustion for lipid equals 9.4 kCal per gram.

## Heat of Combustion: Carbohydrate

The heat of combustion for carbohydrate varies depending on the arrangement of atoms in the particular carbohydrate molecule. The heat of combustion for glucose equals 3.74 kCal per gram, whereas glycogen $(4.19 \mathrm{kCal})$ and starch $(4.20 \mathrm{kCal})$ yield larger values. The heat of combustion for one gram of carbohydrate generally represents 4.2 kCal .

## Heat of Combustion: Protein

Two factors affect energy release during combustion of a food s protein component: (1) the type of protein in the food and (2) the relative nitrogen content of the protein. Common proteins in eggs, meat, corn (maize), and beans (jack, lima, navy, soy) contain approximately $16 \%$ nitrogen and have corresponding heats of combustion that average 5.75 kCal per gram. Proteins in other foods have a somewhat higher nitrogen content (e.g., most nuts and seeds [18.9\%] and wholekernel wheat, rye, millets, and barley [17.2\%]). Whole milk $(15.7 \%)$ and bran $(15.8 \%)$ contain a slightly lower nitrogen percentage. The heat of combustion for protein averages 5.65 kCal per gram.

## Comparing the Energy Value of Macronutrients

The average heats of combustion for the three macronutrients (carbohydrate, $\mathbf{4 . 2} \mathbf{~ k C a l} \cdot \mathrm{g}^{\mathbf{1}}$; lipid, $9.4 \mathbf{k C a l} \cdot \mathrm{~g}^{\mathbf{1}}$; protein, $5.65 \mathbf{k C a l} \cdot \mathbf{g}^{\mathbf{1}}$ ) demonstrate that the complete oxidation of lipid in the bomb calorimeter liberates about $65 \%$ more energy per gram than protein oxidation and $120 \%$ more energy than the oxidation of carbohydrate. Recall from Chapter 1 that lipid molecules contain more hydrogen atoms than either carbohydrate or protein molecules. The common fatty acid palmitic acid, for example, has the structural formula $\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2}$. The ratio of hydrogen atoms to oxygen atoms in fatty acids always exceeds the $2: 1$ ratio in carbohydrates. Simply stated, lipid molecules have more hydrogen atoms available for cleavage and subsequent oxidation for energy than carbohydrates and proteins.

INTEGRATIVE QUESTION
Explain how the oxygen required to burn food can indicate the number of calories in a meal.

One can conclude from the above discussion that lipidrich foods have a higher energy content than foods with less fat. One cup of whole milk contains 160 kCal , whereas the same quantity of skim milk contains only 90 kCal . If a person who normally consumes 1 quart of whole milk each day switches to skim milk, the total calories ingested each year decrease by the equivalent of 25 pounds of body fat. In 3 years, all other things remaining constant, the loss of body fat would approximate 75 pounds! Such a theoretical comparison to cut calories merits serious consideration because of the almost identical nutrient composition (besides the fat) between whole milk and skim milk. Drinking skim rather than whole milk also reduces intake of saturated fatty acids ( 0.4 vs . $5.1 \mathrm{~g} ; 863 \%$ ) and cholesterol ( $0.3 \mathrm{vs} .33 \mathrm{mg} ; 910 \%$ ).

## Net Energy Value of Foods

Differences exist in the energy value of foods when the heat of combustion (gross energy value) determined by direct calorimetry contrasts with the net energy available to the body. This pertains particularly to protein because the body cannot oxidize the nitrogen component of this nutrient. In the body, nitrogen atoms combine with hydrogen to form urea $\left(\mathrm{NH}_{2} \mathrm{CONH}_{2}\right)$, which the kidneys excrete in the urine. Elimination of hydrogen in this manner represents a loss of approximately $19 \%$ of the protein molecule s potential energy. This hydrogen loss reduces protein $s$ heat of combustion to approximately $4.6 \mathbf{k C a l}$ per gram instead of 5.65 kCal per gram released during oxidation in the bomb calorimeter. In contrast, the physiologic fuel values of carbohydrates and lipids (which contain no nitrogen) are identical to their heats of combustion in the bomb calorimeter.

## Coefficient of Digestibility

The efficiency of the digestive process influences the ultimate energy yield from the food macronutrients. Numerically defined as the coefficient of digestibility, digestive efficiency indicates the percentage of ingested food actually digested and absorbed to meet the body s metabolic needs. The food residue remaining unabsorbed in the intestinal tract is voided in the feces. Dietary fiber reduces the coefficient of digestibility; a high-fiber meal has less total energy absorbed than a fiber-free meal of equivalent energy content. This variance occurs because fiber moves food through the intestine more rapidly, reducing time for absorption. Fiber also may cause mechanical erosion of the intestinal mucosa, which is then resynthesized through energy-requiring processes.

Table 4-1 shows different digestibility coefficients, heats of combustion, and net energy values for nutrients in the various food groups. The relative percentage of the macronutrients

TABLE 4.1 Factors for Digestibility, Heats of Combustion, and Net Physiologic Energy Values ${ }^{a}$ of Protein, Lipid, and Carbohydrate

| Food Group | Digestibility <br> $(\%)$ | Heat of Combustion <br> $\left(\mathbf{k C a l} \cdot \mathbf{G}^{-1}\right)$ | Net Energy <br> $\left(\mathbf{k C a l} \cdot \mathbf{G}^{-1}\right)$ |
| :--- | :---: | :---: | :---: |
| Protein |  |  |  |
| Animal food | 97 | 5.65 | 4.27 |
| Meats, fish | 97 | 5.65 | 4.27 |
| Eggs | 97 | 5.75 | 4.37 |
| Dairy products | 97 | 5.65 | 4.27 |
| Vegetable food | 85 | 5.65 | 3.74 |
| Cereals | 85 | 5.80 | 3.87 |
| Legumes | 78 | 5.70 | 3.47 |
| Vegetables | 83 | 5.00 | 3.11 |
| Fruits | 85 | 5.20 | 3.36 |
| Average protein | 92 | 5.65 | 4.05 |
| Lipid |  |  |  |
| Meat and eggs | 95 | 9.50 | 9.03 |
| Dairy products | 95 | 9.25 | 8.79 |
| Animal food | 95 | 9.40 | 8.93 |
| Vegetable food | 90 | 9.30 | 8.37 |
| Average lipid | 95 |  | 8.93 |
| Carbohydrate |  | 3.90 |  |
| Animal food | 98 | 4.20 | 3.82 |
| Cereals | 98 | 4.20 | 4.11 |
| Legumes | 97 | 4.20 | 4.07 |
| Vegetables | 95 | 3.00 | 3.99 |
| Fruits | 90 | 4.15 | 3.60 |
| Sugars | 98 | 4.87 |  |
| Vegetable food | 97 | 4.03 |  |
| Average carbohydrate | 97 | 4.03 |  |
| F |  |  |  |

From Merrill AL, Watt BK. Energy values of foods: basis and derivation. Agricultural Handbook no. 74, Washington, DC: USDA, 1973.
${ }^{a}$ Net physiologic energy values are computed as the coefficient of digestibility times the heat of combustion adjusted for energy loss in urine.
digested and absorbed averages 97\% for carbohydrate, 95\% for lipid, and $92 \%$ for protein. Little difference exists in digestive efficiency between obese and lean individuals, yet considerable variability exists in efficiency percentages for any food within a particular category. Proteins in particular have digestive efficiencies ranging from a low of about $78 \%$ for protein in legumes to a high of $97 \%$ for protein from animal sources. Some advocates promote vegetables in weight-loss diets because of plant protein s relatively low coefficient of digestibility. From the data in Table 4.1, one can round the average net energy values to whole numbers referred to as Atwater general factors. Named for Wilbur Olin Atwater (1844 1907), the 19th-century chemist who pioneered human nutrition and energy balance studies at Wesleyan College, these values indicate the net metabolizable energy available to the body from ingested foods. The Atwater general factors provide a
reasonable estimate of the energy content of the daily diet (see In a Practical Sense, p. 115). For alcohol, $7 \mathrm{kCal}(29.4 \mathrm{~kJ})$ represents each $\mathrm{g}(\mathrm{mL})$ of pure (200-proof) alcohol ingested. In terms of potential energy available to the body, alcohol s efficiency of use equals that of other carbohydrates.

The Atwater 4-9-4 kCal rule generally proves useful to estimate the intake of food energy. Limitations do exist, however, particularly when consuming foods that include carbohydrate bulking agents. For example, polysaccharides obtained from industrial gums, modified starches, and plant cell walls, which are largely combinations of cellulose, hemicellulose and a small amount of lignin, are common bulking agents in prepared foods. These agents may be totally digestible, partially digestible, or indigestible, including soluble or insoluble, depending on their chemical structure. They pass through the intestinal tract with little breakdown because no naturally

## IN A PRACTICAL SENSE

## Determining a Foods Macronutrient Composition and Energy Contribution

Food labels must indicate a foods macronutrient content (g) and total calories (kCal). Knowing the energy value per gram for carbohydrate, lipid, and protein in a food allows the ready computation of the percentage kCal derived from each macronutrient. The net energy value, referred to as Atwater general factors, equals 4 kCal for carbohydrate, 9 kCal for lipid, and 4 kcal for protein.

## CALCULATIONS

The table shows the macronutrient composition for one large serving of McDonalds French fries (weight, 122.3 g [4.3 oz]). [ Note: McDonalds publishes the weight of each of the macronutrients for one serving along with the total kCal value.]

1. Calculate kCal value of each macronutrient (column 4).

Multiply the weight of each nutrient (column 2) by the appropriate Atwater general factor (column 3).
2. Calculate percentage weight of each nutrient (column 5).

Divide weight of each macronutrient (column 2) by the foods total weight.
3. Calculate percentage kCal for each macronutrient (column 6). Divide kCal value of each macronutrient (column 4) by foods total kCal value.

## LEARN TO READ FOOD LABELS

Computing the percentage weight and kCal of each macronutrient in a food promotes wise decisions in choosing foods. Manufacturers must state the absolute and percentage weights for each macronutrient, but computing their absolute and percentage energy contributions completes the more important picture. In the example for French fries, lipid represents only $17 \%$ of the foods total weight. However, the percentage of total calories from lipid jumps to $48.3 \%$, or about 195 kCal of this foods 402 kCal energy content. This information becomes crucial for those interested in maintaining a low-fat diet.

Similar computations can estimate the caloric value of any food serving. Of course, increasing or decreasing portion sizes, adding lipid-rich sauces or creams, or using fruits or calorie-free substitutes affects the caloric content accordingly.

```
Macronutrient Energy Content and Percentage Composition
of McDonalds French Fries, Large (Total Weight, 122.3 g [4.3 oz])
```

| (1) Nutrient | (2) Weight | (3) <br> Atwater General Factor | (4) <br> kCal | (5) \% of Weight | (6) <br> \% of kCal |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Protein | 6 | $4 \mathrm{kCal} \cdot \mathrm{g}^{-1}$ | 24 | 4.9 | 6.0 |
| Carbohydrate | 45.9 | $4 \mathrm{kCal} \cdot \mathrm{g}^{-1}$ | 183.6 | 37.5 | 45.7 |
| Lipid | 21.6 | $9 \mathrm{kCal} \cdot \mathrm{g}^{-1}$ | 194.4 | 17.7 | 48.3 |
| Ash | 3.2 |  | 0 | 2.6 | 0 |
| Water | 45.6 |  | 0 | 37.3 | 0 |
| Total | 122.3 |  | 402 | 100 | 100 |

occurring enzymes are present to cause hydrolysis (hence no energy value to the body). In these cases the Atwater conversions become problematic.

## Atwater General Factors

- 4 kCal per gram for dietary carbohydrate
- 9 kCal per gram for dietary lipid
- 4 kCal per gram for dietary protein


## Use of Tabled Values

Computing the kCal content of foods requires considerable time and labor. Various governmental agencies in the United States and elsewhere have assessed the nutritive values for
thousands of foods. The most comprehensive data bank resources include the United States Nutrient Data Bank (USNDB; www.ars.usda.gov/main/site_main.htm?modecode=12354500), maintained by the U.S. Department of Agriculture s Consumer Nutrition Center, and a computerized data bank maintained by the Bureau of Nutritional Sciences of Health and Welfare Canada. Appendix B (available online at http://thepoint.lww. com/mkk7e) presents the energy and nutritive values for common foods and lists resources for finding values of specialty and fast-food items.

A brief review of Appendix B indicates that large differences exist between the energy values of various foods. Consuming an equal number of calories from different foods often requires a tremendous intake of a particular food or a relatively little amount of another. For example, to

## FOCUS ON RESEARCH

## Obesity-Related Thermogenic Response

## Segal KR, Gutin B. Thermic effects of food and exercise in lean and obese women. Metabolism 1983;32:581.

- Considerable research links obesity and impaired thermogenesis-a diminished capacity to increase metabolism in response to different stimuli. These studies note a lower rise in metabolism for obese individuals than for lean individuals after ingestion of a meal, exposure to cold, infusion of noradrenaline, or the combination of eating and exercising. A diminished thermogenic response probably plays an accessory role in total energy conservation, contributing to the onset and persistence of obesity.

The research of Segal and Gutin evaluated the thermogenic difference between overfat (obese) and lean women in response to food intake, two levels of exercise, and the possible potentiation of the thermic effect of food with physical activity. Subjects included 10 obese (\%fat, 37; body mass, 77.9 kg ) and 10 lean (\%fat, 18.8; body mass, 53.2 kg ) women, measured under six different conditions: (a) resting metabolism $\left(\mathrm{VO}_{2}\right)$ for 4 hours; (b) $\mathrm{VO}_{2}$ for 4 hours following consumption of a $910-\mathrm{kCal}$ meal ( $14 \%$ protein, $46 \%$ carbohydrate, $40 \%$ lipid); (c) $\mathrm{VO}_{2}$ during exercise at a constant submaximal intensity of $300 \mathrm{~kg}-\mathrm{m} \cdot \min { }^{1}$ (cycling for 5 min every 0.5 h for 4 h ); (d) $\mathrm{VO}_{2}$ during exercise at an intensity equal to the subject s lactate threshold (cycling for 5 min every 0.5 h for 4 h ); and (e) and ( $f$ ) same as
protocols c and d , except the subjects consumed the test meal before exercising.

The figure indicates that consumption of the $910-\mathrm{kCal}$ meal increased exercise $\mathrm{VO}_{2}$ more for the lean than for the obese women. Stated somewhat differently, a greater difference emerged between the fed and fasting conditions for the lean group at both exercise intensities. The postprandial exercise $\mathrm{VO}_{2}$ for the lean group also remained elevated above the corresponding fasting value at the end of the 4 hours, while for the obese group, the postprandial value at 4 hours equaled their fasting exercise metabolism. Thus, using a 4 -hour measurement underestimated the total amount that eating augmented energy expenditure during exercise for the lean women. These subjects exhibited a larger thermic effect of food during exercise than during rest. Obese subjects, on the other hand, showed similar thermic effects of food for exercise and rest conditions, with no thermogenic bonus from exercise after eating.

The researchers concluded that exercise potentiated the thermic effect of food for lean but not for obese women. The large differences in response to the combination of food and subsequent exercise emerged despite similar thermogenic responses of the lean and obese women to food alone and exercise alone. The cumulative effect of a lower metabolic rate of the obese (compared with lean subjects) during exercise that follows eating favors energy conservation rather than energy dissipation.


Effects of exercise and a 910-kCal meal on metabolic rates of lean and obese men and women. (A) Exercise at lactate threshold; (B) exercise at $300 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$; and (C) rest. Red circles represent postprandial (after the meal) data; yellow circles represent postabsorptive (after fasting) data. The shaded areas indicate the thermic effect of food under each condition.
consume 100 kCal from each of six common foods-carrots, celery, green peppers, grapefruit, medium-sized eggs, and mayonnaise-one must eat 5 carrots, 20 stalks of celery, 6.5 green peppers, 1 large grapefruit, $11 / 4$ eggs, but only 1 tablespoon of mayonnaise. Consequently, a typical sedentary adult female who expends 2100 kCal each day must consume about 420 celery stalks, 105 carrots, 136 green peppers, 26 eggs, yet only $11 / 2$ cup of mayonnaise or 8 oz of salad oil to meet daily energy needs. These examples illustrate dramatically that foods high in lipid content contain considerably more calories than foods low in lipid and correspondingly higher in water content.

INTEGRATIVE QUESTION
What factors account for a discrepancy between computations of the energy value of daily food intake using the Atwater general factors and direct measurement by bomb calorimetry?

Also note that a calorie reflects the food energy regardless of the food source. Thus, from an energy standpoint, 100 calories from mayonnaise equals the same 100 calories in 20 celery stalks. The more a person eats of any food, the more calories consumed. However, a small amount of fatty food represents a considerable number of calories; thus, the term fattening often describes these foods. An individual s caloric intake equals the sum of all energy consumed from either small or large quantities of foods. Celery would become a fattening food if consumed in excess!

## Summary

1. A calorie or kilocalorie ( kCal ) is a measure of heat that expresses a food s energy value.
2. Burning food in the bomb calorimeter permits direct quantification of the food s energy content.
3. The heat of combustion quantifies the amount of heat liberated in the complete oxidation of a food. Average gross energy values equal 4.2 kCal per gram for carbohydrate, 9.4 kCal per gram for lipid, and 5.65 kCal per gram for protein.
4. The coefficient of digestibility represents the proportion of food consumed actually digested and absorbed.
5. Coefficients of digestibility average $97 \%$ for carbohydrates, $95 \%$ for lipids, and $92 \%$ for proteins. The net energy values equal 4 kCal per gram of carbohydrate, 9 kCal per gram of lipid, and 4 kCal per gram of protein. These Atwater general factors provide an accurate estimate of the net energy value of typical foods a person consumes.
6. The Atwater calorific values allow one to compute the energy (caloric) content of any meal from the carbohydrate, lipid, and protein compositions of the food.
7. Calories represent heat energy regardless of the food source. From an energy standpoint, 500 kCal of rocky road ice cream topped with heavy whipped cream and peppermint sprinkles is no more fattening than 500 kCal of watermelon, 500 kCal of cheese and sausage pizza, or 500 kCal of an onion bagel topped with salmon, onions, and sour cream.

Suggested Readings are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

USDA Nutrient Data Laboratory Home Page www.ars.usda.gov/main/site_main.htm?modecode=12354500

## CHAPTER



## Introduction to Energy Transfer

## CHAPTER OBJECTIVES

> Describe the first law of thermodynamics related to energy balance and work within biologic systems
> Define potential energy and kinetic energy and give examples of each
> Discuss the role of free energy in biologic work
> Give examples of exergonic and endergonic chemical reactions within the body and indicate their importance
> State the second law of thermodynamics and give a practical application of this law
> Discuss the role of coupled reactions in biologic processes
> Differentiate between photosynthesis and respiration and give the biologic significance of each
> Identify and give examples of the three forms of biologic work
> Describe how enzymes and coenzymes affect energy metabolism
> Differentiate between hydrolysis and condensation and explain their importance in physiologic function
> Discuss the role of redox chemical reactions in energy metabolism

The capacity to extract energy from the food macronutrients and continually transfer it at a high rate to the contractile elements of skeletal muscle determines one s capacity for swimming, running, or skiing long distances. Likewise, specific energy-transferring capacities that demand all-out, explosive power output for brief durations determine success in weightlifting, sprinting, jumping, and football line play. Although muscular activity represents the main frame of reference in this text, all forms of biologic work require power generated from the direct transfer of chemical energy.

The sections that follow introduce general concepts about bioenergetics that form the basis for understanding energy metabolism during physical activity.

## ENERGYTHE CAPACITY FOR WORK

Unlike the physical properties of matter, one cannot define energy in concrete terms of size, shape, or mass. Rather the term energy reflects a dynamic state related to change; thus, energy emerges only when change occurs. Within this context, energy relates to the performance of work-as work increases so also does energy transfer and thus change. From a Newtonian (mechanical) perspective, work is the product of a given force acting through a given distance. In the body, cells more commonly accomplish chemical and electrical work than mechanical work. Because it is possible to exchange and convert energy from one form to another, we commonly express biologic work in mechanical units.

Bioenergetics refers to the flow and exchange of energy within a living system. The first law of thermodynamics describes a principle related to biologic work. Its basic tenet states that energy cannot be created or destroyed but transforms from one form to another without being depleted. In essence, this law describes the important conservation of energy principle that applies to both living and nonliving systems. In the body, chemical energy within the bonds of the macronutrients does not immediately dissipate as heat during energy metabolism; instead, a large portion remains as chemical energy, which the musculoskeletal system then changes into mechanical energy (and ultimately to heat energy). The first law of thermodynamics dictates that the body does not produce, consume, or use up energy; instead it transforms it from one state into another as physiologic systems undergo continual change.

## 12

## INTEGRATIVE QUESTION

Based on the first law of thermodynamics, why is it imprecise to refer to energy production in the body?

## Potential and Kinetic Energy

Potential energy and kinetic energy constitute the total energy of a system. Figure 5.1 shows potential energy as energy of position, similar to a boulder tottering atop a cliff or water


Figure 5.1 High-grade potential energy capable of performing work degrades to a useless form of kinetic energy. In the example of falling water, the waterwheel harnesses potential energy to perform useful work. For the falling boulder, all of the potential energy dissipates to kinetic energy (heat) as the boulder crashes to the surface below.
before it flows downstream. In the example of flowing water, the energy change is proportional to the water s vertical drop-the greater the vertical drop, the greater the potential energy at the top. The waterwheel harnesses a portion of the energy from the falling water to produce useful work. In the case of the falling boulder, all potential energy transforms to kinetic energy and dissipates as unusable heat.

Other examples of potential energy include bound energy within the internal structure of a battery, a stick of dynamite, or a macronutrient before releasing its stored energy in metabolism. Releasing potential energy transforms it into kinetic energy of motion. In some cases, bound energy in one substance directly transfers to other substances to increase their potential energy. Energy transfers of this type provide the necessary energy for the body s chemical work of biosynthesis. In this process, specific buildingblock atoms of carbon, hydrogen, oxygen, and nitrogen become activated and join other atoms and molecules to synthesize important biologic compounds and tissues. Some newly created compounds provide structure as in bone or the lipid-containing plasma membrane that encloses each cell. Other synthesized compounds such as adenosine triphosphate (ATP) and phosphocreatine (PCr) serve the cell s energy requirements.

## Energy-Releasing and EnergyConserving Processes

The term exergonic describes any physical or chemical process that releases (frees) energy to its surroundings. Such reactions represent downhill processes because of a decline in free energy- useful energy for biologic work that encompasses all of the cell s energy-requiring, life-sustaining processes. Within a cell, where pressure and volume remain relatively stable, free energy (denoted by the symbol $G$ to honor Willard Gibbs [1839 1903] whose research provided the foundation of biochemical thermodynamics) equals the potential energy within a molecule s chemical bonds (called enthalpy, or $H$ ) minus the energy unavailable because of randomness $(S)$ times the absolute temperature ( $\mathrm{C}+273$ ). The equation $G=H-T S$ describes free energy quantitatively.

Chemical reactions that store or absorb energy are endergonic; these reactions represent uphill processes and proceed with an increase in free energy for biologic work. Exergonic processes sometimes link or couple with endergonic reactions to transfer some energy to the endergonic process. In the body, coupled reactions conserve in usable form a large portion of the chemical energy stored within the macronutrients.

Figure 5.2 illustrates the flow of energy in exergonic and endergonic chemical reactions. Changes in free energy occur when the bonds in the reactant molecules form new product molecules with different bonding. The equation that expresses these changes, under conditions of constant temperature, pressure, and volume, takes the following form:

$$
\Delta G=\Delta H-T \Delta S
$$

The symbol $\Delta$ designates change. The change in free energy represents a keystone of chemical reactions. In exergonic reactions, $\Delta G$ is negative; the products contain less free energy than the reactants, with the energy differential released as heat. For example, the union of hydrogen and oxygen to
form water releases 68 kCal per mole (molecular weight of a substance in grams) of free energy in the following reaction:

$$
\mathrm{H}_{2}+\mathrm{O} \rightarrow \mathrm{H}_{2} \mathrm{O}-\Delta G 68 \mathrm{kCal} \cdot \mathrm{~mole}^{-1}
$$

In the reverse endergonic reaction, $\Delta G$ remains positive because the product contains more free energy than the reactants. The infusion of 68 kCal of energy per mole of water causes the chemical bonds of the water molecule to split apart, freeing the original hydrogen and oxygen atoms. This uphill process of energy transfer provides the hydrogen and oxygen atoms with their original energy content to satisfy the principle of the first law of thermodynamics-the conservation of energy.

$$
\mathrm{H}_{2}+\mathrm{O} \leftarrow \mathrm{H}_{2} \mathrm{O}+\Delta G 68 \mathrm{kCal} \cdot \mathrm{~mole}^{-1}
$$

Energy transfer in cells follows the same principles as those in the waterfall waterwheel example. Carbohydrate, lipid, and protein macronutrients possess considerable potential energy within their chemical bonds. The formation of product substances progressively reduces the nutrient molecule s original potential energy with a corresponding increase in kinetic energy. Enzyme-regulated transfer systems harness or conserve a portion of this chemical energy in new compounds for use in biologic work. In essence, living cells serve as transducers with the capacity to extract and use chemical energy stored within a compound s atomic structure. Conversely, and equally important, cells also bond atoms and molecules together to raise them to a higher level of potential energy.

The transfer of potential energy in any spontaneous process always proceeds in a direction that decreases the capacity to perform work. The tendency of potential energy to degrade to kinetic energy of motion with a lower capacity for work (i.e., increased entropy) reflects the second law of thermodynamics. A flashlight battery provides a good illustration. The electrochemical energy stored within its cells slowly dissipates, even if the battery remains unused. The


Figure 5.2 Energy flow in chemical reactions. A. Energy supply prepares an endergonic reaction to proceed because the reactions product contains more energy than the reactant. B. Exergonic reaction releases energy, resulting in less energy in the product than in the reactant.
energy from sunlight also continually degrades to heat energy when light strikes and becomes absorbed by a surface. Food and other chemicals represent excellent stores of potential energy, yet this energy continually decreases as the compounds decompose through normal oxidative processes. Energy, like water, always runs downhill so potential energy decreases. Ultimately, all of the potential energy in a system degrades to the unusable form of kinetic or heat energy.

## INTERCONVERSIONS OF ENERGY

The total energy in an isolated system remains constant; a decrease in one form of energy matches an equivalent increase in another form. During energy conversions, a loss of potential energy from one source often produces a temporary increase in
the potential energy of another source. In this way, nature harnesses vast quantities of potential energy for useful purposes. Even under such favorable conditions, the net flow of energy in the biologic world moves toward entropy, ultimately producing a loss of potential energy.

In 1877, Austrian physicist Ludwig Boltzmann (1844 1906) established the relationship between entropy and the statistical analysis of molecular motion. Entropy reflects the continual process of energy change. All chemical and physical processes proceed in a direction where total randomness or disorder increases and the energy available for work decreases. In coupled reactions during biosynthesis, part of a system may show a decrease in entropy while another part shows an increase. No way exists to circumvent the second law-the entire system always shows a net increase in


Figure 5.3 Interconversions among six forms of energy.
entropy. In a more global sense, the biochemical reactions within the body s trillions of cells (as within the universe as a whole) tilt in the direction of spontaneity that favors disorder and randomness of an irreversible process (i.e., entropy) as originally theorized by Boltzmann.

## Forms of Energy

Figure 5.3 shows energy categorized into one of six forms: chemical, mechanical, heat, light, electrical, and nuclear.

## Examples of Energy Conversions

The conversion of energy from one form to another occurs readily in the inanimate and animate worlds. Photosynthesis and respiration represent the most fundamental examples of energy conversion in living cells.

Photosynthesis. In the sun, nuclear fusion releases part of the potential energy stored in the nucleus of the hydrogen atom. This energy, in the form of gamma radiation, then converts to radiant energy.

Figure 5.4 depicts the dynamics of photosynthesis, an endergonic process powered by energy from sunlight. The pigment chlorophyll, contained in large chloroplast organelles within the leaf s cells, absorbs radiant (solar) energy to synthesize glucose from carbon dioxide and water, while oxygen flows to the environment. The plant also converts carbohydrates to lipids and proteins for storage as a future reserve for energy and to sustain growth. Animals then ingest plant nutrients to serve their own energy and growth needs. In essence, solar energy coupled with photosynthesis powers the animal world with food and oxygen.

Respiration. Figure 5.5 shows the exergonic reactions of respiration, the reverse of photosynthesis, as the plant s stored energy is recovered for biologic work. In the presence of oxygen, the cells extract the chemical energy stored in the carbohydrate, lipid, and protein molecules. For glucose, respiration releases 689 kCal per mole ( 180 g ) oxidized. A portion of the energy released during cellular respiration is conserved in other chemical compounds for use in energyrequiring processes; the remaining energy flows to the environment as heat.


Figure 5.4 The endergonic process of photosynthesis in plants, algae, and some bacteria serves as the mechanism to synthesize carbohydrates, lipids, and proteins. In this example, a glucose molecule forms when carbon dioxide binds with water with a positive free energy (useful energy) change $(+\Delta G)$.


Figure 5.5 The exergonic process of cellular respiration. Exergonic reactions, such as the burning of gasoline or the oxidation of glucose, release potential energy. This produces a negative standard free energy change (i.e., reduction in total energy available for work or $-\Delta G$ ). In this illustration, cellular respiration harvests the potential energy in food to form ATP. Subsequently, the energy in ATP powers all forms of biologic work.

## INTEGRATIVE QUESTION

From the perspective of human bioenergetics, discuss the significance of a bumper sticker that reads: Have you thanked a green plant today?

## BIOLOGIC WORK IN HUMANS

Figure 5.5 also illustrates that biologic work takes one of three forms:

1. Mechanical work of muscle contraction
2. Chemical work that synthesizes cellular molecules
3. Transport work that concentrates substances in the intracellular and extracellular fluids

## Mechanical Work

Mechanical work generated by muscle contraction and subsequent movement provides the most obvious example of energy transformation. The molecular motors in a muscle fiber s protein filaments directly convert chemical energy into mechanical energy. This does not represent the body s only form of mechanical work. In the cell nucleus, contractile elements literally tug at chromosomes to facilitate cell division. Specialized structures (such as cilia) also perform mechanical
work in many cells. In a Practical Sense, see p. 125, shows the method for quantifying work (and power) for three common exercises.

## Chemical Work

All cells perform chemical work for maintenance and growth. Continuous synthesis of cellular components takes place as other components break down. The muscle tissue synthesis that occurs in response to chronic overload in resistance training vividly illustrates chemical work.

## Transport Work

The biologic work of concentrating substances in the body (transport work) progresses much less conspicuously than mechanical or chemical work. Cellular materials normally flow from an area of high concentration to one of lower concentration. This passive process of diffusion does not require energy. Under normal physiologic conditions, some chemicals require transport uphill from an area of lower to higher concentration. Active transport describes this energy-requiring process. Secretion and reabsorption in the kidney tubules rely on active transport mechanisms, as does neural tissue to establish the proper electrochemical gradients about its plasma membranes. These quiet forms of biologic work require a continual expenditure of stored chemical energy.

## FACTORS THAT AFFECT THE RATE OF BIOENERGETICS

The upper limits of exercise intensity ultimately depend on the rate that cells extract, conserve, and transfer chemical energy in food nutrients to the contractile filaments of skeletal muscle. The sustained pace of a marathon runner at close to $90 \%$ of aerobic capacity, or the sprinter s rapid speed in all-out exercise, directly reflects the bodys capacity to transfer chemical energy to mechanical work. Enzymes and coenzymes greatly alter the rate of energy release during chemical reactions.

## fyi

## What Is in a Name?

Because of confusion in the naming of enzymes, the International Union of Biochemistry and Molecular Biology (www.chem.qmul.ac.uk/iubmb/) developed a systematic system that classified and named enzymes according to their specific functions. Each enzyme class has a general name as well as a recommended name. Except for older enzyme names such as renin, trypsin, and pepsin, the suffix ase appends to the enzyme based on its mode of operation or substance with which it interacts.

The six classifications of enzymes are as follows:

1. Oxidoreductases-Catalyze oxidationreduction reactions where the substrate oxidized is regarded as hydrogen or electron donor; includes dehydrogenases, oxidates, oxygenases, reductases, peroxidases, and hydroxylases. (Example = lactate dehydrogenase)
2. Transferases - Catalyze the transfer of a group (for example, the methyl group or a glycosyl group) from one compound (generally regarded as donor) to another compound (generally regarded as acceptor) and include kinases, transcarboxylases, and transaminases. (Example $=$ hexokinase $)$
3. Hydrolases-Catalyze reactions that add water and include esterases, phosphatases, and peptidases. (Example $=$ lipase)
4. Lyases-Catalyze reactions that cleave C C, C O, C N, and other bonds by other means than by hydrolysis or oxidation. They differ from other enzymes in that two substrates are involved in one reaction direction, but only one in the other direction. Include synthases, deaminases, and decarboxylases. (Example = carbonic anhydrase)
5. Isomerases-Catalyze reactions that rearrange molecular structure and include isomerases and epimerases. These enzymes catalyze changes within one molecule. (Example $=$ phosphoglycerate mutase)
6. Ligases-Catalyze bond formation between two substrate molecules with concomitant hydrolysis of the diphosphate bond in ATP or a similar triphosphate. (Example $=$ pyruvate carboxylase)

## Enzymes as Biologic Catalysts

Enzymes are highly specific and large protein catalysts that accelerate the forward and reverse rates of chemical reactions without being consumed or changed in the reaction. Enzymes only govern reactions that normally take place, but at a much slower rate. In a way, enzymes reduce required activation energy-the energy input to initiate a reactionso its rate changes. Enzyme action takes place without altering equilibrium constants and total energy released (free energy change, or $\Delta G$ ) in the reaction. Figure 5.6 contrasts the effectiveness of a catalyst in initiating a chemical reaction with initiation in the uncatalyzed state. The vertical axis represents energy required to activate each reaction; the


Figure 5.6 The presence of a catalyst greatly reduces the activation energy to initiate a chemical reaction compared with the energy for an uncatalyzed reaction. For the uncatalyzed reaction to proceed, the reactant must have a higher free energy level than the product.

## IN A PRACTICAL SENSE

## Measurement of Work on a Treadmill, Cycle Ergometer, and Step Bench

An ergometer is an exercise apparatus that quantifies and standardizes physical exercise in terms of work and/or power output. The most common ergometers include treadmills, cycle and arm-crank ergometers, stair steppers, and rowers.

Work (W) represents application of force (F) through a distance (D):

$$
W=F \times D
$$

For example, for a body mass of 70 kg and vertical jump score of 0.5 m , work accomplished equals 35 kilogram-meters ( $70 \mathrm{~kg} \times 0.5 \mathrm{~m}$ ). The most common units of measurement to express work include kilogram-meters (kg-m), foot-pounds (ft-lb), joules (J), Newtonmeters (Nm), and kilocalories (kCal).

Power ( $P$ ) represents $W$ performed per unit time $(T)$ :

$$
P=F \times D \div T
$$

## CALCULATION OF TREADMILL WORK

Consider the treadmill as a moving conveyor belt with variable angle of incline and speed. Work performed on a treadmill equals the product of the weight (mass) of the person (F) and the vertical distance (vert dist) the person achieves walking or running up the incline. Vert dist equals the sine of the treadmill angle (theta, or $\theta$ ) multiplied by the distance traveled $(D)$ along the incline (treadmill speed $\times$ time).

$$
W=\text { body mass (force) } \times \text { vertical distance }
$$

## EXAMPLE

For an angle $\theta$ of 8 (measured with an inclinometer or determined by knowing the percent grade of the treadmill), the sine of angle $\theta$ equals 0.1392 (see table). The vert dist represents treadmill speed multiplied by exercise duration multiplied by sine $\theta$. For example, vert dist on the incline while walking at $5000 \mathrm{~m} \cdot \mathrm{~h}^{-1}$ for 1 hour equals $696 \mathrm{~m}(5000 \times 0.1392)$. If a person with a body mass of 50 kg walked on a treadmill at an incline of 8 (grade approximately 14\%) for 60 minutes at $5000 \mathrm{~m} \cdot \mathrm{~h}^{-1}$, work accomplished computes as:

$$
\begin{aligned}
\boldsymbol{W} & =\boldsymbol{F} \times \text { vert dist }(\text { sine } \boldsymbol{\theta} \times \boldsymbol{D}) \\
& =50 \mathrm{~kg} \times(0.1392 \times 5000 \mathrm{~m}) \\
& =34,800 \mathrm{~kg}-\mathrm{m}
\end{aligned}
$$

The value for power equals $34,800 \mathrm{~kg}-\mathrm{m} \div 60$ minutes, or $580 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$.

## CALCULATION OF CYCLE ERGOMETER WORK

The mechanically braked cycle ergometer contains a flywheel with a belt around it connected by a small spring at one end and an


| Angle ( ) | Sine ( $\theta$ ) | Grade (\%) |
| :---: | :---: | :---: |
| 1 | 0.0175 | 1.75 |
| 2 | 0.0349 | 3.49 |
| 3 | 0.0523 | 5.23 |
| 4 | 0.0698 | 6.98 |
| 5 | 0.0872 | 8.72 |
| 6 | 0.1045 | 10.51 |
| 7 | 0.1219 | 12.28 |
| 8 | 0.1392 | 14.05 |
| 9 | 0.1564 | 15.84 |
| 10 | 0.1736 | 17.63 |
| 15 | 0.2588 | 26.80 |
| 20 | 0.3420 | 36.40 |

adjustable tension lever at the other end. A pendulum balance indicates the resistance against the flywheel as it turns. Increasing the tension on the belt increases flywheel friction, which increases resistance to pedaling. The force (flywheel friction) represents braking load in kg or kilopounds ( $\mathrm{kp}=$ force acting on $1-\mathrm{kg}$ mass at the normal acceleration of gravity). The distance traveled equals number of pedal revolutions times flywheel circumference.

## EXAMPLE

A person pedaling a bicycle ergometer with a 6-m flywheel circumference at 60 rpm for 1 minute covers a distance (D) of 360 m each minute ( $6 \mathrm{~m} \times 60$ ). If the frictional resistance on the flywheel equals 2.5 kg , total work computes as:

$$
\begin{aligned}
W & =F \times D \\
& =\text { frictional resistance } \times \text { distance traveled } \\
& =2.5 \mathrm{~kg} \times 360 \mathrm{~m} \\
& =900 \mathrm{~kg}-\mathrm{m}
\end{aligned}
$$

Adjustable tension knob -
ob $\qquad$

## IN A PRACTICAL SENSE

Continued

Power generated by the effort equals 900 kg -m in 1 minute or 900 $\mathrm{kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ ( $900 \mathrm{~kg}-\mathrm{m} \div 1 \mathrm{~min}$ ).

## CALCULATION OF WORK DURING BENCH STEPPING

Only the vertical (positive) work can be calculated in bench stepping. Distance (D) computes as bench height times the number of times the person steps; force ( $F$ ) equals the persons body mass $(\mathrm{kg}$ ).

## EXAMPLE

If a $70-\mathrm{kg}$ person steps on a bench $0.375-\mathrm{m}$ high at a rate of 30 steps per minute for 10 minutes, total work computes as

$$
\begin{aligned}
& W=F \times D \\
&=\text { body mass, } \mathrm{kg} \times(\text { vertical distance }[\mathrm{m}] \times \\
&\quad \text { steps per } \min \times 10 \mathrm{~min}) \\
&=70 \mathrm{~kg} \times(0.375 \mathrm{~m} \times 30 \times 10) \\
&=7875 \mathrm{~kg}-\mathrm{m}
\end{aligned}
$$

Power generated during stepping equals $787 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ (7875 kg-m $\div 10 \mathrm{~min}$ ).

horizontal axis plots the reaction s progress. Clearly, initiation (activation) of an uncatalyzed reaction requires considerably more energy than a catalyzed one. Without enzyme action, the complete digestion of a breakfast meal might take 50 years!

Enzymes possess the unique property of not being readily altered by reactions they affect. Consequently, enzyme turnover in the body remains relatively slow, and the specific enzymes are continually reused. A typical mitochondrion may contain up to 10 billion enzyme molecules, each carrying out millions of operations within a brief time. During all-out exercise, enzyme activity increases tremendously as energy demands rise about 100 times above the resting level. A single cell can contain thousands of different enzymes, each with a specific function that catalyzes a distinct cellular reaction. For example, glucose breakdown to carbon dioxide and water requires 19 different chemical reactions, each catalyzed by its own specific enzyme. Many enzymes operate outside the cell-in the bloodstream, digestive mixture, or intestinal fluids.

## Reaction Rates

Enzymes do not all operate at the same rate; some operate slowly, others more rapidly. Consider the enzyme carbonic anhydrase, which catalyzes the hydration of carbon dioxide to form carbonic acid. Its maximum turnover number-number of moles of substrate that react to form product per mole of enzyme per unit time-is 800,000 . In contrast, the turnover number is only 2 for tryptophan synthetase, which catalyzes the final step in tryptophan synthesis. Enzymes also act along small regions of substrate, each time working at a different rate than previously. Some enzymes delay initiating their work. The precursor digestive enzyme trypsinogen, manufactured by the pancreas in inactive form, serves as a good example. Trypsinogen enters the small intestine where upon activation by intestinal enzyme action it becomes the active enzyme trypsin, which digests complex proteins into simple amino acids. Proteolytic action describes this catabolic process. Without the delay in activity, trypsinogen would literally digest the pancreatic tissue that produced it.


Figure 5.7 Effects of $(\mathbf{A})$ temperature and $(\mathbf{B}) \mathrm{pH}$ on the enzyme action turnover rate.

Figure 5.7 shows that pH and temperature dramatically alter enzyme activity. For some enzymes, peak activity requires relatively high acidity, whereas others function optimally on the alkaline side of neutrality. Note that the two enzymes pepsin and trypsin exhibit different pH profiles that modify their activity rates and determine optimal function. Pepsin operates optimally at a pH between 2.4 and 2.6 , whereas trypsin s optimum range approximates that of saliva and milk ( 6.2 to 6.6 ). This pH effect on enzyme dynamics takes place because changing a fluid s hydrogen ion concentration alters the balance between positively and negatively charged complexes in the enzyme s amino acids. Increases in temperature generally accelerate enzyme reactivity. As temperature rises above 40 to 50 C , the protein enzymes permanently denature and their activity ceases.

## Mode of Action

Interaction with its specific substrate represents a unique characteristic of an enzyme s 3-dimensional globular protein structure. Interaction works like a key fitting a lock, as illustrated in Figure 5.8. The enzyme turns on when its active site (usually a groove, cleft, or cavity on the protein s surface) joins in a perfect fit with the substrate $s$ active site. Upon forming an enzyme substrate complex, the splitting of chemical bonds forms a new product with new bonds. This frees the enzyme to act on additional substrate. The example depicts the interaction sequence of the enzyme maltase as it disassembles (hydrolyzes) maltose into its component two glucose building blocks:

Step 1: The active site of the enzyme and substrate line up to achieve a perfect fit, forming an enzyme substrate complex.
Step 2: The enzyme catalyzes (greatly speeds up) the chemical reaction with the substrate. Note that the hydrolysis reaction adds a water molecule.
Step 3: An end product forms (two glucose molecules), releasing the enzyme to act on another substrate.

First proposed in the early 1890s by the German chemist and Nobel laureate Emil Fischer (1852 1919), a lock-and-key mechanism describes the enzyme substrate interaction. This process ensures that the correct enzyme mates with its specific substrate to perform a particular function. Once the enzyme and substrate join, a conformational change in enzyme shape takes place as it molds to the substrate. Even if an enzyme links with a substrate, unless the specific conformational change occurs in the enzyme s shape, it will not interact chemically with the substrate. A more contemporary hypothesis considers the lock and key more of an induced fit because of the required conformational characteristics of enzymes.


Figure 5.8 Sequence of steps in the lock-and-key mechanism of an enzyme with its substrate. The example shows how two monosaccharide glucose molecules form when maltase interacts with its disaccharide substrate maltose.

The lock-and-key mechanism serves a protective function so only the correct enzyme activates a given substrate. Consider the enzyme hexokinase, which accelerates a chemical reaction by linking with a glucose molecule. When this occurs, a phosphate molecule transfers from ATP to a specific binding site on one of glucose s carbon atoms. Once the two binding sites join to form a glucose hexokinase complex, the substrate begins its stepwise degradation (controlled by other specific enzymes) to form less complex molecules during energy metabolism.

## Coenzymes

Some enzymes remain totally dormant unless activated by additional substances termed coenzymes. These nonprotein organic substances facilitate enzyme action by binding the substrate with its specific enzyme. Coenzymes then regenerate to assist in further similar reactions. The metallic ions iron and zinc play coenzyme roles, as do the B vitamins or their derivatives. Oxidation reduction reactions use the B vitamins riboflavin and niacin, while other vitamins serve as transfer agents for groups of compounds in different metabolic processes (see Table 2.1).

## Vitamins Serve As Coenzymes But Do Not Provide Energy

Some advertisements for vitamins imply that taking vitamin supplements provides immediate usable energy for exercise. This simply does not occur. Vitamins often serve as coenzymes to make reactions go, but they contain no chemical energy for biologic work.

A coenzyme requires less specificity in its action than an enzyme because the coenzyme affects a number of different reactions. It either acts as a cobinder or serves as a temporary carrier of intermediary products in the reaction. For example, the coenzyme nicotinamide adenine dinucleotide $\left(\mathbf{N A D}^{+}\right)$forms NADH in transporting hydrogen atoms and electrons released from food fragments during energy metabolism. The electrons then pass to other special transporter molecules in another series of chemical reactions that ultimately deliver the electrons to oxygen.

Enzyme Inhibition. A variety of substances inhibit enzyme activity to slow the rate of a reaction. Competitive inhibitors closely resemble the structure of the normal substrate for an enzyme. They bind to the enzyme s active site but the enzyme cannot change them. The inhibitor repetitively occupies the active site and blunts the enzyme s interaction with its substrate. Noncompetitive inhibitors do not resemble the enzyme s substrate and do not bind to its active site. Instead, they bind to the enzyme at a site other than the active site. This changes the enzyme s structure and ability to catalyze
the reaction because of the presence of the bound inhibitor. Many drugs act as noncompetitive enzyme inhibitors.

## HYDROLYSIS AND CONDENSATION: THE BASIS FOR DIGESTION AND SYNTHESIS

In general, hydrolysis reactions digest or break down complex molecules into simpler subunits; condensation reactions build larger molecules by bonding their subunits together.

## Hydrolysis Reactions

Hydrolysis catabolizes carbohydrates, lipids, and proteins into simpler forms the body easily absorbs and assimilates. This basic decomposition process splits chemical bonds by adding $\mathrm{H}^{+}$and OH (constituents of water) to the reaction byproducts. Examples of hydrolytic reactions include digestion of starches and disaccharides to monosaccharides, proteins to amino acids, and lipids to their glycerol and fatty acid constituents. Specific enzymes catalyze each step of the breakdown process. For disaccharides, the enzymes are lactase (lactose), sucrase (sucrose), and maltase (maltose). The lipid enzymes (lipases) degrade the triacylglycerol molecule by adding water. This cleaves the fatty acids from their glycerol backbone. During protein digestion, protease enzymes accelerate amino acid release when the addition of water splits the peptide linkages. The following represents the general form for all hydrolysis reactions:

$$
\mathrm{AB}+\mathrm{HOH} \rightarrow \mathrm{~A}-\mathrm{H}+\mathrm{B}-\mathrm{OH}
$$

Water added to the substance AB causes the chemical bond that joins AB to decompose to produce the breakdown products A-H (H refers to a hydrogen atom from water) and B-OH (OH refers to the hydroxyl group from water). Figure 5.9A illustrates the hydrolysis reaction for the disaccharide sucrose to its endproduct molecules, glucose and fructose. The figure also shows the hydrolysis of a dipeptide (protein) into its two constituent amino acid units. Intestinal absorption occurs quickly following hydrolysis of the carbohydrate, lipid, and protein macronutrients.

## Condensation Reactions

The reactions of hydrolysis can occur in the opposite direction as the compound AB synthesizes from A-H and B-OH. A water molecule also forms in this building process of condensation (also termed dehydration synthesis). The structural components of the nutrients bind together in condensation reactions to form more complex molecules and compounds. Figure 5.9B shows the condensation reactions for maltose synthesis from two glucose units and the synthesis of a more complex protein from two amino acid units. During protein synthesis, a hydroxyl removed from one amino acid and a hydrogen from the other amino acid join to create a water molecule. Peptide bond describes the new bond that forms for the

## (A) Hydrolysis



## B Condensation



Figure 5.9 A. Hydrolysis of the disaccharide sucrose to the end-product molecules glucose and fructose and the hydrolysis of a dipeptide (protein) into two amino acid constituents. B. A condensation chemical reaction for synthesizing maltose from two glucose units and creation of a protein dipeptide from two amino acid subunits. Note that the reactions in B illustrate the reverse of the hydrolysis reaction for the dipeptide. The symbol $R$ represents the remainder of the molecule.
protein. Water also forms in the synthesis of more complex carbohydrates from simple sugars; for lipids, water forms when glycerol and fatty acid components combine to form a triacylglycerol molecule.

## Oxidation and Reduction Reactions

Literally thousands of simultaneous chemical reactions occur in the body that involve the transfer of electrons from one substance to another. Oxidation reactions transfer oxygen atoms, hydrogen atoms, or electrons. A loss of electrons always occurs in oxidation reactions, with a corresponding net gain in valence. For example, removing hydrogen from a substance yields a net gain of valence electrons. Reduction
involves any process in which the atoms in an element gain electrons, with a corresponding net decrease in valence.

The term reducing agent describes the substance that donates or loses electrons as it oxidizes. The substance being reduced or gaining electrons is called the electron acceptor, or oxidizing agent. Electron transfer requires both oxidizing and reducing agents. Oxidation and reduction reactions become characteristically coupled. Whenever oxidation occurs, the reverse reduction also takes place; when one substance loses electrons, the other substance gains them. The term redox reaction commonly describes a coupled oxidation reduction reaction.

An excellent example of a redox reaction involves the transfer of electrons within the mitochondria. Here, special


Figure 5.10 The mitochondrion, its intramitochondrial structures, and primary chemical reactions. The inset table summarizes the different chemical events in relation to mitochondrial structures.
carrier molecules transfer oxidized hydrogen atoms and their removed electrons for delivery to oxygen, which becomes reduced. The carbohydrate, fat, and protein substrates provide a ready source of hydrogen atoms. Dehydrogenase (oxidase) enzymes speed up the redox reactions. Two hydrogen-accepting dehydrogenase coenzymes are the vitamin B containing $\mathrm{NAD}^{+}$and flavin adenine dinucleotide (FAD). Transferring electrons from NADH and $\mathrm{FADH}_{2}$ harnesses energy in the form of ATP.

Energy release in glucose oxidation occurs when electrons reposition (shift) as they move closer to oxygen atoms-their final destination. The close-up illustration of a mitochondrion in Figure 5.10 shows the various chemical events that take place on the outer and inner mitochondrial membranes and matrix. The inset table summarizes the mitochondrion s molecular reactions related to its structures. Most of the energy-generating action, including the redox reactions, takes place within the mitochondrial matrix. The inner membrane is rich in protein ( $70 \%$ ) and lipid (30\%), two key macromolecules whose configurations encourage transfer of chemicals through membranes.

## INTEGRATIVE QUESTION

What biologic benefit comes from the coupling of oxidation and reduction reactions?

The transport of electrons by specific carrier molecules constitutes the respiratory chain. Electron transport represents the final common pathway in aerobic (oxidative) metabolism. For each pair of hydrogen atoms, two electrons flow
down the chain and reduce one oxygen atom. The process ends when oxygen accepts two hydrogens and forms water. This coupled redox process constitutes hydrogen oxidation and subsequent oxygen reduction. Chemical energy trapped (conserved) during cellular oxidation reduction forms ATP, the energy-rich molecule that powers all biologic work.

Figure 5.11 illustrates a redox reaction during vigorous physical activity. As exercise intensifies, hydrogen atoms are stripped from the carbohydrate substrate faster than their oxidation in the respiratory chain. To continue energy metabolism, a substance other than oxygen must accept the nonoxidized excess hydrogens. This occurs when a pyruvate molecule, an intermediate compound formed in the initial phase of carbohydrate catabolism, temporarily accepts a pair of hydrogens (electrons). A new compound, lactate (ionized lactic acid in the body), forms when reduced pyruvate accepts additional hydrogens. Fig. 5.11 illustrates that as more intense exercise produces a greater flow of excess hydrogens to pyruvate, lactate concentration rises rapidly within the blood and active muscle. During recovery, the excess hydrogens in lactate oxidize (electrons removed and passed to $\mathrm{NAD}^{+}$) to re-form a pyruvate molecule. The enzyme lactate dehydrogenase (LDH) accelerates this reversal. Chapter 6 more fully discusses oxidation reduction reactions in human energy metabolism.

## Measuring Energy Release in Humans

The gain or loss of heat in a biologic system provides a simple way to determine the energy dynamics of any chemical process. In food catabolism within the body, a human calorimeter (see Fig. 8.1), similar to the bomb calorimeter


Figure 5.11 Example of a redox (oxidation reduction) reaction. During progressively more strenuous exercise when oxygen supply (or use) becomes inadequate, some pyruvate formed in energy metabolism gains two hydrogens (two electrons) and becomes reduced to a new compound, lactate. In recovery, when oxygen supply (or use) becomes adequate, lactate loses two hydrogens (two electrons) and oxidizes back to pyruvate. This example shows how a redox reaction continues energy metabolism, despite limited oxygen availability (or use) in relation to exercise energy demands.

## FOCUS ON RESEARCH

## Valid Determination of Oxygen Consumption


#### Abstract

Wilmore JH, Costill DL. Adequacy of the Haldane transformation in the computation of exercise $\mathrm{VO}_{2}$ in man. J Appl Physiol 1973;35:85.


$>$ Oxygen consumption using open-circuit spirometry represents a fundamental measurement in exercise physiology. This methodology assumes no nitrogen production or retention by the body, so the nitrogen volume remains equal in the inspired and expired air. Because of this intrinsic relationship, no need exists to collect and analyze both inspired and expired air volumes during measurement of oxygen consumption and carbon dioxide production. The following mathematical relationship, known as the Haldane transformation, exists between inspired and expired air volumes:

$$
\mathrm{VI}=\mathrm{VE} \times \mathrm{FEN}_{2} \div \mathrm{FIN}_{2}
$$

where Vi equals air volume inspired, Ve equals air volume expired, and $\mathrm{FEN}_{2}$ and $\mathrm{Fin}_{2}$ equal the fractional concentrations of nitrogen in the expired and inspired air. Because the fractional concentrations for inspired oxygen, carbon dioxide, and nitrogen are known, only VE (or $\mathrm{VI}^{\prime}$ ) and the concentrations in expired air of $\mathrm{CO}_{2}\left(\mathrm{FECO}_{2}\right)$ and $\mathrm{O}_{2}\left(\mathrm{FEO}_{2}\right)$ are required to calculate the oxygen consumed each minute $\left(\mathrm{VO}_{2}\right)$ :

$$
\mathrm{VO}_{2}=\mathrm{VE} \times \mathrm{FEN}_{2} / \mathrm{FIN}_{2} \times \mathrm{FIO}_{2}-\mathrm{VE} \times \mathrm{FEO}_{2}
$$

In this formula, $\mathrm{FEN}_{2}$ usually equals $1.00-\left(\mathrm{FEO}_{2}+\right.$ $\mathrm{FeCO}_{2}$ ).

The Wilmore and Costill study determined any nitrogen retention or production and how it influenced the accuracy of oxygen consumption computations using the traditional Haldane transformation during light-to-intense exercise. Six subjects completed treadmill exercise by walking on the level at 4 mph ; a 5-minute jog followed at 6.0 mph , followed again by a 5 -minute run at 7.5 mph . Oxygen consumption, continuously monitored using opencircuit spirometry, included measurement of inspired and expired ventilation volumes. Measurements also included barometric pressure, inspired and expired gas temperatures, relative humidity, and $\mathrm{FEO}_{2}, \mathrm{FECO}_{2}, \mathrm{FIO}_{2}$, and $\mathrm{FICO}_{2}$.

The figure shows $\mathrm{VO}_{2}$ calculated from the inspired and expired air volumes (actual) for all subjects compared with the values estimated from the Haldane transformation. The slope of the regression line deviates only 0.003 units from unity (the intercept equals nearly zero), demonstrating the closeness between the actual oxygen consumption and that predicted by the Haldane transformation. The largest difference between the 68 actual and estimated $\mathrm{VO}_{2}$ values was 230 mL , an error of $7.3 \%$. The average difference of $0.8 \%$ for all subjects fell within the measurement error of the
instruments. For the nitrogen data, a difference of $1.6 \%$ occurred between the minute volume of nitrogen inspired and expired for any subject at any exercise intensity; 11 of 17 subjects work rates exhibited less than $1 \%$ difference. The largest difference, 1099 mL of $\mathrm{N}_{2} \cdot \mathrm{~min}{ }^{1}$, occurred during intense exercise ( $2.1 \%$ difference).

The major sources of variation in assessing $\mathrm{VO}_{2}$ included the measurement of ventilation volume, gas meter calibration, and determination of the inspired air s water vapor pressure $\left(\mathrm{PH}_{20}\right)$. Ventilation volume posed a problem because accuracy depended on the subject being switched in and switched out at the same phase of the tidal volume at the beginning and end of the collection period. This remains difficult (if not impossible) to achieve, so an inspired-to-expired volume differential nearly always occurs. Also, a 10 percentage point difference in inspired $\mathrm{PH}_{20}$ (e.g., from 50 to $60 \%$ relative humidity) produces more than a $100-\mathrm{mL}$ difference between the inspired and expired $\mathrm{N}_{2}$ volumes.

This study supported the continued use of the Haldane transformation to calculate exercise $\mathrm{VO}_{2}$. Although production and/or retention of $\mathrm{N}_{2}$ can occur during exercise, it exerts little or no effect on the $\mathrm{VO}_{2}$ computation.


Actual versus estimated exercise oxygen consumption for six subjects. The solid line represents the line of identity, and the dashed line represents the regression line that predicts oxygen consumption estimated from the Haldane transformation (y axis) from the actual oxygen consumption (x axis). Note the slope of nearly 1.00 and intercept of 0 . Colored data points indicate the same subjects measured under each condition.
described in Chapter 4 (Fig. 4.1), measures the energy change directly as heat ( kCal ) liberated from the chemical reactions.

The complete combustion of food takes place at the expense of molecular oxygen, so the heat generated in these exergonic reactions can be inferred readily from oxygen consumption measurements. Oxygen consumption measurement forms the basis of indirect calorimetry to determine the energy expended by humans during rest and diverse physical activities (see Focus on Research, p. 132). Chapter 8 discusses how direct calorimetry and indirect calorimetry determine heat production (energy metabolism) in humans.

## INTEGRATIVE QUESTION

Discuss the implications of the second law of thermodynamics for measuring energy expenditure.

## Summary

1. Energy, defined as the ability to perform work, emerges only when a change takes place.
2. Energy exists in either potential or kinetic form. Potential energy refers to energy associated with a substance s structure or position; kinetic energy refers to energy of motion. Potential energy can be measured when it transforms into kinetic energy.
3. The six forms of energy are chemical, mechanical, heat, light, electrical, and nuclear. Each energy form can convert or transform to another form.
4. Exergonic energy reactions release energy to the surroundings. Endergonic energy reactions store, conserve, or increase free energy. All potential energy ultimately degrades into kinetic (heat) energy.
5. Living organisms temporarily conserve a portion of potential energy within the structure of new compounds, some of which power biologic work.
6. Entropy describes the tendency of potential energy to degrade to kinetic energy with a lower capacity for work.
7. Plants transfer the energy of sunlight to the potential energy bound within carbohydrates, lipids, and proteins through the endergonic process of photosynthesis.
8. Respiration, an exergonic process, releases stored energy in plants for coupling to other chemical compounds for biologic work.
9. Energy transfer in humans supports three forms of biologic work: chemical (biosynthesis of cellular molecules), mechanical (muscle contraction), or transport (transfer of substances among cells).
10. Enzymes represent highly specific protein catalysts that accelerate chemical reaction rates without being consumed or changed in the reaction.
11. Coenzymes consist of nonprotein organic substances that facilitate enzyme action by binding a substrate to its specific enzyme.
12. Hydrolysis (catabolism) of complex organic molecules performs critical functions in macronutrient digestion and energy metabolism. Condensation (anabolism) reactions synthesize complex biomolecules for tissue maintenance and growth.
13. The linking (coupling) of oxidation reduction (redox) reactions enables oxidation (a substance loses electrons) to coincide with the reverse reaction of reduction (a substance gains electrons). Redox reactions provide the basis for the body s energy-transfer processes.
14. The transport of electrons by specific carrier molecules constitutes the respiratory chain. Electron transport represents the final common pathway in aerobic metabolism.

Suggested Readings are available online at
http://thepoint.lww.com/mkk7e.

## On the Internet

International Union of Biochemistry and Molecular Biology Recommendations on Biochemical and Organic Nomenclature, Symbols \& Terminology
www.chem.qmul.ac.uk/iubmb/

## CHAPTER



## Energy Transfer in the Body

## CHAPTER OBJECTIVES

> Identify the high-energy phosphates and discuss their contributions for energizing biologic work
> Quantify the body s reserves of adenosine triphosphate (ATP) and phosphocreatine ( PCr ) and give examples of physical activities where each energy source predominates
> Outline electron transport oxidative phosphorylation
> Discuss the role of oxygen in energy metabolism
> List the important functions of carbohydrate in energy metabolism
> Describe cellular energy release during anaerobic metabolism
> Contrast the energy-conserving efficiencies of aerobic versus anaerobic metabolism
$>$ Discuss the dynamics of lactate formation and its accumulation in the blood during increasing exercise intensity
> Describe the role of the citric acid cycle in energy metabolism
> Outline the general pathways for energy release during macronutrient catabolism
> Contrast ATP yield from the catabolism of a molecule of carbohydrate, fat, and protein
> Discuss the role of the Cori cycle in exercise energy metabolism
> Outline the interconversions among carbohydrate, fat, and protein
> Explain why fats burn in a carbohydrate flame

The human body demands a continual supply of chemical energy to maintain numerous complex functions. Energy derived from food oxidation does not release suddenly at some kindling temperature (Fig. 6.1A) because the body, unlike a mechanical engine, cannot use heat energy. If it could, body fluids would boil and tissues would burst into flames. Instead, human energy dynamics involve transferring energy via chemical bonds. Potential energy within carbohydrate, fat, and protein bonds releases stepwise in small quantities with the splitting of chemical bonds. A portion of this energy is conserved when new bonds form during enzymatically controlled reactions in the relatively cool, watery medium of the cell (Fig. 6.1B). Energy lost by one molecule transfers to the chemical structure of other molecules without appearing as heat. This provides for a high efficiency of energy transformations. Biologic work occurs when compounds relatively low in potential energy become juiced up from energy transfer via high-energy phosphate bonds. In a sense, the cells receive as much energy as they require.

The story of how the body maintains its continuous energy supply begins with ATP, the special carrier molecule of free energy.

## Part 1 PHOSPHATE BOND ENERGY

## ADENOSINE TRIPHOSPHATE: THE ENERGY CURRENCY

The energy in food does not transfer directly to cells for biologic work. Rather, energy from macronutrient oxidation is harvested and funneled through the energy-rich compound adenosine triphosphate (ATP). The potential energy within this nucleotide molecule powers all of the cell s energyrequiring processes. In essence, the energy donor energy receiver role of ATP represents the cells two major energytransforming activities:

1. Extract potential energy from food and conserve it within the bonds of ATP
2. Extract and transfer the chemical energy in ATP to power biologic work

ATP serves as the ideal energy-transfer agent. It traps within its phosphate bonds a large portion of the original food molecule s potential energy. ATP also readily transfers this


Figure 6.1 A. Heat generated by fire exceeds the activation energy requirement of a macronutrient (e.g., glucose). This causes all of the molecule s potential energy to release suddenly at kindling temperature and dissipate as heat. B. Human energy dynamics involve release of the same amount of potential energy from carbohydrate in small quantities when bonds split during enzymatically controlled reactions. The formation of new molecules conserves energy.


Figure 6.2 Structure of ATP, the energy currency that powers all forms of biologic work. The symbol represents high-energy bonds.
trapped energy to other compounds to raise them to a higher activation level. The cell contains other high-energy compounds (e.g., phosphoenolpyruvate; 1,3, diphosphoglycerate; phosphocreatine), but ATP is the most important. Figure 6.2 shows how ATP forms from a molecule of adenine and ribose (called adenosine) linked to three phosphates, each consisting of phosphorus and oxygen atoms. The bonds that link the two outermost phosphates (symbolized ) represent high-energy bonds because they release considerable useful energy during hydrolysis. A new compound, adenosine diphosphate (ADP) forms when ATP joins with water, catalyzed by the enzyme adenosine triphosphatase (ATPase). The reaction cleaves ATP s outermost phosphate bond to release a phosphate ion (inorganic phosphate) and approximately 7.3 kCal of free energy, or $-\Delta G$ (i.e., energy available for work) per mole of ATP hydrolyzed to ADP. The symbol $\Delta G$ refers to the standard free energy change measured under laboratory conditions ( 25 C ; 1 atmosphere pressure; concentrations maintained at 1 molal at $\mathrm{pH}=7.0$ ). Although standard laboratory conditions are seldom achieved in the body, this expression of free energy change makes possible comparisons under different conditions.

In the intracellular environment, the value may actually approach $10 \mathrm{kCal} \cdot \mathrm{mol}^{1}$.

$$
\mathrm{ATP}+\mathrm{H}_{2} \mathrm{O} \xrightarrow{\text { ATPase }} \mathrm{ADP}+\mathrm{P}_{\mathrm{i}}-\Delta \mathrm{G} 7.3 \mathrm{kCal} \cdot \mathrm{~mol}^{-1}
$$

The free energy liberated in ATP hydrolysis reflects the energy difference between the reactant and end products. This reaction generates considerable free energy, making ATP known as a high-energy phosphate compound. Infrequently, additional energy releases when another phosphate splits from ADP. In some reactions of biosynthesis, ATP donates its two terminal phosphates simultaneously to construct new cellular material. Adenosine monophosphate (AMP) becomes the remaining molecule with a single phosphate group.

The energy liberated during ATP breakdown directly transfers to other energy-requiring molecules. In muscle, the energy stimulates specific sites on the contractile elements to activate the molecular motors that power muscle fibers to shorten. Energy from ATP hydrolysis powers all forms of biologic work; thus, ATP constitutes the cells energy currency. Figure 6.3 illustrates the role of ATP as energy currency for biologic work and its subsequent reconstruction


Figure 6.3 Catabolism anabolism interactions. Continual recycling of ATP for biologic work from intracellular ADP, $\mathrm{P}_{\mathrm{i}}$, and energy released from stored macronutrients.
from ADP and a phosphate ion $\left(\mathrm{P}_{\mathrm{i}}\right)$ via oxidation of the stored macronutrients.

ATP splits almost instantly without oxygen. This capability to hydrolyze ATP anaerobically to generate rapid energy transfer would not occur if energy metabolism required oxygen at all times. Bodily movements requiring this type of energy include sprinting 10 seconds for a bus, lifting an object, swinging a golf club, spiking a volleyball, or performing a pull-up or push-up. In each case, energy metabolism proceeds uninterrupted because the energy required for the activity derives almost exclusively from intramuscular ATP hydrolysis.

The body maintains a continuous ATP supply through different metabolic pathways; some are located in the cell s cytosol, whereas others operate within the mitochondria (Fig. 6.4). For example, the cytosol contains the pathways for ATP production from the anaerobic breakdown of PCr, glucose, glycerol, and the carbon skeletons of some deaminated amino acids. Three reactive processes that harness cellular energy to generate ATP aerobically-the citric acid cycle, $\beta$ oxidation, and respiratory chain-reside within the mitochondria.

## ATP: A Limited Currency

Cells contain a small quantity of ATP and must therefore continually resynthesize it at its rate of use. Only under extreme exercise conditions do ATP levels in skeletal muscle decrease. A limited ATP supply provides a biologically useful mechanism to regulate energy metabolism. By maintaining only a small amount of ATP, its relative concentration (and corresponding ADP, $\mathrm{P}_{\mathrm{i}}$, and AMP concentrations) changes rapidly in response to only a minimal ATP decrease. Any increase in energy requirement immediately disrupts the balance between ATP and ADP and $\mathrm{P}_{\mathrm{i}}$. The imbalance stimulates the breakdown of other stored energy-containing compounds to resynthesize ATP. In this way, the beginning of muscular movement rapidly activates several systems to increase energy transfer. As one might expect, increases in energy transfer depend on exercise
intensity. Energy transfer increases about fourfold in the transition from sitting in a chair to slow walking. Changing from a slow walk to an all-out sprint almost immediately accelerates the rate of energy transfer within active muscles about 120fold.

The body stores only 80 to 100 g (about 3.0 oz ) of ATP at any time under normal resting conditions. This quantity makes available each second approximately 2.4 mmol of ATP per kg wet muscle weight, or about $1.44 \times 10^{10}$ molecules of ATP. This represents enough intramuscular stored energy to


Figure 6.4 Contributors to the anaerobic and aerobic resynthesis of ATP.
power several seconds of explosive, all-out exercise. Thus, ATP alone does not represent a significant energy reserve. This provides an advantage because of the relatively heavy weight of the ATP molecule. A sedentary person resynthesizes an amount of ATP each day equal to about $75 \%$ of body mass. For an endurance athlete who generates 20 times the resting energy expenditure throughout a 2.5 -hour marathon race, this amounts to 80 kg of ATP resynthesis during the run! To appreciate the tremendous quantity of ATP production over the adult portion of a lifespan (assume body weight of 80 kg , relatively sedentary for 50 years after age 20), total ATP production ( 60 kg daily for 50 years) equals the approximate takeoff weight of two Boeing 787 aircraft!

## PHOSPHOCREATINE: THE ENERGY RESERVOIR

To overcome its storage limitation, ATP resynthesis proceeds uninterrupted to continuously supply energy for all of the body s biologic work. Fat and glycogen represent the major energy sources for maintaining as-needed ATP resynthesis. Some energy for ATP resynthesis also comes directly from the anaerobic splitting of a phosphate from phosphocreatine (PCr), another intracellular high-energy phosphate compound. Figure 6.5 schematically illustrates the release and use of phosphate-bond energy in ATP and PCr. The term highenergy phosphates describes these compounds.

The PCr and ATP molecules share a similar characteristic; a large amount of free energy releases when the bond cleaves between the PCr s creatine and phosphate molecules. The double-pointing arrow in the reaction indicates a reversible reaction. In other words, phosphate $(\mathrm{P})$ and creatine $(\mathrm{Cr})$ rejoin to form PCr . This also applies to ATP; ADP plus P re-forms ATP. Because PCr has a larger free energy of hydrolysis than ATP, its hydrolysis catalyzed by the enzyme


Figure 6.5 ATP and PCr provide anaerobic sources of phosphate-bond energy. The energy liberated from the hydrolysis (splitting) of PCr rebonds ADP and $\mathrm{P}_{\mathrm{i}}$ to form ATP.
creatine kinase ( 4 to $6 \%$ on the outer mitochondrial membrane, 3 to $5 \%$ in the sarcomere, and $90 \%$ in the cytosol) drives ADP phosphorylation to ATP. Cells store approximately four to six times more PCr than ATP.

Transient increases in ADP within the muscles contractile unit during exercise shift the creatine kinase reaction toward PCr hydrolysis and ATP production; the reaction does not require oxygen and reaches a maximum energy yield in about 10 seconds. ${ }^{39}$ Thus, PCr serves as a reservoir of highenergy phosphate bonds. The rapidity of ADP phosphorylation considerably exceeds anaerobic energy transfer from stored muscle glycogen because of the high activity rate of creatine kinase. ${ }^{18}$ If maximal effort continues beyond 10 seconds, energy for continual ATP resynthesis must originate from less-rapid catabolism of the stored macronutrients. Chapter 23 discusses the potential for exogenous creatine supplementation to enhance short-term, explosive exercise performance.

The adenylate kinase reaction represents another single-enzyme mediated reaction for ATP regeneration. The reaction uses two ADP molecules to produce one molecule of ATP and AMP as follows:

$$
2 \mathrm{ADP} \stackrel{\text { adenylate kinase }}{\leftrightarrows} \text { ATP }+ \text { AMP }
$$

The creatine kinase and adenylate kinase reactions not only augment the muscle s ability to rapidly increase energy output (ATP availability), they also produce the molecular byproducts AMP, $\mathrm{P}_{\mathrm{i}}$, and ADP that activate the initial stages of glycogen and glucose catabolism and the respiration pathways of the mitochondrion.

## CELLULAR OXIDATION

Most energy for phosphorylation derives from the oxidation ( biologic burning ) of the dietary carbohydrate, lipid, and protein macronutrients. Recall from Chapter 5 that a molecule becomes reduced when it accepts electrons from an electron donor. In turn, the molecule that gives up the electron becomes oxidized. Oxidation reactions (those that donate electrons) and reduction reactions (those that accept electrons) remain coupled and constitute the biochemical mechanism that underlies energy metabolism. This process continually provides hydrogen atoms from the catabolism of stored macronutrients. The mitochondria, the cell s energy factories, contain carrier molecules that remove electrons from hydrogen (oxidation) and eventually pass them to oxygen (reduction). ATP synthesis occurs during oxidation reduction (redox) reactions.

## Electron Transport

Figure 6.6 illustrates the general schema for hydrogen oxidation and accompanying electron transport to oxygen. During cellular oxidation, hydrogen atoms are not merely turned loose in intracellular fluids. Rather, substrate-specific dehydrogenase enzymes catalyze hydrogen s release from


Figure 6.6 A general scheme for oxidizing (removing electrons) hydrogen and the accompanying electron transport. In this process, oxygen is reduced (gain of electrons) and water forms. The liberated energy powers the synthesis of ATP from ADP.
the nutrient substrate. The coenzyme component of the dehydrogenase (usually the niacin-containing nicotinamide adenine dinucleotide $\left[\mathrm{NAD}^{+}\right]$) accepts pairs of electrons (energy) from hydrogen. Although the substrate oxidizes and gives up hydrogens (electrons), $\mathrm{NAD}^{+}$gains hydrogen and two electrons and reduces to NADH; the other hydrogen appears as $\mathrm{H}^{+}$in the cell fluid. The riboflavin-containing coenzyme, flavin adenine dinucleotide (FAD) serves as another electron acceptor to oxidize food fragments. Like $\mathrm{NAD}^{+}$, FAD catalyzes dehydrogenation and accepts electron pairs. Unlike $\mathrm{NAD}^{+}$, FAD becomes $\mathrm{FADH}_{2}$ by accepting both hydrogens. NADH and $\mathrm{FADH}_{2}$ provide energy-rich molecules because they carry electrons with high energy-transfer potential.

The cytochromes, a series of iron-protein electron carriers dispersed on the inner membranes of the mitochondrion, then pass (in bucket brigade fashion) pairs of electrons carried by NADH and $\mathrm{FADH}_{2}$. The iron portion of each cytochrome exists in either its oxidized (ferric or $\mathrm{Fe}^{3+}$ ) or reduced (ferrous, or $\mathrm{Fe}^{2+}$ ) ionic state. By accepting an electron, the ferric portion of a specific cytochrome reduces to its ferrous form. In turn, ferrous iron donates its electron to the next cytochrome and so on down the line. By shuttling between these two iron forms, the cytochromes transfer electrons to ultimately reduce oxygen to form water. $\mathrm{NAD}^{+}$and FAD then recycle for subsequent electron transfer. The NADH generated during glycolysis (see p. 145) converts back to NAD via shuttling of the hydrogens from NADH across the mitochondrial membrane.

Electron transport by specific carrier molecules constitutes the respiratory (or cytochrome) chain, the final common pathway where electrons extracted from hydrogen pass to oxygen. For each pair of hydrogen atoms, two electrons flow down the chain and reduce one atom of oxygen to form one water molecule. During the passage of electrons down the five-cytochrome chain, enough energy releases to rephosphorylate ADP to ATP at three of the sites. Only at the last cytochrome site, cytochrome oxidase (cytochrome $\mathrm{aa}_{3}$, with strong affinity for oxygen), discharges its electron directly to oxygen. Figure 6.7A shows the route for hydrogen oxidation, electron transport, and energy transfer in the respiratory chain that releases free energy in relatively small amounts. In several of the electron transfers, the formation of high-energy phosphate bonds conserves energy. Each electron acceptor in the respiratory chain has a progressively greater affinity for electrons. In biochemical terms, this affinity for electrons represents a substance s reduction potential. Oxygen, the last electron receiver in the transport chain, possesses the largest reduction potential. Thus, mitochondrial oxygen ultimately drives the respiratory chain and other catabolic reactions that require continual availability of $\mathrm{NAD}^{+}$and FAD .

## Oxidative Phosphorylation

Oxidative phosphorylation synthesizes ATP by transferring electrons from NADH and $\mathrm{FADH}_{2}$ to oxygen. Figure 6.8 illustrates that the energy generated in the reactions of electron transport pumps protons across the inner mitochondrial


Figure 6.7 Examples of harnessing potential energy. A. In the body, the electron transport chain removes electrons from hydrogens for ultimate delivery to oxygen. In oxidation reduction, much of the chemical energy stored within the hydrogen atom does not dissipate to kinetic energy, but instead becomes conserved within ATP. B. In industry, energy from falling water becomes harnessed to turn the waterwheel, which in turn performs mechanical work.
membrane into the intermembrane space. The electrochemical gradient generated by this reverse flow of protons represents stored potential energy. It provides the coupling mechanism that binds ADP and a phosphate ion to synthesize ATP. The mi-
tochondrion s inner membrane remains impermeable to ATP, so the protein complex ATP/ADP translocase exports the newly synthesized ATP molecule. In turn, ADP and $\mathrm{P}_{\mathrm{i}}$ move into the mitochondrion for subsequent synthesis to ATP.


1. Energy-releasing reactions of oxidation-reduction (electron transport) create a proton $\left(\mathrm{H}^{+}\right)$gradient across the inner mitochondrial membrane
2. Stored energy of the proton gradient plus the inner mitochondrial membrane potential provide the electrochemical basis for coupling electron transport to oxidative phosphorylation to form ATP

Figure 6.8 The mitochondrion: the site for aerobic energy metabolism. Electron transport creates a proton $\left(\mathrm{H}^{+}\right)$gradient across the inner mitochondrial membrane. This produces a net flow of protons to provide the coupling mechanism to drive ATP resynthesis.

Biochemists refer to this union as chemiosmotic coupling, the cells primary endergonic means to extract and trap chemical energy in the high-energy phosphates. More than $90 \%$ of ATP synthesis takes place in the respiratory chain by oxidative reactions coupled with phosphorylation.

In a way, oxidative phosphorylation can be likened to a waterfall divided into several separate cascades by intervention of waterwheels at different heights. Figure 6.7B depicts the waterwheels that harness the energy of falling water; similarly, electrochemical energy generated during electron transport becomes harnessed and transferred (coupled) to ADP. Energy transfer from NADH to ADP to re-form ATP happens at three distinct coupling sites during electron transport (Fig. 6.7A). Oxidation of hydrogen and subsequent phosphorylation occurs as follows:

$$
\begin{aligned}
& \mathrm{NADH}+\mathrm{H}^{+}+3 \mathrm{ADP}+3 \mathrm{P}_{\mathrm{i}}+1 / 2 \mathrm{O}_{2} \rightarrow \mathrm{NAD}^{+} \\
&+\mathrm{H}_{2} \mathrm{O}+3 \mathrm{ATP}
\end{aligned}
$$

The ratio of phosphate bonds formed to oxygen atoms consumed ( $\mathbf{P} / \mathbf{O}$ ratio) reflects quantitatively the coupling of ATP production to electron transport. In the above reaction note that the P/O ratio equals 3 for each NADH plus $\mathrm{H}^{+}$oxidized. However, if $\mathrm{FADH}_{2}$ originally donates hydrogen, only two ATP molecules form for each hydrogen pair oxidized $(\mathrm{P} / \mathrm{O}$ ratio $=2)$. This occurs because $\mathrm{FADH}_{2}$ enters the respiratory chain at a lower energy level at a point beyond the site of the first ATP synthesis (Fig. 6.7A).

Biochemists have recently adjusted their accounting transpositions regarding conservation of energy in the resynthesis of an ATP molecule in aerobic pathways. Energy provided by oxidation of NADH and $\mathrm{FADH}_{2}$ resynthesizes ADP to ATP, yet additional energy $\left(\mathrm{H}^{+}\right)$is also required to shuttle the NADH from the cells cytoplasm across the mitochondrial membrane to deliver $\mathrm{H}^{+}$to electron transport. This added energy exchange of NADH shuttling across the mitochondrial membrane reduces the net ATP yield for glucose metabolism
and changes the overall efficiency of ATP production (see below). On average, only 2.5 ATP molecules form from oxidation of one NADH molecule. This decimal value for ATP does not indicate formation of one-half ATP molecule but rather indicates the average number of ATP produced per NADH oxidation with the energy for mitochondrial transport subtracted. When $\mathrm{FADH}_{2}$ donates hydrogen, then on average only 1.5 molecules of ATP form for each hydrogen pair oxidized.

## Efficiency of Electron Transport Oxidative Phosphorylation

Each mole of ATP formed from ADP conserves approximately 7 kCal of energy. Because 2.5 moles of ATP regenerate from the total of 52 kCal of energy released to oxidize 1 mole of NADH , about $18 \mathrm{kCal}\left(7 \mathrm{kCal} \cdot \mathrm{mol}^{-1} \times 2.8\right)$ is conserved as chemical energy. This represents a relative efficiency of $34 \%$ for harnessing chemical energy via electron transport oxidative phosphorylation $(18 \mathrm{kCal} \div 52 \mathrm{kCal} \times$ 100). The remaining $66 \%$ of the energy dissipates as heat. If the intracellular energy change for ATP synthesis approaches $10 \mathrm{kCal} \cdot \mathrm{mol}^{1}$, then efficiency of energy conservation approximates $50 \%$. Considering that a steam engine transforms its fuel into useful energy at only about $30 \%$ efficiency, the value of $34 \%$ or above for the human body represents a relatively high efficiency rate.

## OXYGENS ROLE IN ENERGY METABOLISM

Three prerequisites exist for the continual resynthesis of ATP during coupled oxidative phosphorylation. Satisfying the following three conditions causes hydrogen and electrons to shuttle uninterrupted down the respiratory chain to oxygen during energy metabolism:

1. Availability of the reducing agent NADH (or $\mathrm{FADH}_{2}$ ) in the tissues
2. Presence of the oxidizing agent oxygen in the tissues
3. Sufficient concentration of enzymes and mitochondria to ensure that energy transfer reactions proceed at their appropriate rate

In strenuous exercise, inadequacy in oxygen delivery (condition 2) or its rate of use (condition 3 ) creates a relative imbalance between hydrogen release and its terminal oxidation. If either of these deficiencies exists, electron flow down the respiratory chain backs up and hydrogens accumulate bound to $\mathrm{NAD}^{+}$and FAD. On page 148 , we describe how the compound pyruvate, a product of carbohydrate breakdown, temporarily binds excess hydrogens (electrons) to form lactate. Lactate formation allows electron transport oxidative phosphorylation to continue to provide energy.

Aerobic metabolism refers to energy-generating catabolic reactions where oxygen serves as the final electron acceptor in the respiratory chain to combine with hydrogen to
form water. In one sense, the term aerobic seems misleading because oxygen does not participate directly in ATP synthesis. On the other hand, oxygen s presence at the end of the line largely determines the capacity for aerobic ATP production and the sustainability of intense endurance exercise.

## Summary

1. Energy within the molecular structure of carbohydrate, fat, and protein does not suddenly release in the body at some kindling temperature. Rather, energy releases slowly in small amounts during complex, enzymatically controlled reactions to promote more efficient energy transfer and conservation.
2. About $40 \%$ of the potential energy in food nutrients transfers to the high-energy compound ATP.
3. Splitting the terminal phosphate bond from ATP liberates free energy to power all forms of biologic work. This makes ATP the body s energy currency despite its limited quantity of only about 3.0 ounces.
4. PCr interacts with ADP to form ATP; this nonaerobic, high-energy reservoir replenishes ATP almost instantaneously.
5. Phosphorylation refers to energy transfer via phosphate bonds as ADP with creatine continually recycle into ATP and PCr.
6. Cellular oxidation occurs on the inner lining of the mitochondrial membranes; it involves transferring electrons from NADH and $\mathrm{FADH}_{2}$ to oxygen.
7. Electron transport oxidative phosphorylation produces coupled transfer of chemical energy to form ATP from ADP plus phosphate ion.
8. During aerobic ATP resynthesis, oxygen serves as the final electron acceptor in the respiratory chain to combine with hydrogen to form water.

## Part 2 ENERGY RELEASE FROM MACRONUTRIENTS

Energy release in macronutrient catabolism serves one crucial purpose-to phosphorylate ADP to reform the energy-rich compound ATP. Figure 6.9 outlines three broad stages that ultimately lead to the release and conservation of energy by the cell for biologic work:

Stage 1 involves the digestion, absorption, and assimilation of relatively large food macromolecules into smaller subunits for use in cellular metabolism.

Stage 2 degrades amino acid, glucose, and fatty acid and glycerol units within the cytosol into acetyl-coenzyme A (formed within the mitochondrion), with limited ATP and NADH production.

Stage 3 within the mitochondrion, acetyl-coenzyme A degrades to $\mathrm{CO}_{2}$ and $\mathrm{H}_{2} \mathrm{O}$ with considerable ATP production.

Stage 1
Micronutrient digestion, absorption, and assimilation into useful form

Stage 2
Degradation of subunits into acetyl-CoA

## Stage 3

Oxidation of acetyl-CoA to $\mathrm{CO}_{2}$ and $\mathrm{H}_{2} \mathrm{O}$


Figure 6.9 Three broad stages for macronutrient use in energy metabolism.


Figure 6.10 Macronutrient fuel sources that supply substrates to regenerate ATP. The liver provides a rich source of amino acids and glucose, while adipocytes generate large quantities of energy-rich fatty acid molecules. After their release, the bloodstream delivers these compounds to the muscle cell. Most of the cells energy production takes place within the mitochondria. Mitochondrial proteins carry out their roles in oxidative phosphorylation on the inner membranous walls of this architecturally elegant complex. The intramuscular energy sources consist of the high-energy phosphates ATP and PCr and triacylglycerols, glycogen, and amino acids.

The specific pathways of degradation differ depending on the nutrient substrate catabolized. In the sections that follow, we show how ATP resynthesis occurs from extraction of the potential energy in carbohydrate, fat, and protein macronutrients.

Figure 6.10 outlines the following six macronutrient fuel sources that supply substrate for oxidation and subsequent ATP formation:

1. Triacylglycerol and glycogen molecules stored within muscle cells
2. Blood glucose (derived from liver glycogen)
3. Free fatty acids (derived from triacylglycerols in liver and adipocytes)
4. Intramuscular- and liver-derived carbon skeletons of amino acids
5. Anaerobic reactions in the cytosol in the initial phase of glucose or glycogen breakdown (small amount of ATP)
6. Phosphorylation of ADP by PCr under enzymatic control by creatine kinase and adenylate kinase

## ENERGY RELEASE FROM CARBOHYDRATE

Carbohydrates primary function supplies energy for cellular work. Our discussion of macronutrient energy metabolism begins with carbohydrate for five reasons:

1. Carbohydrate provides the only macronutrient substrate whose stored energy generates ATP anaerobically. This takes on importance in maximal exercise that requires rapid energy release above levels supplied by aerobic metabolism. In such a case, intramuscular glycogen supplies most of the energy for ATP resynthesis.
2. During light and moderate aerobic exercise, carbohydrate supplies about one third of the body senergy requirements.
3. Processing a large quantity of fat for energy requires minimal carbohydrate catabolism.
4. Aerobic breakdown of carbohydrate for energy occurs more rapidly than energy generation from fatty acid breakdown. Thus, depleting glycogen reserves considerably reduces exercise power output. In prolonged aerobic exercise such as marathon running, athletes often experience nutrient-related fatigue-a state associated with muscle and liver glycogen depletion.
5. The central nervous system requires an uninterrupted stream of carbohydrate to function properly. The brain normally uses blood glucose almost exclusively as its fuel. In poorly regulated diabetes, during starvation, or with prolonged low carbohydrate intake, the brain adapts after about 8 days and metabolizes relatively large amounts of fat (as ketones) for alternative fuel.
The complete breakdown of one mole of glucose to carbon dioxide and water yields a maximum of 686 kCal of chemical free energy available for work.

$$
\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}+6 \mathrm{O}_{2} \rightarrow 6 \mathrm{CO}_{2}+6 \mathrm{H}_{2} \mathrm{O}-\Delta G 686 \mathrm{kCal} \cdot \mathrm{~mol}^{-1}
$$

Complete glucose breakdown conserves only some of the released energy as ATP. Recall that the synthesis of 1 mole of ATP from ADP and a phosphate ion requires 7.3 kCal of energy. Coupling all of the energy from glucose oxidation to phosphorylation could theoretically form 94 moles of ATP per mole of glucose ( $686 \mathrm{kCal} \div 7.3 \mathrm{kCal} \cdot \mathrm{mol}{ }^{1}=94 \mathrm{~mol}$ ). In the muscle, phosphate bond formation conserves only $34 \%$, or 233 kCal , of energy, with the remainder dissipated as heat. As such, glucose breakdown regenerates 32 moles of ATP $\left(233 \mathrm{kCal} \div 7.3 \mathrm{kCal} \cdot \mathrm{mol}^{-1}=32 \mathrm{~mol}\right)$ with an accompanying free energy gain of 233 kCal .

Two forms of carbohydrate breakdown exist in a series of fermentation reactions collectively termed glycolysis ( the dissolution of sugar ), or the Embden Meyerhof pathway for its two German chemist discoverers. In one form, lactate (formed from pyruvate) becomes the end product. In the other form, pyruvate remains the end product. With pyruvate as the end substrate, carbohydrate catabolism proceeds and couples to further break down (citric acid cycle) and electron transport
production of ATP. Carbohydrate breakdown of this form (sometimes termed aerobic [with oxygen] glycolysis) is a relatively slow process resulting in substantial ATP formation. In contrast, glycolysis that results in lactate formation (referred to as anaerobic [without oxygen] glycolysis) represents rapid but limited ATP production. The net formation of either lactate or pyruvate depends more on the relative glycolytic and mitochondrial activities than on the presence of molecular oxygen. Most often, relative lactate pyruvate ratio exceeds 10.0 , promoting anaerobic glycolysis and lactate formation. The relative demand for rapid or slow ATP production determines the form of glycolysis. The glycolytic process itself, from beginning substrate (glucose) to end substrate (lactate or pyruvate), does not involve oxygen. We agree with other authors that rapid (anaerobic) and slow (aerobic) glycolysis are the appropriate terms to describe glycolysis.

Glucose degradation occurs in two stages. In stage one, glucose breaks down rapidly into two molecules of pyruvate. Energy transfer for phosphorylation occurs without oxygen (anaerobic). In stage two, pyruvate degrades further to carbon dioxide and water. Energy transfers from these reactions require electron transport and accompanying oxidative phosphorylation (aerobic).

## Glycolysis Generates Energy from Glucose

Figure 6.11 illustrates the first stage of glucose degradation in glycolysis. Glycolysis occurs in the watery medium of the cell outside the mitochondrion. In a sense, glycolysis represent a more primitive form of rapid energy transfer highly developed in amphibians, reptiles, fish, and marine mammals. In humans, the cells capacity for glycolysis remains crucial during maximum-effort physical activities for up to about 90 seconds.

In reaction 1, ATP acts as a phosphate donor to phosphorylate glucose to glucose 6 -phosphate. In most tissues, this traps the glucose molecule in the cell. The liver (and kidney cells) contains the enzyme phosphatase that splits the phosphate from glucose 6 -phosphate. This frees glucose from the cell for transport throughout the body. In the presence of the enzyme glycogen synthase, glucose links, or polymerizes, with other glucose molecules to form a large glycogen molecule (see Fig. 1.3). During energy metabolism, glucose 6 -phosphate changes to fructose 6 -phosphate. At this stage, energy is not yet extracted, yet some energy incorporates into the original glucose molecule at the expense of one ATP molecule. In a sense, phosphorylation primes the pump for continued energy metabolism. The fructose 6 -phosphate molecule gains an additional phosphate and changes to fructose 1,6-diphosphate under control of phosphofructokinase (PFK). The activity level of this enzyme probably limits the rate of glycolysis during maximum-effort exercise. Fructose 1,6 -diphosphate then splits into two phosphorylated molecules with three carbon chains (3-phosphoglycerasdehyde); these further decompose to pyruvate in five successive reactions. Fast-twitch (type II) muscle fibers (see Chapter 7, p. 167) contain relatively large quantities of PFK; this makes them ideally suited for generating anaerobic energy via glycolysis.


## Metabolism of Glucose to Glycogen and Glycogen to Glucose

The cytoplasm of liver and muscle cells contains glycogen granules and the enzymes for glycogen synthesis (glycogenesis) and glycogen breakdown (glycogenolysis). Under normal conditions following a meal, glucose does not accumulate in the blood. Rather, surplus glucose either enters the pathways of energy metabolism or stores as glycogen or converts to fat. In high cellular activity, available glucose oxidizes via the glycolytic pathway, citric acid cycle, and respiratory chain to form ATP. In contrast, low cellular activity and/or depleted glycogen reserves inactivate key glycolytic enzymes. This causes surplus glucose to form glycogen.

Glycogenolysis describes the cleavage of glucose from the glycogen molecule. The glucose residue then reacts with a phosphate ion to produce glucose 6-phosphate, bypassing step 1 of the glycolytic pathway. Thus, when glycogen provides a glucose molecule for glycolysis, a net gain of three ATPs occurs rather than two ATPs during glucose breakdown.

Regulation of Glycogen Metabolism. In the liver, glycogen phosphorylase enzymes become inactive following a meal, while glycogen synthase activity increases to facilitate storage of the glucose obtained from food. Conversely, between meals when glycogen reserves decrease, liver phosphorylase becomes active (concurrent depression of glycogen synthase activity) to maintain stability in blood glucose for use by body tissues. Skeletal muscle at rest shows higher synthase activity, whereas physical activity increases phosphorylase activity with a concomitant blunting of the synthase enzyme. Epinephrine, a sympathetic nervous system hormone, accelerates the rate that phosphorylase cleaves one glucose component at a time from the glycogen molecule. ${ }^{7,9}$

Epinephrine s action has been termed the glycogenolysis cascade because the hormone affects progressively greater phosphorylase activation to ensure rapid glycogen mobilization. Phosphorylase activity remains most active during intense exercise when sympathetic activity increases and carbohydrate represents the optimum fuel. Sympathetic outflow and subsequent glycogen catabolism decrease considerably during low-to-moderate-intensity exercise when the slower rate of fatty acid oxidation adequately maintains ATP concentrations in active muscle.

## Substrate-Level Phosphorylation in Glycolysis

Most of the energy generated in glycolysis does not result in ATP resynthesis but instead dissipates as heat. Note that in reactions 7 and 10 in Figure 6.11, the energy released from glucose intermediates stimulates direct transfer of
phosphate groups to four ADP molecules, generating four ATP molecules. Because two molecules of ATP contribute to the initial phosphorylation of the glucose molecule, glycolysis generates a net gain of two ATP molecules. This represents an endergonic conservation of $14.6 \mathrm{kCal} \cdot \mathrm{mol}^{-1}$, all without involvement of molecular oxygen. Instead, the energy transferred from substrate to ADP by phosphorylation in rapid glycolysis occurs via phosphate bonds in the anaerobic reactions often called substrate-level phosphorylation. Energy conservation during this form of glycolysis operates at an efficiency of about $30 \%$.

Rapid glycolysis generates only about 5\% of the total ATP during the glucose molecule s complete degradation to energy. Examples of activities that rely heavily on ATP generated by rapid glycolysis include sprinting at the end of a mile run, swimming all-out from start to finish in a $50-$ or a $100-\mathrm{m}$ swim, routines on gymnastics apparatus, and sprint running up to 200 m .

## Regulation of Glycolysis

Three factors regulate glycolysis:

1. Concentrations of the key glycolytic enzymes hexokinase, phosphofructokinase, and pyruvate kinase
2. Levels of the substrate fructose 1,6-disphosphate
3. Oxygen, which in abundance inhibits glycolysis

In addition, glucose delivery to cells influences its subsequent use in energy metabolism.

Glucose locates in the surrounding extracellular fluid for transport across the cell s plasma membrane. A family of five proteins, collectively termed facilitative glucose transporters, mediates this process of facilitative diffusion. Muscle fibers and adipocytes contain an insulin-dependent transporter known as Glu T4, or GLUT 4. This transporter, in response to both insulin and physical activity (independent of insulin), migrates from vesicles within the cell to the plasma membrane. ${ }^{33}$ Its action facilitates glucose transport into the sarcoplasm, where it subsequently catabolizes to form ATP. Another glucose transporter, GLUT 1, accounts for basal levels of glucose transport into muscle.

## Hydrogen Release in Glycolysis

Glycolytic reactions strip two pairs of hydrogen atoms from the glucose substrate and pass their electrons to $\mathrm{NAD}^{+}$ to form NADH (Fig. 6.11, reaction 6). Normally, if the respiratory chain processed these electrons directly, 2.5 ATP molecules would form for each NADH molecule oxidized $(\mathrm{P} / \mathrm{O}$ ratio $=2.5)$. Within heart, kidney, and liver cells, extramitochondrial hydrogen (NADH) appears as NADH in

[^19]the mitochondrion (via a mechanism termed the malate aspartate shuttle). This produces 2.5 ATP molecules from the oxidation of each NADH molecule. The mitochondria in skeletal muscle and brain cells remain impermeable to cytoplasmic NADH formed during glycolysis. Consequently, electrons from extramitochondrial NADH shuttle indirectly into the mitochondria. This route terminates when electrons pass to FAD to form $\mathrm{FADH}_{2}$ (via a mechanism termed the glycerol-phosphate shuttle) at a point below the first formation of ATP (see Fig. 6.7A). Thus 1.5 rather than three ATP molecules form when the respiratory chain oxidizes cytoplasmic NADH ( $\mathrm{P} / \mathrm{O}$ ratio $=1.5$ ). From two molecules of NADH formed in glycolysis, four molecules of ATP generate aerobically by subsequent coupled electron transport oxidative phosphorylation in skeletal muscle.

## More About Lactate

Sufficient oxygen bathes the cells during light-to-moderate levels of energy metabolism. The hydrogens (electrons) stripped from the substrate and carried by NADH oxidize within the mitochondria to form water when they join with oxygen. In a biochemical sense, a steady state, or more precisely a steady rate, exists because hydrogen oxidizes at about the same rate it becomes available.

In strenuous exercise, when energy demands exceed either oxygen supply or its rate of use, the respiratory chain cannot process all of the hydrogen joined to NADH. Continued release of anaerobic energy in glycolysis depends on $\mathrm{NAD}^{+}$ availability to oxidize 3-phosphoglyceraldehyde (see reaction 6, Fig. 6.11); otherwise, the rapid rate of glycolysis grinds to a halt. During rapid anaerobic glycolysis, $\mathrm{NAD}^{+}$frees up or regenerates when pairs of excess nonoxidized hydrogens combine with pyruvate to form lactate. Lactate formation requires one additional step (catalyzed by lactate dehydrogenase) in a reversible reaction (Fig. 6.12).

During rest and moderate exercise, some lactate continually forms in two ways: (1) energy metabolism of red blood cells that contain no mitochondria and (2) limitations posed by enzyme activity in muscle fibers with high glycolytic capacity. Any lactate that forms in this manner readily oxidizes for energy in neighboring muscle fibers with high oxidative capacity or in more distant tissues such as the heart and ventilatory muscles. Lactate can also be used as an indirect precursor of liver glycogen (see below). Consequently, lactate does not accumulate because its removal rate equals its rate of production. Endurance athletes show an enhanced ability for lactate clearance (or turnover) during exercise. ${ }^{22}$

As previously discussed, there exists a direct pathway for liver glycogen synthesis from dietary carbohydrate. However, liver glycogen synthesis also occurs indirectly from the conversion of the three-carbon precursor lactate to glucose. Although other tissues (e.g., erythrocytes and adipocytes) contain glycolytic enzymes, skeletal muscle possesses the largest quantity. Thus, much of the lactate-toglucose conversion likely occurs in this tissue. This indirect pathway, from lactate to liver glycogen synthesis (particularly


Figure 6.12 Under physiologic conditions within muscle, lactate forms when hydrogens from NADH combine temporarily with pyruvate. This frees up NAD to accept additional hydrogens generated in glycolysis.
after eating), is referred to as the glucose paradox. We discuss the concept of the glucose paradox as part of the lactate shuttle to explain formation, distribution, and utilization of lactate in carbohydrate metabolism, on page 149.

The temporary storage of hydrogen with pyruvate represents a unique aspect of energy metabolism because it provides a ready collector for temporary storage of the end product of anaerobic glycolysis. Once lactate forms in muscle, it diffuses into the interstitial space and blood for buffering and removal from the site of energy metabolism or provides gluconeogenic substrate for glycogen synthesis. In this way, glycolysis continues to supply anaerobic energy for ATP resynthesis. This avenue for extra energy remains temporary, however, if blood and muscle lactate levels increase and ATP formation fails to keep pace with its rate of use. Fatigue soon sets in and exercise performance diminishes. Increased intracellular acidity under anaerobic conditions mediates fatigue by inactivating various enzymes in energy transfer thus impairing the muscle $s$ contractile properties. ${ }^{2,6,17,23}$

A Valuable Waste Product. Lactate should not be viewed as a metabolic waste product. To the contrary, it provides a valuable source of chemical energy that accumulates with intense exercise. ${ }^{12,13}$ When sufficient oxygen becomes available during recovery, or when exercise pace slows, $\mathrm{NAD}^{+}$scavenges hydrogens attached to lactate to form ATP via oxidation. The carbon skeletons of the pyruvate molecules re-formed from lactate during exercise (one pyruvate molecule +2 hydrogens forms a molecule of lactate) become either oxidized for energy or synthesized to glucose (gluconeogenesis) in muscle itself or in the Cori cycle (Fig. 6.13). The Cori


Figure 6.13 The biochemical reactions of the Cori cycle in the liver synthesize glucose from the lactate released from active muscles. This gluconeogenic process helps to maintain carbohydrate reserves.
cycle removes lactate and also uses it to replenish glycogen reserves depleted from intense exercise. ${ }^{37}$

In intense exercise ( $>80 \%$ aerobic capacity) with elevated carbohydrate catabolism, the glycogen within inactive tissues supplies the needs of active muscle. Active glycogen turnover through the exchangeable lactate pool progresses because inactive tissues release lactate into the circulation. The lactate provides a precursor to synthesize carbohydrate (via the Cori cycle in liver and kidneys) to support blood glucose levels and the exercise energy requirements. ${ }^{3,22}$

Lactate Shuttle: Blood Lactate as an Energy Source. Isotope tracer studies show that lactate produced in fast-twitch muscle fibers (and other tissues) circulates to other fast-twitch or slow-twitch fibers for conversion to pyruvate. Pyruvate, in turn, converts to acetyl-CoA for entry into the citric acid cycle for aerobic energy metabolism. This process of lactate shuttling among cells enables glycogenolysis in one cell to supply
other cells with fuel for oxidation. This makes muscle not only a major site of lactate production, but also a primary tissue for lactate removal via oxidation. ${ }^{43,15}$

## Citric Acid Cycle

The anaerobic reactions of glycolysis release only about 5\% of the energy within the original glucose molecule. Extraction of the remaining energy continues when pyruvate irreversibly converts to acetyl-CoA, a form of acetic acid. Acetyl-CoA enters the citric acid cycle (also termed Krebs cycle for its discoverer, 1953 Nobel chemist Sir Hans Krebs, or tricarboxylic acid cycle), the second stage of carbohydrate breakdown. As shown schematically in Figure 6.14, the citric acid cycle degrades the acetyl-CoA substrate to carbon dioxide and hydrogen atoms within the mitochondria. ATP forms when hydrogen atoms oxidize during electron transport oxidative phosphorylation.

Figure 6.15 shows pyruvate preparing to enter the citric acid cycle by joining with coenzyme A ( $A$ for acetic acid) to form the 2-carbon compound acetyl-CoA. The two released hydrogens transfer their electrons to $\mathrm{NAD}^{+}$to form one molecule of carbon dioxide as follows:

$$
\begin{aligned}
\text { Pyruvate }+\mathrm{NAD}^{+}+\mathrm{CoA} & \rightarrow \text { Acetyl-CoA } \\
& +\mathrm{CO}_{2}+\mathrm{NADH}^{+}+\mathrm{H}^{+}
\end{aligned}
$$

The acetyl portion of acetyl-CoA joins with oxaloacetate to form citrate (the same 6-carbon citric acid compound found in citrus fruits), which then proceeds through the citric acid cycle. This cycle continues to operate because it retains the original oxaloacetate molecule to join with a new acetyl fragment that enters the cycle.

Each acetyl-CoA molecule entering the citric acid cycle releases two carbon dioxide molecules and four pairs of hydrogen atoms. One molecule of ATP also regenerates directly by substrate-level phosphorylation from citric acid cycle reactions (reaction 7, Fig. 6.15). As summarized at the bottom of Figure 6.15, the formation of two acetyl-CoA molecules from two pyruvate molecules created in glycolysis releases four hydrogens, while the citric acid cycle releases 16 hydrogens. The primary function of the citric acid cycle generates electrons $\left(\mathrm{H}^{+}\right)$for passage in the respiratory chain to $N A D^{+}$and $F A D$.

Oxygen does not participate directly in citric acid cycle reactions. The chemical energy within pyruvate transfers to ADP through electron transport oxidative phosphorylation. With adequate oxygen, including enzymes and substrate, $\mathrm{NAD}^{+}$and FAD regenerate, and citric acid cycle metabolism proceeds unimpeded. The citric acid cycle, electron transport, and oxidative phosphorylation represent the three components of aerobic metabolism.

## Total Energy Transfer from Glucose Catabolism

Figure 6.16 summarizes the pathways for energy transfer during glucose catabolism in skeletal muscle. Two ATPs (net gain) form from substrate-level phosphorylation in glycolysis;


Figure 6.14 Aerobic energy metabolism. Phase 1. In the mitochondria, the citric acid cycle generates hydrogen atoms during acetyl-CoA breakdown. Phase 2. Significant quantities of ATP regenerate when these hydrogens oxidize via the aerobic process of electron transport oxidative phosphorylation (electron transport chain).
similarly, two ATPs emerge from acetyl-CoA degradation in the citric acid cycle. The 24 released hydrogen atoms can be accounted for as follows:

1. Four extramitochondrial hydrogens ( 2 NADH ) generated in glycolysis yield 5 ATPs during oxidative phosphorylation.
2. Four hydrogens ( 2 NADH ) released in the mitochondrion when pyruvate degrades to acetyl-CoA yield 5 ATPs.
3. Two guanosine triphosphates (GTP; a molecule similar to ATP) are produced in the citric acid cycle via substrate level phosphorylation.


Carbon dioxide and hydrogen released in hydrolysis of 2 pyruvate molecules

2 molecules pyruvate
2 molecules acetyl-CoA
$\begin{array}{lll}\text { Total } & \frac{4}{6} \quad \frac{16}{20}\end{array}$

Figure 6.15 Flow sheet for the release of hydrogen and carbon dioxide in the mitochondrion during the breakdown of one pyruvate molecule. All values are doubled when computing the net gain of hydrogen and carbon dioxide because two molecules of pyruvate form from one glucose molecule in glycolysis. Enzymes colored yellow/purple are key regulatory enzymes.


Figure 6.16 A net yield of 32 ATPs from energy transfer during the complete oxidation of one glucose molecule in glycolysis, citric acid cycle, and electron transport.
4. Twelve of the 16 hydrogens ( 6 NADH ) released in the citric acid cycle yield 15 ATPs ( 6 NADH $\times 2.5$ ATP per NADH $=15$ ATP).
5. Four hydrogens joined to FAD ( $2 \mathrm{FADH}_{2}$ ) in the citric acid cycle yield 3 ATPs.

The complete breakdown of glucose yields a total of 34 ATPs. Because 2 ATPs initially phosphorylate glucose, 32 ATP molecules equal the net ATP yield from glucose catabolism in skeletal muscle. Four ATP molecules form directly from substrate-level phosphorylation (glycolysis and citric
acid cycle), whereas 28 ATP molecules regenerate during oxidative phosphorylation.

Some textbooks quote a 36 to 38 net ATP yield from glucose catabolism. The disparity depends on which shuttle system (the glycerol phosphate or malate aspartate) transports $\mathrm{NADH}+\mathrm{H}^{+}$into the mitochondrion and the ATP yield per NADH oxidation used in the computations. One must temper the theoretical values for ATP yield in energy metabolism in light of biochemical information that suggests they overestimate, because only 30 to 32 ATP actually enter the cell s cytoplasm. The differentiation between theoretical versus actual ATP yield may result from the added energy cost to transport ATP out of the mitochondria. ${ }^{10}$

## What Regulates Energy Metabolism?

Electron transfer and subsequent energy release normally tightly couple to ADP phosphorylation. Without ADP availability for phosphorylation to ATP, electrons generally do not shuttle down the respiratory chain to oxygen. Metabolites that either inhibit or activate enzymes at key control points in the oxidative pathways modulate regulatory control of glycolysis and the citric acid cycle. ${ }^{14,16,28,31}$ Each pathway contains at least one enzyme considered rate limiting because the enzyme controls the overall speed of that pathway s reactions. Cellular ADP concentration exerts the greatest effect on the rate-limiting enzymes that control macronutrient energy metabolism. This mechanism for respiratory control makes sense because any increase in ADP signals a need to supply energy to restore depressed ATP levels. Conversely, high cellular ATP levels indicate a relatively low energy requirement. From a broader perspective, ADP concentrations function as a cellular feedback mechanism to maintain a relative constancy (homeostasis) in the level of energy currency required for biologic work. Other rate-limiting modulators include cellular levels of phosphate, cyclic AMP, AMP-activated protein kinase (AMPK), calcium, $\mathrm{NAD}^{+}$, citrate, and pH . More specifically, ATP and NADH serve as enzyme inhibitors, while intracellular calcium, ADP, and $\mathrm{NAD}^{+}$ function as activators. This chemical feedback allows rapid metabolic adjustment to the cells energy needs. Within the resting cell, the ATP concentration considerably exceeds the concentration of ADP by about 500:1. A decrease in the ATP/ADP ratio and intramitochondrial $\mathrm{NADH} / \mathrm{NAD}^{+}$ratio, as occurs when exercise begins, signals a need for increased metabolism of stored nutrients. In contrast, relatively low levels of energy demand maintain high ratios of ATP/ADP and $\mathrm{NADH} / \mathrm{NAD}^{+}$, which depress the rate of energy metabolism. ${ }^{1}$

Independent Effects. No single chemical regulator dominates mitochondrial ATP production. In vitro (artificial environment outside the living organism) and in vivo (in the living organism) experiments show that changes in each of these compounds independently alter the rate of oxidative phosphorylation. All exert regulatory effects, each contributing differently depending on energy demands, cellular conditions, and the specific tissue involved.

## ENERGY RELEASE FROM FAT

Stored fat represents the bodys most plentiful source of potential energy. Relative to carbohydrate and protein, stored fat provides almost unlimited energy. The fuel reserves from fat in a typical young adult male come from two main sources: (1) between 60,000 and $100,000 \mathrm{kCal}$ (enough energy to power about 25 to 40 marathon runs) from triacylglycerol in fat cells (adipocytes) and (2) about 3000 kCal from intramuscular triacylglycerol ( $12 \mathrm{mmol} \cdot \mathrm{kg}$ muscle ${ }^{-1}$ ). In contrast, carbohydrate energy reserves generally amount to less than 2000 kCal .

Three specific energy sources for fat catabolism include:

1. Triacylglycerols stored directly within the muscle fiber in close proximity to the mitochondria (more in slow-twitch than in fast-twitch muscle fibers)
2. Circulating triacylglycerols in lipoprotein complexes that become hydrolyzed on the surface of a tissue s capillary endothelium
3. Circulating free fatty acids mobilized from triacylglycerols in adipose tissue
Prior to energy release from fat, hydrolysis (lipolysis) in the cell s cytosol splits the triacylglycerol molecule into a glycerol molecule and three water-insoluble fatty acid molecules. Hormone-sensitive lipase (activated by cyclic AMP; see p. 156) catalyzes triacylglycerol breakdown as follows:

$$
\text { Triacylglycerol }+3 \mathrm{H}_{2} \mathrm{O} \xrightarrow{\text { lipase }} \text { Glycerol }+3 \text { Fatty acids }
$$

## INTEGRATIVE QUESTION

Discuss the claim that regular low-intensity exercise stimulates greater body fat loss than high-intensity exercise of equal total caloric expenditure.

## Adipocytes: The Site of Fat Storage and Mobilization

Figure 6.17 outlines the dynamics of fatty acid mobilization (lipolysis) in adipose tissue and delivery to skeletal muscle. Lipid metabolism involves seven discrete processes as follows:

1. Breakdown of triacylglycerol to free fatty acids
2. Transport of free fatty acids in the blood
3. Uptake of free fatty acids from blood to muscle
4. Preparation of fatty acids for catabolism (energy activation)
5. Entry of activated fatty acid into muscle mitochondria
6. Breakdown of fatty acid to acetyl-CoA via $\beta$-oxidation and the production of NADH and $\mathrm{FADH}_{2}$
7. Coupled oxidation in citric acid cycle and electron transport chain.


Figure 6.17 Dynamics of fat mobilization and fat use. Hormone-sensitive lipase stimulates triacylglycerol breakdown into its glycerol and fatty acid components. The blood transports free fatty acids (FFAs) released from adipocytes and bound to plasma albumin. Energy is released when triacylglycerols stored within the muscle fiber also degrade to glycerol and fatty acids.

Although all cells store some fat, adipose tissue serves as the major supplier of fatty acid molecules. Adipocytes specialize in synthesizing and storing triacylglycerols. Triacylglycerol fat droplets occupy up to $95 \%$ of adipocyte cell volume. Once hormone-sensitive lipase stimulates fatty acids to diffuse from the adipocyte into the circulation, nearly all of them bind to plasma albumin for transport to active tissues as free fatty acids (FFAs). ${ }^{8,34}$ Hence, FFAs are not truly free entities. At the muscle site, the albumin FFA complex releases FFAs for transport by diffusion and/or a protein-mediated carrier system across the plasma membrane. Once inside the muscle fiber, FFAs accomplish two tasks: first, reesterify to form triacylglycerols and second, bind with intramuscular proteins and enter the mitochondria for energy metabolism by action of carnitine acyltransferase located on the inner mitochondrial membrane. This enzyme catalyzes the transfer of an acyl group to carnitine to form acyl carnitine, a compound that readily crosses the mitochondrial membrane. Medium- and short-chain fatty acids do not depend on this enzyme-mediated transport. Instead, these fatty acids diffuse freely into the mitochondria.

The water-soluble glycerol molecule formed during lipolysis diffuses from the adipocyte into the circulation. This allows plasma glycerol levels to reflect the level of triacylglycerol catabolism. ${ }^{32}$ When delivered to the liver, glycerol serves as a precursor for glucose synthesis. The relatively slow rate of this process explains why supplementing with exogenous glycerol (consumed in liquid form) contributes little as an energy substrate (or glucose replenisher) during exercise. ${ }^{27}$

Adipose tissue release of FFAs and their subsequent use for energy in light and moderate exercise increase directly with blood flow through adipose tissue (threefold increase not uncommon) and active muscle. FFA catabolism increases principally in slow-twitch muscle fibers whose ample blood supply and large, numerous mitochondria make them ideal for fat breakdown.

Circulating triacylglycerols carried in lipoprotein complexes also provide an energy source. Lipoprotein lipase (LPL), an enzyme synthesized within the cell and localized on the surface of its surrounding capillaries, catalyzes the hydrolysis of these triacylglycerols. LPL also facilitates a cell s uptake of fatty acids for energy metabolism or for resynthesis (reesterfication) of triacylglycerols stored within muscle and adipose tissues. ${ }^{34}$

## INTEGRATIVE QUESTION

If an average person stores enough energy as body fat to power a 750-mile run, why do athletes often experience impaired performance toward the end of a 26.2-mile marathon performed under high-intensity, steady-rate aerobic metabolism?

## Hormonal Effects

Epinephrine, norepinephrine, glucagon, and growth hormone augment lipase activation and subsequent lipolysis and FFA mobilization from adipose tissue. Plasma concentrations of

## FOCUS ON RESEARCH

## Aerobic Metabolism And Exercise

Hill AV, Lupton H. Muscular exercise, lactic acid and the supply and utilization of oxygen. Q J Med 1923;16:135.
$>$ Perhaps no scientist has contributed more to the field of exercise physiology than Archibald Vivian Hill. He won the Nobel Prize in physiology or medicine for studies of energy metabolism using mostly frog muscle, but also pioneered studies of the physiology of running in humans. His careful experiments on oxygen consumption $\left(\mathrm{VO}_{2}\right)$ during exercise and recovery enhanced understanding of the dynamics of exercise energy metabolism and mechanical efficiency. Hill and Luptons 1923 research investigated interrelationships among exercise intensity, lactate production, and recovery $\mathrm{VO}_{2}$. This lengthy article reported the results of many experiments on several individuals (including the researchers) performing different athletic events like running, continuous jumping, and violent gymnastics for 10 to 40 minutes. Measurements included $\mathrm{VO}_{2}$ and blood lactate during exercise and recovery, using what currently seem crude techniques.

The subject finished the exercise in front of a stand carrying a wide pipe with nine projecting tubes. To one of
these tubes the valves and mouthpiece were fixed; to the others were attached rubber bags through single-way stopcocks. The subject on cessation of exercise adopted the standard resting position, adjusted the valves and nose clip, and commenced to expire into the first bag. At the end of about one-half minute (end of nearest expiration) the first bag was turned off, and the second one turned on for a like interval. This process was continued, the intervals of collection being gradually increased.

Topics covered in this article included the following: role of lactate in muscle; heat release in exercise; metabolic efficiency and speed of recovery from different levels of exercise; lactate production in humans; interrelation between lactate formation and oxygen debt; maximal lactate accumulation in exercise; exercise steady state; maximal $\mathrm{VO}_{2}$; relation between exercise intensity and $\mathrm{VO}_{2}$; and acid base balance during exercise.

The inclusion of a detailed description of the $\mathrm{VO}_{2}$ in recovery from different exercise intensities represents a notable feature of this pioneering article in exercise physiology. The figure shows that the time course of recovery of $\mathrm{VO}_{2}$ related to the intensity of previous exercise and accompanying lactate accumulation (not shown). Nearly


Postexercise oxygen consumption $\left(\mathrm{VO}_{2}\right)$ during recovery from moderate (Exp. 1) and intense (Exp. 3) exercise. Note the elevated and more prolonged duration of recovery from the intense exercise bout. The inset table presents average values for $\mathrm{VO}_{2}$ in diverse forms of intense exercise obtained by A. V. Hill s group (last row) and other researchers between 1913 and 1934.

## FOCUS ON RESEARCH

80 years of subsequent research has confirmed most of Hill and Lupton s astute observations.

The researchers also presented data for near-maximal (peak) oxygen consumption $\left(\mathrm{VO}_{2 \text { peak }}\right)$. Prior to 1923 , little information existed on oxygen consumption in individuals of athletic disposition during high-intensity exercise. Hill and Lupton reported $\mathrm{VO}_{2 \text { peak }}$ for five men during run-
ning (last row of values in table inset). We also include other $\mathrm{VO}_{2 \text { peak }}$ data for high-intensity exercise, collected between 1913 and 1934. Compare the average value of $3.95 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ for the Hill and Lupton data with the $\mathrm{VO}_{2 \text { max }}$ data presented in Figure 11.8 (assume $70-\mathrm{kg}$ body mass to convert data to $\mathrm{mL} \mathrm{O}_{2} \cdot \mathrm{~kg}^{1} \cdot \mathrm{~min}^{-1}$ ). How might you account for the discrepancy in the values?
these lipogenic hormones increase during exercise to continually supply active muscles with energy-rich substrate. An intracellular mediator, adenosine 3 ,5-cyclic monophosphate (cyclic AMP), activates hormone-sensitive lipase and thus regulates fat breakdown. Various lipid-mobilizing hormones, which themselves do not enter the cell, activate cyclic AMP. ${ }^{35}$ Circulating lactate, ketones, and particularly insulin inhibit cyclic AMP activation. ${ }^{8}$ Exercise training induced increases in the activity level of skeletal muscle and adipose tissue lipases, including biochemical and vascular adaptations in the muscles themselves, enhance fat use for energy during moderate exercise. ${ }^{19,20,21,24}$ Paradoxically, excess body fat decreases the availability of fatty acids during exercise. ${ }^{25}$ Chapter 20 presents a more detailed evaluation of hormone regulation in exercise and training.

The availability of fatty acid molecules regulates fat breakdown or synthesis. After a meal, when energy metabolism remains relatively low, digestive processes increase FFA and triacylglycerol delivery to cells; this in turn stimulates triacylglycerol synthesis. In contrast, moderate exercise increases fatty acid use for energy, which reduces their cellular concentration. The decrease in intracellular FFAs stimulates triacylglycerol breakdown into glycerol and fatty acid components. Concurrently, hormonal release triggered by exercise stimulates adipose tissue lipolysis to further augment FFA delivery to active muscle.

## Catabolism of Glycerol and Fatty Acids

Figure 6.18 summarizes the pathways for degrading the glycerol and fatty acid fragments of the triacylglycerol molecule.

## Glycerol

The anaerobic reactions of glycolysis accept glycerol as 3-phosphoglyceraldehyde. This molecule then degrades to pyruvate to form ATP by substrate-level phosphorylation. Hydrogen atoms pass to $\mathrm{NAD}^{+}$, and the citric acid cycle oxidizes pyruvate. The complete breakdown of the single glycerol molecule synthesizes 19 ATP molecules. Glycerol also provides carbon skeletons for glucose synthesis (see In a Practical Sense , p. 158). The gluconeogenic role of glycerol becomes important when glycogen reserves deplete from either dietary restriction of carbohydrates, long-term exercise, or intense training.

## INTEGRATIVE QUESTION

Explain: If elite marathoners run at an exercise intensity that does not cause appreciable accumulation of blood lactate, why do some athletes appear disoriented and fatigued and forced to slow down toward the end of the competition?

## Fatty Acids

The fatty acid molecule transforms into acetyl-CoA in the mitochondrion during beta ( $\boldsymbol{\beta}$ )-oxidation. This involves successive splitting of 2-carbon acyl fragments from the long chain of the fatty acid. ATP phosphorylates the reactions, water is added, hydrogens pass to $\mathrm{NAD}^{+}$and FAD, and the acyl fragment joins with coenzyme A to form acetylCoA. $\beta$-oxidation provides the same acetyl unit as that generated from glucose catabolism. $\beta$-oxidation continues until the entire fatty acid molecule degrades to acetyl-CoA for direct entry into the citric acid cycle. The hydrogens released during fatty acid catabolism oxidize through the respiratory chain. Note that fatty acid breakdown relates directly to oxygen consumption. Oxygen must join with hydrogen for $\beta$-oxidation to proceed. Under anaerobic conditions, hydrogen remains with $\mathrm{NAD}^{+}$and FAD, thus halting fat catabolism.

## Total Energy Transfer from Fat Catabolism

The breakdown of a fatty acid molecule progresses as follows:

1. $\beta$-oxidation produces NADH and $\mathrm{FADH}_{2}$ by cleaving the fatty acid molecule into 2-carbon acyl fragments.
2. Citric acid cycle degrades acetyl-CoA into carbon dioxide and hydrogen atoms.
3. Hydrogen atoms oxidize via electron transport oxidative phosphorylation.

For each 18 -carbon fatty acid molecule, 147 molecules of ADP phosphorylate to ATP during $\beta$-oxidation and citric acid cycle metabolism. Each triacylglycerol molecule contains 3 fatty acid molecules to form 441 ATP molecules from the fatty acid components ( $3 \times 147$ ATP). Also, 19 ATP molecules form during glycerol breakdown to generate 460 molecules of ATP for each triacylglycerol molecule catabolized. This represents a considerable energy yield compared to the


Figure 6.18 General schema for the breakdown of the glycerol and fatty acid components of a triacylglycerol molecule. Glycerol enters the energy pathways during glycolysis. Fatty acids prepare to enter the citric acid cycle through $\beta$-oxidation. The electron transport chain accepts hydrogens released during glycolysis, $\beta$-oxidation, and citric acid cycle metabolism.
net 32 ATPs formed when a skeletal muscle catabolizes a glucose molecule. The efficiency of energy conservation for fatty acid oxidation amounts to about $40 \%$, a value similar to that with glucose oxidation.

Intracellular and extracellular lipid molecules usually supply between 30 and $80 \%$ of the energy for biologic work, depending on a persons nutritional status, level of training, and the intensity and duration of physical activity. ${ }^{38}$ Fat becomes the primary energy fuel for exercise and recovery when high-intensity, long-duration exercise depletes glycogen. ${ }^{21}$ Furthermore, enzymatic adaptations occur with prolonged exposure to a high-fat, low-carbohydrate diet because this dietary regimen enhances capacity for fat oxidation during exercise. ${ }^{26}$

## ENERGY RELEASE FROM PROTEIN

Chapter 1 emphasized that protein plays a contributory role as an energy substrate during endurance activities and intense training. When used for energy, the amino acids (primarily the
branched-chain amino acids leucine, isoleucine, valine, glutamine, and aspartate) first convert to a form that readily enters the energy pathways. This conversion requires nitrogen removal (deamination) from the amino acid molecule. Whereas the liver serves as the main site for deamination, skeletal muscle also contains enzymes that remove nitrogen from an amino acid and pass it to other compounds during transamination (see Fig. 1.24). For example, the citric acid cycle intermediate $\alpha$-ketoglutarate accepts a nitrogen-containing amine group $\left(\mathrm{NH}_{2}\right)$ to form a new amino acid, glutamate. The muscle cell then uses the carbon-skeleton byproducts of donor amino acids to form ATP. The levels of enzymes for transamination increase with exercise training to further facilitate proteins use as an energy substrate.

Some amino acids are glucogenic; when deaminated, they yield pyruvate, oxaloacetate, or malateall intermediates for glucose synthesis via gluconeogenesis. Pyruvate, for example, forms when alanine loses its amino group and gains a double-bonded oxygen. The gluconeogenic role of some amino acids provides an important component of the

## IN A PRACTICAL SENSE

## Potential for Glucose Synthesis from Triacylglycerol Components

Circulating glucose provides vital fuel for brain and red blood cell functions. Maintaining blood glucose homeostasis remains a challenge in prolonged starvation or high-intensity endurance exercise because muscle and liver glycogen reserves deplete rapidly. When this occurs, the central nervous system eventually metabolizes ketone bodies as an energy fuel. Concurrently, muscle protein (amino acids) degrades to gluconeogenic constituents to sustain plasma glucose levels. Excessive muscle protein catabolism eventually produces a muscle-wasting effect. Reliance on protein catabolism, coincident with depleted glycogen, continues because fatty acids from triacylglycerol hydrolysis in muscle and adipose tissue fail to provide gluconeogenic substrates.

## NO GLUCOSE SYNTHESIS FROM FATTY ACIDS

The figure illustrates why humans cannot convert fatty acids (palmitate in example) from triacylglycerol breakdown to glucose. Fatty acid oxidation within the mitochondria produces acetyl-CoA. Because the pyruvate dehydrogenase and pyruvate kinase reactions proceed irreversibly, acetyl-CoA cannot simply form pyruvate by carboxylation and synthesize glucose by reversing glycolysis. Instead, the 2-carbon acetyl group formed from acetyl-CoA degrades further when it enters the citric acid cycle. In humans, fatty acid hydrolysis produces no net synthesis of glucose.

## LIMITED GLUCOSE FROM TRIACYLGLYCEROLDERIVED GLYCEROL

The figure also shows that triacylglycerol hydrolysis via hormonesensitive lipase (HSL) produces a single 3-carbon glycerol molecule. Unlike fatty acids, the liver can use glycerol for glucose synthesis. After delivery of glycerol in the blood to the liver, glycerol kinase phosphorylates it to glycerol 3-phosphate. Further reduction produces dihydroxyacetone phosphate, a substance that provides the carbon skeleton for glucose synthesis.

There is a clear practical application to sports and exercise nutrition from an understanding of the limited metabolic pathways available for glucose synthesis from the body s triacylglycerol energy depots. Replenishment and maintenance of liver and muscle glycogen reserves depend on exogenous carbohydrate intake. The physically active person must make a concerted effort to regularly consume nutritious, low-to-moderate glycemic sources of this macronutrient.


Mitochondrion

Cori cycle to furnish glucose during prolonged exercise. Regular exercise training enhances the liver s capacity for glucose synthesis from alanine. ${ }^{37}$ Some amino acids such as glycine are ketogenic; when deaminated, they yield the intermediates acetyl-CoA or acetoacetate. These compounds cannot be used to synthesize glucose; rather, they synthesize to triacylglycerol or catabolize for energy in the citric acid cycle.

## INTEGRATIVE QUESTION

Explain how the amount of ATP produced in the cell varies depending on where a deaminated amino acid enters the catabolic pathways.

Protein Breakdown Facilitates Water Loss. When protein provides energy, the body must eliminate the
nitrogen-containing amine group and other solutes produced from protein breakdown. These waste products leave the body dissolved in obligatory fluid (urine). For this reason, excessive protein catabolism increases the body s water needs.

## THE METABOLIC MILL: INTERRELATIONSHIPS AMONG CARBOHYDRATE, FAT, AND PROTEIN METABOLISM

The metabolic mill depicts the citric acid cycle as the vital link between food (macronutrient) energy and chemical energy in ATP (Fig. 6.19). The citric acid cycle also serves as a metabolic hub to provide intermediates that cross the mitochondrial membrane into the cytosol to synthesize bionutrients for maintenance and growth. For example, excess carbohydrates provide the glycerol and acetyl fragments to synthesize triacylglycerol. Acetyl-CoA functions as the starting point for synthesizing cholesterol and many hormones. Fatty acids cannot contribute to glucose synthesis because the conversion of pyruvate to acetyl-CoA does not reverse (notice the one-way arrow in Fig. 6.18). Many of the carbon compounds generated in citric acid cycle reactions also provide the organic starting points to synthesize nonessential amino acids.

## Glucose Conversion to Fat

Lipogenesis describes the formation of fat, mostly in the cytoplasm of liver cells. It occurs when ingested glucose or protein not used to sustain energy metabolism converts into stored triacylglycerol. For example, when muscle and liver glycogen stores fill (as after a large carbohydrate-containing meal), pancreatic release of insulin causes a 30 -fold increase in glucose transport into adipocytes. Insulin initiates the translocation of a latent pool of GLUT 4 transporters from the adipocyte cytosol to the plasma membrane. GLUT $4 \mathrm{ac}-$ tion facilitates glucose transport into the cytosol for synthesis to triacylglycerols and subsequent storage within the adipocyte. This lipogenic process requires ATP energy working in concert with the B vitamins biotin, niacin, and pantothenic acid.

Lipogenesis begins with carbons from glucose and the carbon skeletons from amino acid molecules that metabolize to acetyl-CoA (refer to section on protein metabolism, p. 157). Liver cells bond the acetate parts of the acetyl-CoA molecules in a series of steps to form the 16 -carbon saturated fatty acid palmitic acid. This molecule then lengthens to an 18- or 20-carbon chain fatty acid in either the cytosol or the mitochondria. Three fatty acid molecules ultimately join (esterify) with one glycerol molecule (produced during glycolysis) to yield one triacylglycerol molecule. Triacylglycerol releases into the circulation as a very lowdensity lipoprotein (VLDL); cells may use VLDL for ATP production or store it in adipocytes along with other fats from dietary sources.

## Protein Conversion to Fat

Surplus dietary protein (similar to carbohydrate) readily converts to fat. After protein s digestion, the amino acids absorbed by the small intestine are transported in the circulation to the liver. Figure 6.19 illustrates that the carbon skeletons from these amino acids after deamination convert to pyruvate. This six-carbon molecule then enters the mitochondrion for conversion to acetyl-CoA for either (1) catabolism in the citric acid cycle or (2) fatty acid synthesis.

## Fats Burn in a Carbohydrate Flame

In metabolically active tissues, fatty acid breakdown depends somewhat on continual background levels of carbohydrate catabolism. Recall that acetyl-CoA enters the citric acid cycle by combining with oxaloacetate to form citrate. Oxaloacetate then regenerates from pyruvate during carbohydrate breakdown. This conversion occurs under enzymatic control of pyruvate carboxylase, which adds a carboxyl group to the pyruvate molecule. The degradation of fatty acids in the citric acid cycle continues only if sufficient oxaloacetate and other intermediates from carbohydrate breakdown combine with the acetyl-CoA formed during $\beta$-oxidation. These intermediates are continually lost or removed from the cycle and need to be replenished. Pyruvate formed during glucose metabolism plays an important role in maintaining a proper level of oxaloacetate (Figs. 6.15 and 6.19). Low pyruvate levels (as occurs with inadequate carbohydrate breakdown) reduce levels of citric acid cycle intermediates (oxaloacetate and malate), which slows citric acid cycle activity to impede fat breakdown. ${ }^{5,11,30,36,40}$ In this sense, fats burn in a carbohydrate flame.

## A Slower Rate of Energy Release from Fat

A rate limit exists for fatty acid use by active muscle. ${ }^{41}$ The power generated solely by fat breakdown represents only about one-half that achieved with carbohydrate as the chief aerobic energy source. Thus, depleting muscle glycogen must decrease a muscle s maximum aerobic power output. Just as the hypoglycemic condition coincides with a central or neural fatigue, muscle glycogen depletion probably causes peripheral or local muscle fatigue during exercise. ${ }^{29}$

Gluconeogenesis provides a metabolic option to synthesize glucose from noncarbohydrate sources. This process does not replenish or even maintain glycogen stores without adequate carbohydrate consumption. Appreciably reducing carbohydrate availability seriously limits energy transfer capacity. Glycogen depletion can occur under the following conditions:

1. Prolonged exercise (marathon running)
2. Consecutive days of intense training
3. Inadequate energy intake
4. Dietary elimination of carbohydrates (as advocated with high-fat, low-carbohydrate ketogenic diets )
5. Diabetes, which impairs cellular glucose uptake


Figure 6.19 The metabolic mill allows important interconversions for catabolism and anabolism among carbohydrates, fats, and proteins.

Depletion of glycogen depresses aerobic exercise intensity, even if large amounts of fatty acid substrate still circulate to muscle. With extreme carbohydrate depletion, the acetate fragments produced in $\beta$-oxidation (acetoacetate and $\alpha$ hydroxybutyrate) accumulate in extracellular fluids because they cannot enter the citric acid cycle. The liver then converts these compounds to ketone bodies, some of which pass in the urine. If ketosis persists, the acid quality of the body fluids can increase to potentially toxic levels.

## Summary

1. Food macronutrients provide the major sources of potential energy to form ATP (when ADP and a phosphate ion rejoin).
2. The complete breakdown of 1 mole of glucose liberates 689 kCal of energy. Of this, the bonds within ATP conserve about $224 \mathrm{kCal}(34 \%)$, with the remaining energy dissipated as heat.
3. During glycolytic reactions in the cell s cytosol, a net of two ATP molecules forms during anaerobic substrate-level phosphorylation.
4. Pyruvate converts to acetyl-CoA during the second stage of carbohydrate breakdown within the mitochondrion. Acetyl-CoA then progresses through the citric acid cycle.
5. The respiratory chain oxidizes the hydrogen atoms released during glucose breakdown; a portion of the released energy couples with ADP phosphorylation.
6. The complete oxidation of a glucose molecule in skeletal muscle yields a total (net gain) of 32 ATP molecules.
7. Oxidation of hydrogen atoms at their rate of formation establishes a biochemical steady state or steady rate of aerobic metabolism.
8. During intense exercise when hydrogen oxidation fails to keep pace with its production, pyruvate temporarily binds hydrogen to form lactate. This allows progression of anaerobic glycolysis for an additional duration.
9. Compounds that either inhibit or activate enzymes at key control points in the oxidative pathways modulate regulatory control of glycolysis and the citric acid cycle.
10. Cellular ADP concentration exerts the greatest effect on the rate-limiting enzymes that control energy metabolism.
11. The complete oxidation of a triacylglycerol molecule yields about 460 ATP molecules. Fatty acid catabolism requires oxygen; the term aerobic describes such reactions.
12. Protein serves as a potentially important energy substrate. After nitrogen removal from the amino acid molecule during deamination, the remaining carbon skeleton enters metabolic pathways to produce ATP aerobically.
13. Numerous interconversions take place among the food nutrients. Fatty acids represent a noteworthy exception because they cannot produce glucose.
14. Fats require intermediates generated in carbohydrate breakdown for their continual catabolism for energy in the metabolic mill. To this extent, fats burn in a carbohydrate flame.
15. The power generated solely by fat breakdown represents only about one-half of that achieved with carbohydrate as the chief aerobic energy source. Thus, depleting muscle glycogen considerably decreases a muscle s maximum aerobic power output.

References and Suggested Readings are available online at http://thepoint.lww.com/mkk7e.

## CHAPTER

## 7



## Energy Transfer During Exercise

## CHAPTER OBJECTIVES

> Identify the three energy systems and outline the relative contribution of each for exercise intensity and duration; relate your discussion to specific sport activities
> Discuss the blood lactate threshold and indicate differences between sedentary and endurancetrained individuals
> Outline the time course for oxygen consumption during 10 minutes of moderate-intensity exercise
> Draw a figure to illustrate oxygen consumption during progressive increments in exercise intensity up to maximum
> Differentiate between type I and type II muscle fibers
> Discuss differences in recovery oxygen consumption patterns from moderate and exhaustive exercise. What factors account for the excess postexercise oxygen consumption (EPOC) from each form of exercise?
> Outline optimal recovery procedures from steadyrate and non steady-rate exercise
> Discuss the rationale for intermittent exercise applied to interval training

Physical activity provides the greatest demand for energy transfer. In sprint running and swimming, for example, energy output from active muscles exceeds their resting value by 120 times or more. During less intense but sustained marathon running, the whole-body energy requirement increases 20 to 30 times above resting levels. The relative contribution of the different energy transfer systems differs markedly depending on intensity and duration of exercise and the participant s specific fitness status.

## IMMEDIATE ENERGY: <br> THE ATP PCR SYSTEM

High-intensity exercise of short duration (e.g., $100-\mathrm{m}$ dash, $25-\mathrm{m}$ swim, or lifting a heavy weight) requires an immediate energy supply. This energy comes almost exclusively from the intramuscular high-energy phosphate (or phosphagen) sources, adenosine triphosphate (ATP) and phosphocreatine (PCr). Each kilogram of skeletal muscle contains 3 to 8 mmol of ATP and 4 to 5 times more PCr. For a $70-\mathrm{kg}$ person with a muscle mass of 30 kg , this represents between 570 and 690 mmol of high-energy phosphates. Assuming that 20 kg of muscle becomes active during big-muscle exercise, sufficient stored phosphagen energy can power brisk walking for 1 minute, running at marathon pace for 20 to 30 seconds, or sprint running for 5 to 8 seconds. The quantity of these highenergy compounds probably becomes fully depleted within 20 to 30 seconds of maximal exercise. ${ }^{8,19}$ The maximum rate of energy transfer from the high-energy phosphates exceeds by 4 to 8 times the maximal energy transfer from aerobic metabolism. In a world record $100-\mathrm{m}$ sprint (current record set on May 31, 2008 by Osain Bolt of Jamaica: 9.72 s, or 27.0 mph ), the runner cannot maintain maximum speed throughout the run. During the last few seconds, the runner begins to slow, often with the winner slowing down least.

While all movements use high-energy phosphates as an energy source, some rely almost exclusively on this means of energy transfer. For example, success in football, weightlifting, field events, baseball, and volleyball requires brief but maximal efforts during the performance. Sustaining exercise beyond a brief period and recovering from all-out effort requires a continuous energy supply. If this fails to occur, the fuel supply diminishes and high-intensity movement ceases.

## SHORT-TERM ENERGY: THE LACTIC ACID SYSTEM

Resynthesis of the high-energy phosphates must proceed at a rapid rate to continue intense, short-duration exercise. The energy to phosphorylate ADP during such exercise comes mainly from stored muscle glycogen breakdown via (rapid) anaerobic glycolysis with resulting lactate formation. Rapid glycolysis allows ATP to form rapidly without oxygen. Anaerobic energy for ATP resynthesis in glycolysis can be viewed as reserve fuel activated when a person accelerates at the start of exercise or during the last few hundred yards of a mile run or performs all-out from start to finish during a 440-m run or $100-\mathrm{m}$ swim. Rapid and large accumulations of blood lactate occur during maximal exercise that lasts between 60 and 180 seconds.


Blood lactate: untrained
Blood lactate: trained
Figure 7.1 Blood lactate concentration for trained and untrained subjects at different levels of exercise expressed as a percentage of maximal oxygen consumption $\left(\mathrm{VO}_{2 \text { max }}\right)$.

Decreasing the intensity of such exercise to extend the exercise period correspondingly decreases the rate of lactate accumulation and the final blood lactate level.

## Lactate Accumulation

Blood lactate does not accumulate at all levels of exercise. Figure 7.1 illustrates for endurance athletes and untrained subjects the general relationship between oxygen consumption, expressed as a percentage of maximum, and blood lactate during light, moderate, and strenuous exercise. During light and moderate exercise ( $<50 \%$ aerobic capacity) blood lactate production equals lactate disappearance and oxygen-consuming reactions (aerobic glycolysis, and lipid and protein metabolism) adequately meet the exercise energy demands. In biochemical terms, energy generated from the oxidation of hydrogen provides the predominant ATP fuel for muscular activity. Any lactate formed in one part of a working muscle becomes rapidly oxidized by muscle fibers with high oxidative capacity in the same muscle or less active nearby muscles (heart and other fibers). ${ }^{11,32}$ When lactate oxidation equals its production, blood lactate level remains stable even though increases occur in exercise intensity and oxygen consumption.

For healthy, untrained persons, blood lactate begins to accumulate and rise in an exponential fashion at about 50 to $55 \%$ of the maximal capacity for aerobic metabolism. The traditional explanation for blood lactate accumulation in exercise assumes a relative tissue hypoxia. When glycolytic metabolism predominates, nicotinamide adenine dinucleotide (NADH) production exceeds the cell s capacity for shuttling its hydrogens (electrons) down the respiratory chain because of insufficient oxygen supply (or use) at the tissue level. The
imbalance in hydrogen release and subsequent oxidation (more precisely, the cytoplasmic $\mathrm{NAD}^{+} / \mathrm{NADH}$ ratio) causes pyruvate to accept the excess hydrogens (i.e., 2 hydrogen ions attach to the pyruvate molecule). The original pyruvate with 2 additional hydrogens forms a new molecule, lactic acid (as lactate in the body), which begins to accumulate. ${ }^{33}$

A more recent hypothesis explaining lactate buildup in muscle and its subsequent appearance in blood is based on radioactive tracer studies that label the carbon in the glucose molecule. ${ }^{10}$ Such studies reveal that lactate continuously forms during rest and moderate exercise. Under aerobic conditions, lactate oxidation by other tissues ( $70 \%$ ), its conversion to glucose in muscle and liver ( $20 \%$ ), or conversion to amino acids ( $10 \%$ ) results in no net lactate accumulation (i.e., blood lactate concentration remains stable). Blood lactate accumulates only when its disappearance (oxidation or substrate conversion) does not match its production. Aerobic training adaptations allow high rates of lactate turnover at a given exercise intensity; thus, lactate begins to accumulate at higher exercise levels than in the untrained state. ${ }^{43}$ Another explanation for lactate buildup during exercise includes the tendency for the enzyme lactate dehydrogenase (LDH) in fast-twitch muscle fibers to favor the conversion of pyruvate to lactate. In contrast, the LDH level in slow-twitch fibers favors conversion of lactate to pyruvate. Recruitment of fasttwitch fibers with increasing exercise intensity therefore favors lactate formation, independent of tissue oxygenation.

Lactate production and accumulation accelerate as exercise intensity increases. In such cases, the muscle cells can neither meet the additional energy demands aerobically nor oxidize lactate at its rate of formation. A similar pattern exists for untrained subjects and endurance athletes, except the threshold for lactate buildup, termed the blood lactate threshold, occurs at a higher percentage of the athlete s aerobic capacity. ${ }^{21,48,49}$ Trained endurance athletes perform steady-rate aerobic exercise at intensities between 80 and $90 \%$ of maximum capacity for aerobic metabolism. ${ }^{46}$ This favorable aerobic response most likely relates to three factors:

1. Athletes specific genetic endowment (e.g., muscle fiber type, muscle blood flow responsiveness)
2. Specific local training adaptations that favor less lactate production ${ }^{14,20}$
3. More rapid rate of lactate removal (greater lactate turnover and/or conversion) at any exercise intensity ${ }^{11,35}$

It is noteworthy that capillary density and the size and number of mitochondria increase with endurance training, as does the concentration of enzymes and transfer agents in aerobic metabolism, ${ }^{30,44}$ a response that remains unimpaired with aging. ${ }^{15}$ Such training adaptations enhance cellular capacity to generate ATP aerobically through glucose and fatty acid catabolism. Maintaining a low lactate level also conserves glycogen reserves, which extends the duration of intense aerobic effort. Chapter 14 further develops the concept of the blood lactate threshold, its measurement, and its relation to endurance performance. In Chapter 21, we discuss adaptations in the blood lactate threshold with exercise training.

## Lactate-Producing Capacity

Producing high blood lactate levels during maximal exercise increases with specific sprint-power anaerobic training and decreases when training ceases. Sprint-power athletes often achieve 20 to $30 \%$ higher blood lactate levels than untrained counterparts during maximal short-duration exercise. One or more of the following three mechanisms explains this response:

1. Improved motivation that accompanies exercise training
2. Increased intramuscular glycogen stores that accompany training (which probably allow a greater contribution of energy via anaerobic glycolysis)
3. Training-induced increase in glycolytic-related enzymes, particularly phosphofructokinase. The 20\% increase in glycolytic enzymes falls well below the two- to threefold increase in aerobic enzymes with endurance training

## LONG-TERM ENERGY: THE AEROBIC SYSTEM

As discussed previously, glycolytic reactions produce relatively few ATP. Consequently, aerobic metabolism provides nearly all of the energy transfer when intense exercise continues beyond several minutes.

## Oxygen Consumption During Exercise

Figure 7.2 illustrates oxygen consumption-also referred to as pulmonary oxygen uptake because oxygen measurements


Figure 7.2 Time course for oxygen consumption during a continuous jog at a relatively slow pace by an endurancetrained and an untrained individual. The orange and purple regions indicate the oxygen deficit-the quantity of oxygen that would have been consumed had oxygen consumption reached steady rate immediately.
occur at the lung and not the active muscles-during each minute of a slow 10 -minute run. Oxygen consumption rises exponentially during the first minutes of exercise (fast component of exercise oxygen consumption) to attain a plateau between the third and fourth minutes. It then remains relatively stable for the duration of effort. The term steady state, or steady rate, generally describes the flat portion (plateau) of the oxygen consumption curve. Steady rate reflects a balance between energy required by the working muscles and ATP production in aerobic metabolism. Within the steady-rate region, oxygen-consuming reactions supply the energy for exercise; any lactate produced either oxidizes or reconverts to glucose. No appreciable blood lactate accumulates under steady-rate (aerobic) metabolic conditions.

Once a steady rate of aerobic metabolism occurs, exercise could theoretically progress indefinitely if the individual possessed the will to continue. This assumes that steadyrate aerobic metabolism singularly determines the capacity to sustain submaximal exercise. Fluid loss and electrolyte depletion often pose limiting factors, especially during exercise in hot weather. Maintaining adequate reserves of both liver glycogen for central nervous system function and muscle glycogen to power exercise takes on added importance at high intensities of prolonged aerobic effort. Glycogen depletion dramatically reduces exercise capacity.

Individuals possess many steady-rate levels of exercise. For some, the spectrum ranges from sitting and watching TV to pushing a power lawn mower for 40 minutes. An elite endurance runner can maintain a steady rate of aerobic metabolism throughout a 26.2 -mile marathon, averaging slightly less than 5 minutes per mile, or during a 658 -mile ultramarathon, averaging 118 miles a day over 5.6 days! These exceptional endurance accomplishments result from two factors:

1. High capacity of the central circulation to deliver oxygen to working muscles
2. High capacity of the exercised muscles to use available oxygen

## Oxygen Deficit

At the onset of exercise, the oxygen consumption curve in Figure 7.2 does not increase instantaneously to steady rate. In the beginning transitional stage of constant-load exercise, oxygen consumption remains below a steady-rate level, even though the energy requirement remains unchanged throughout exercise. A lag in oxygen consumption early in exercise should not be surprising because energy for muscle contraction comes directly from the immediate anaerobic breakdown of ATP. Even with experimentally increased oxygen availability and increased oxygen diffusion gradients at the tissue level, the initial increase in exercise oxygen consumption is always lower than the steady-rate oxygen consumption. ${ }^{24,25}$ Owing to the interaction of intrinsic inertia in cellular metabolic signals and enzyme activation and relative sluggishness of oxygen delivery to the mitochondria, the hydrogens produced in energy metabolism do not immediately oxidize and
combine with oxygen. ${ }^{39,45}$ Oxygen consumption increases rapidly, however, in subsequent energy transfer reactions when oxygen combines with the hydrogens liberated in glycolysis, $\beta$-oxidation of fatty acids, or the reactions of the citric acid cycle. After several minutes of submaximal exercise, hydrogen production and subsequent oxidation (and ATP production) become proportional to the exercise energy requirement. At this stage, oxygen consumption attains a balance indicating a steady rate between energy requirement and aerobic energy transfer.

The oxygen deficit quantitatively expresses the difference between the total oxygen consumption during exercise and the total that would be consumed had steady-rate oxygen consumption (as an indicator of aerobic energy transfer) been achieved from the start. This oxygen deficit in the early stage of exercise represents the immediate anaerobic energy transfer from the hydrolysis of intramuscular high-energy phosphates and glycolysis until steady-rate energy transfer matches the energy demands.

Figure 7.3 depicts the relationship between the size of the oxygen deficit and the contribution of energy from the ATP PCr and lactate energy systems. The high-energy phosphates are substantially depleted in exercise that generates


Figure 7.3 Muscle ATP and PCr depletion and muscle lactate concentration in relation to the oxygen deficit. (Adapted from Pernow B, Karlsson J. Muscle ATP, PCr and lactate in submaximal and maximal exercise. In: Pernow B, Saltin B, eds. Muscle metabolism during exercise. New York: Plenum, 1971.)
about a 3- to 4-L oxygen deficit. Consequently, further exercise progresses only on a pay-as-you-go basis. Continual ATP resynthesis occurs through either anaerobic glycolysis or the aerobic breakdown of macronutrients. Interestingly, lactate begins to increase in active muscle well before the high-energy phosphates reach their lowest levels. This indicates that rapid glycolysis also contributes anaerobic energy in the initial stages of vigorous exercise, well before full use of the high-energy phosphates. Energy for exercise does not simply occur from activating a series of energy systems that switch on and switch off, but rather from smooth blending with considerable overlap of one mode of energy transfer to another. ${ }^{26,43}$

## Oxygen Deficit in the Trained and Untrained

Trained and untrained individuals attain similar steady-rate oxygen consumption values in exercise. Furthermore, oxygen consumption kinetics at the onset of exercise do not differ in children and adults. ${ }^{27}$ The endurance-trained person reaches steady rate more rapidly, with a smaller oxygen deficit than sprint-power athletes, cardiac patients, older adults, or untrained individuals (Fig. 7.2). ${ }^{7,16,31,34}$ Consequently, a faster aerobic kinetic response allows the trained person to consume a greater total amount of oxygen to steady-rate exercise and makes the anaerobic component of exercise energy transfer proportionately smaller. A facilitated rate of aerobic metabolism in the beginning of exercise with aerobic training occurs from (1) a more rapid increase in muscle bioenergetics, (2), an increase in overall blood flow (cardiac output), and (3) a disproportionately large regional blood flow to active muscle complemented by cellular adaptations. Many of these adaptations increase capacity to generate ATP aerobically (see Chapter 21).

INTEGRATIVE QUESTION
How would you answer the question: At what exercise level does the body switch to anaerobic energy metabolism?

## Maximal Oxygen Consumption

Figure 7.4 depicts oxygen consumption during a series of constant-speed runs up six progressively steeper hills. The laboratory simulates these hills by increasing treadmill or step bench elevation or increasing the resistance to pedaling at a constant rate on a bicycle ergometer. Each successive hill requires a greater energy output that places additional demand on the capacity for aerobic resynthesis of ATP. During the first several hills, oxygen consumption increases rapidly, with each new steady-rate value in direct proportion to exercise intensity. The runner maintains speed up the two last hills, but oxygen consumption fails to increase as rapidly or to the same extent as in the previous hills. No increase in oxygen consumption occurs during the run up the last hill. The region where oxygen consumption plateaus or increases only slightly with additional increases in exercise intensity represents the maximal oxygen consumptionalso called maximal oxygen uptake, maximal aerobic power, aerobic capacity, or simply $\boldsymbol{V O} \mathbf{2 m a x}$. Energy transfer in glycolysis allows one to perform more-intense exercise with resulting lactate accumulation. Under these conditions, the runner soon becomes exhausted and fails to continue.

The $\mathrm{VO}_{2 \text { max }}$ provides a quantitative measure of a person s capacity for aerobic ATP resynthesis. This makes the


Figure 7.4 Attainment of maximal oxygen consumption $\left(\mathrm{VO}_{2 \max }\right)$ while running up hills of progressively increasing slope. $\mathrm{VO}_{2 \text { max }}$ occurs in the region (not a single point) where further increases in exercise intensity produce a less-than-expected increase (or no increase) in oxygen consumption. Dots represent measured values of oxygen consumption while traversing the hills.


Figure 7.5 The oxygen transport system. The physiologic significance of $\mathrm{VO}_{2 \text { max }}$ depends on the functional capacity and integration of systems required for oxygen supply, transport, delivery, and use.
$\mathrm{VO}_{2 \text { max }}$ an important determinant of ability to sustain intense exercise for longer than 4 or 5 minutes. Attainment of a high $\mathrm{VO}_{2 \text { max }}$ has important physiologic meaning in addition to its role in sustaining energy metabolism. High $\mathrm{VO}_{2 \text { max }}$ requires the integrated and high-level response of diverse physiologic support systems illustrated in Figure 7.5. In subsequent chapters, we discuss various aspects of $\mathrm{VO}_{2 \max }$, including its physiologic significance, measurement, and role in exercise performance and cardiovascular health.

## Fast- and Slow-Twitch Muscle Fibers

Extracting about 20 to 40 mg of tissue (the size of a grain of rice) during surgical biopsy gives exercise physiologists a way to study functional and structural characteristics of human skeletal muscle. Two distinct types of muscle fiber exist in humans. A fast-twitch (FT), or type II, fiber has two primary subdivisions, type IIa and type IIx; each possesses rapid contraction speed and high capacity for anaerobic ATP production in glycolysis. The subdivision type IIa fiber also possesses somewhat high aerobic capacity. Type II fibers become active during change-of-pace and stop-and-go activities such as basketball, field hockey, lacrosse, soccer, and ice hockey. They also increase force output when running or cycling up a hill while maintaining a constant speed or during all-out effort that requires rapid, powerful movements
that depend almost exclusively on energy from anaerobic metabolism.

The second fiber type, the slow-twitch (ST), or type I muscle fiber, generates energy primarily through aerobic pathways. This fiber possesses a relatively slow contraction speed compared with its fast-twitch counterpart. Capacity to generate ATP aerobically intimately relates to its numerous large mitochondria and high levels of enzymes required for aerobic metabolism, particularly fatty acid catabolism. Slowtwitch muscle fibers primarily sustain continuous activities requiring a steady rate of aerobic energy transfer. Fatigue in prolonged running associates with glycogen depletion in the leg muscles type I and type IIa muscle fibers. ${ }^{2,22}$ This selective glycogen depletion pattern also occurs in the arms of wheelchair-dependent athletes during extended exercise durations. ${ }^{42}$ More than likely, the predominance of slow-twitch muscle fibers contributes to high blood lactate thresholds observed among elite endurance athletes.

Figure 7.6 illustrates the muscle-fiber type composition of two athletes in sports that rely on distinctly different energy transfer systems favored by a specific fiber type predominance. For the $50-\mathrm{m}$ sprint swim champion, type II fibers represent nearly $80 \%$ of the total muscle fibers, whereas the endurance cyclist possesses $80 \%$ type I fibers. From a practical perspective, most sports require relatively slow, sustained muscle actions interspersed with short bursts


Figure 7.6 Differences in muscle-fiber type composition between a sprint swimmer and endurance cyclist. The type I and type II muscle fibers were sampled from the vastus lateralis muscle and stained for myofibrillar ATPase after incubation at pH 4.3. Type I fibers stain dark, while type II fibers remain unstained. (Photos and photomicrographs courtesy of Dr. R. Billeter, Department of Anatomy, University of Bern, Switzerland.)
of powerful effort (e.g., basketball, soccer, field hockey). Not surprisingly, these activities require activation of both muscle fiber types.

The preceding discussion suggests that a muscle s predominant fiber type contributes to success in certain sports or physical activities. Chapter 18 explores this idea more fully, including other considerations concerning metabolic, contractile, and fatigue characteristics of each fiber type, the various subdivisions, proposed classification system, and effects of exercise training.

## ENERGY SPECTRUM OF EXERCISE

Figure 7.7 illustrates the relative contribution of anaerobic and aerobic energy sources related to maximal exercise duration. Table 7.1 also shows the relative contributions of the major energy fuels during various running competitions. These data,
based on laboratory experiments that involve all-out running, readily transpose to other activities by drawing the appropriate time relationships. For example, a $100-\mathrm{m}$ sprint run corresponds to any all-out exercise for 10 seconds, while an $800-\mathrm{m}$ run and $200-\mathrm{m}$ swim last about 2 minutes. All-out 1 -minute exercise includes the $400-\mathrm{m}$ run, the $100-\mathrm{m}$ swim, and repeated full-court presses during basketball.

The allocation of energy for exercise from each energy transfer form progresses along a continuum. At one extreme, the intramuscular high-energy phosphates supply almost all of the energy for exercise. The ATP PCr and lactic acid systems supply about one half the energy for intense exercise lasting 2 minutes; aerobic reactions supply the remainder. To excel under these exercise conditions requires a well-developed anaerobic and aerobic metabolic capacity. Intense exercise of intermediate duration performed for 5 to 10 minutes (e.g., middle-distance running and swimming, or basketball) places greater demand on

## IN A PRACTICAL SENSE

## Interpreting $\mathrm{VO}_{2 \text { Max }}$ Establishing Cardiovascular Fitness Categories

Cardiovascular fitness reflects the maximal amount of oxygen consumed during each minute of near-maximal exercise. Values for maximal oxygen consumption, or $\mathrm{VO}_{2_{\text {max }}}$ generally are expressed in milliliters of oxygen per kilogram of body mass per minute ( $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ ). Individual values can range from about $10 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ in cardiac patients to 80 or $90 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ in world-class runners and cross-country skiers. Men and women distance runners, swimmers, cyclists, and cross-country skiers
generally attain $\mathrm{VO}_{2 \text { max }}$ values nearly double those of sedentary persons (see Fig. 11.8).

Researchers have measured the $\mathrm{VO}_{2 \text { max }}$ of thousands of individuals of different ages. The average values and respective ranges for men and women of different ages establish category values to classify individuals for cardiovascular fitness. The table presents a five-part classification based on data from the literature for nonathletes.

## Cardiovascular Fitness Classifications

| Gender | Age | Poor | Fair | Average | Good | Excellent |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| Men | $\leq 29$ | $\leq 24.9$ | 2533.9 | 3443.9 | 4452.9 | $\geq 53$ |
|  | 3039 | $\leq 22.9$ | 2330.9 | 3141.9 | 4249.9 | $\geq 50$ |
|  | 4049 | $\leq 19.9$ | 2026.9 | 2738.9 | 3944.9 | $\geq 45$ |
|  | 5059 | $\leq 17.9$ | 1824.9 | 2537.9 | 3842.9 | $\geq 43$ |
| Women | 6069 | $\leq 15.9$ | 1622.9 | 2335.9 | 3640.9 | $\geq 41$ |
|  | $\leq 29$ | $\leq 23.9$ | 2430.9 | 3138.9 | 3948.9 | $\geq 49$ |
|  | 3039 | $\leq 19.9$ | 2027.9 | 2836.9 | 3744.9 | $\geq 45$ |
|  | 4049 | $\leq 16.9$ | 1724.9 | 2534.9 | 3541.9 | $\geq 42$ |
|  | 5059 | $\leq 14.9$ | 1521.9 | 2233.9 | 3439.9 | $\geq 40$ |
|  | 6069 | $\leq 12.9$ | 1320.9 | 2132.9 | 3336.9 | $\geq 37$ |

aerobic energy transfer. Long-duration marathon running, distance swimming, cycling, recreational jogging, and trekking require a constant aerobic energy supply with little reliance on energy transfer from anaerobic sources.

An understanding of the energy demands of diverse physical activities helps explain why a world-record holder in the 1-mile run does not necessarily excel in distance running. Conversely, premier marathon runners rarely run 1 mile in less than 4 minutes yet can complete a marathon at a 5-minute-per-mile pace. The appropriate approach to exercise training analyzes an activity for its specific energy components and then formulates training strategies to ensure optimal adaptations in physiologic and metabolic function. Improved capacity for energy transfer usually translates into improved exercise performance.

## The Specificity of Speed

Haile Gebrselassie, the world record holder for the marathon (September 28, 2008), can run a mile in four minutes 44 seconds and repeat the performance 26 times in a row, yet cannot run one sub-four minute mile.

## INTEGRATIVE QUESTION

 If athletes generally perform marathon running under intense but steady-rate conditions, explain why some have reduced capacity to sprint to the finish at race end.
## OXYGEN CONSUMPTION DURING RECOVERY

Following exercise, bodily processes do not immediately return to resting levels. After relatively light, short-duration physical effort, recovery proceeds rapidly and unnoticed. In contrast, intense exercise such as running a one-half mile race or swimming 200 yards as fast as possible requires considerable time for resting metabolism to return to preexercise levels. How rapidly an individual responds in recovery from light, moderate, and strenuous exercise depends on specific metabolic and physiologic processes during and in recovery from each type of effort.

Figure 7.8 illustrates oxygen consumption during exercise and recovery from different exercise intensities. Light exercise (A), with rapid attainment of steady-rate oxygen consumption, produces a small oxygen deficit. The magnitude of recovery


Figure 7.7 Relative contribution of aerobic and anaerobic energy metabolism during maximal physical effort of various durations. Note that 2 minutes of maximal effort requires about $50 \%$ of the energy from combined aerobic and anaerobic processes. A world-class 4-minute-mile pace derives approximately $65 \%$ of its energy from aerobic metabolism, with the remainder generated from anaerobic processes. A 2.5 hour marathon, in contrast, generates almost all of its energy from aerobic processes. (Adapted from strand PO, Rodahl K. Textbook of work physiology. New York: McGraw-Hill, 1977.)
oxygen consumption, coincidently, approximates the size of the oxygen deficit at the beginning of exercise. Recovery proceeds rapidly. Oxygen consumption follows a logarithmic curve, decreasing by about $50 \%$ over each subsequent 30 -second period until reaching the preexercise level.

Oxygen consumption during steady-rate and non steadyrate (intense) exercise and recovery plots as a logarithmic function in relation to time. ${ }^{6,47}$ The function increases in exercise or decreases in recovery by some constant fraction for each unit of time as oxygen consumption approaches an asymptote (level) value. Consider the example of recovery from 10 minutes of light, steady-rate exercise at an oxygen consumption of $2000 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$. If recovery oxygen consumption decreased by one-half over 30 seconds, then oxygen consumption would equal $1000 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ at 30 -seconds recovery and 500 mL . $\min ^{-1}$ at 60 seconds, with the resting value of $250 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ achieved in about 90 seconds.

Moderate-to-intense aerobic exercise (Fig. 7.8B) requires a longer time to achieve steady rate, which creates a larger oxygen deficit than less-intense exercise. Consequently, it takes longer for the recovery oxygen consumption to return to the preexercise level. The oxygen consumption recovery curve demonstrates an initial rapid decline (similar to recovery from light exercise) followed by a more gradual decline to baseline resting levels. In Figure 7.8A and $B$, the oxygen deficit and recovery oxygen consumption are computed by using the steady-rate oxygen consumption to represent the oxygen (energy) requirement of exercise. Figure 7.8C shows that exhaustive exercise does not produce a steady rate of aerobic metabolism. Such exercise demands a larger energy requirement than supplied by aerobic processes. Anaerobic energy transfer increases and blood lactate accumulates, with considerable time required to achieve complete recovery. Failure to achieve steadyrate oxygen consumption makes it unfeasible to accurately quantify the true oxygen deficit.

TABLE 7.1 Estimate of the Percent Contribution of Different Fuels to ATP Generation in Various Running Events

Percent Contribution to ATP Generation

|  | Percent Contribution to ATP Generation |  |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: |
| Event | Phosphocreatine | Anaerobic | Alycogen | Blood Glucose <br> (Liver Glycogen) | Triacylglycerol <br> (Fatty Acids) |
| 100 m | 50 | 50 | - | - | - |
| 200 m | 25 | 65 | 10 | - | - |
| 400 m | 12.5 | 62.5 | 25 | - | - |
| 800 m | 6 | 50 | 44 | - | - |
| 1500 m | $a$ | 25 | 75 | - | - |
| 5000 m | $a$ | 12.5 | 87.5 | - | - |
| $10,000 \mathrm{~m}$ | - | - | 87 | - | - |
| Marathon | - | - | 75 | 5 | 0 |
| Ultramarathon $(80 \mathrm{~km})$ | - | - | 10 | 5 | 80 |
| 24-h race | - | 70 | 20 | - | - |
| Soccer game | 10 |  | - |  |  |

${ }^{a}$ In such events phosphocreatine is used for the first few seconds and, if it has been resynthesized during the race, in the sprint to the finish. From Newsholme EA, et al. Physical and mental fatigue: metabolic mechanisms and importance of plasma amino acids. Br Med Bull 1992;48:477.


Figure 7.8 Oxygen consumption during exercise and in recovery from (A) light steady-rate exercise, (B) moderate-to-intense steady-rate exercise, and (C) exhaustive exercise that does not produce a steady rate of aerobic metabolism. Note that in exhaustive exercise, the exercise oxygen requirement exceeds the actual exercise oxygen consumption.

Each of the curves in Fig. 7.8 shows that oxygen consumption in recovery always exists in excess of the resting value, independent of exercise intensity. The excess has classically been termed the oxygen debt, or recovery oxygen consumption, and more recently the excess postexercise oxygen consumption, or EPOC (indicated by the yellow shaded area under each recovery curve). It computes as the total oxygen consumed in recovery minus the total oxygen theoretically consumed at rest during the recovery period. For example, if a total of 5.5 L of oxygen were consumed in recovery until attaining the resting value of $0.310 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, and recovery required 10 minutes, the recovery oxygen consumption would equal
5.5 L minus 3.1 $\mathrm{L}(0.310 \mathrm{~L} \times 10 \mathrm{~min})$, or 2.4 L . This indicates that the preceding exercise caused physiologic alterations during exercise and during recovery that required an additional 2.4 L of oxygen before oxygen consumption returned to the preexercise resting level. The inference assumes that resting oxygen consumption remains unaltered during exercise and recovery. As we discuss below, this assumption is not entirely correct (particularly following strenuous exercise).

The curves in Figure 7.8 illustrate two important characteristics of recovery oxygen consumption:

1. With mild aerobic exercise of relatively short duration (little disruption in body temperature and hormonal milieu), about one-half of the total recovery oxygen consumption occurs within 30 seconds, with complete recovery within several minutes. The decline in oxygen consumption follows a singlecomponent exponential curve termed the fast component of recovery oxygen consumption.
2. Recovery from strenuous exercise presents a different picture, presumably because blood lactate, body temperature, and thermogenic hormone levels increase substantially. In addition to the fast component of the recovery phase, a second phase of recovery, termed the slow component, exists. Depending on the intensity and duration of the previous exercise, the slow component can take up to 24 hours to return to preexercise oxygen consumption. ${ }^{5,23,42}$ Even with shorter, intermittent bouts of supermaximal exercise (e.g., three 2-min bouts at $108 \% \mathrm{VO}_{2 \text { max }}$ interspersed with a 3-min rest), recovery oxygen consumption remains elevated for 1 hour or longer. ${ }^{4}$
Trained subjects have a faster rate of recovery oxygen consumption when exercising at either the same absolute or relative exercise intensities compared to untrained counterparts. ${ }^{41}$ More than likely, training adaptations that facilitate the rapid achievement of steady rate also facilitate a rapid recovery process.

## Metabolic Dynamics of Recovery Oxygen Consumption

A precise biochemical explanation for the recovery oxygen consumption, particularly the role of lactate, remains elusive because no comprehensive explanation exists about specific contributory factors.

## Early Theories About the Postexercise Oxygen Consumption (The So-Called Oxygen Debt)

In 1922, Nobel laureate Archibald Vivian Hill and colleagues first coined the term oxygen debt. These pioneer scientists discussed energy metabolism during exercise and recovery in financial accounting terms. ${ }^{28}$ Within this framework, the body s carbohydrate stores were likened to energy credits. Expending stored credits during exercise incurred an energy debt. The greater the energy deficit (use of available stored energy credits), the larger the energy debt. Hill
believed that the recovery oxygen consumption represented the cost of repaying this debt-hence the term oxygen debt.

Lactate accumulation from the anaerobic component of exercise represented use of glycogen, the stored energy credit. The ensuing oxygen debt served two purposes:

1. Reestablishing the original glycogen stores (credits) by synthesizing approximately $80 \%$ of the lactate back to glycogen in the liver (Cori cycle)
2. Catabolizing the remaining lactate through the pyruvate citric acid cycle pathway. The ATP generated presumably powered glycogen resynthesis from lactate.

This early explanation of the dynamics of recovery oxygen consumption was subsequently termed the lactic acid theory of oxygen debt.

In 1933, following the work of Hill, researchers at the Harvard Fatigue Laboratory explained that the initial phase of recovery oxygen consumption ended before blood lactate began to decline. ${ }^{36}$ They showed that one could incur an oxygen debt of almost 3 L without any appreciable blood lactate accumulation. To resolve these findings, they proposed two phases of oxygen debt: (1) alactic (or alactacid) oxygen debt (without lactate buildup) and (2) lactic acid (or lactacid) oxygen debt associated with elevated blood lactate levels. They based these two explanations on speculation because their early chemical methods did not allow them to measure ATP and PCr replenishment or the relationship between blood lactate and glucose and glycogen levels.

## Contemporary Concepts

The elevated aerobic metabolism in recovery restores the body to its preexercise condition. In short-duration, light-tomoderate exercise, recovery oxygen consumption generally replenishes the high-energy phosphates depleted by exercise. Recovery typically proceeds rapidly within several minutes. In longer-duration ( $>60 \mathrm{~min}$ ), intense aerobic exercise, recovery oxygen consumption remains elevated considerably longer. ${ }^{9}$ Figure 7.9 clearly illustrates the effect of exercise duration on the magnitude of recovery oxygen consumption. ${ }^{40}$ Eight trained women walked at $70 \%$ of $\mathrm{VO}_{2 \max }$ for 20 , 40, or 60 minutes. Recovery oxygen consumption totaled 8.6 L for the 20 -minute exercise period and 9.8 L for the 40 -minute session, while the amount of oxygen consumed during the $60-$ minute workout nearly doubled to 15.2 L . The increase in recovery oxygen consumption in each bout of steady-rate exercise failed to relate to lactate accumulation. Rather, other disequilibriums in physiologic function elevate the recovery metabolism.

In exhaustive exercise with its large anaerobic component and lactate accumulation, a small portion of EPOC resynthesizes lactate to glycogen. There is some suggestion that the gluconeogenic mechanism also progresses during exercise, particularly among trained individuals. ${ }^{17,35}$ A significant component of EPOC relates to physiologic processes that take place during recovery, in addition to metabolic events during exercise. Such


Figure 7.9 Total excess postexercise oxygen consumption (EPOC) during a 3-hour recovery from 20, 40, and 60 minutes of treadmill walking at $70 \% \mathrm{VO}_{2 \text { max }}$. EPOC for the 60 -minute exercise significantly exceeded the 20- or 40minute workouts. (From Quinn TJ, et al. Postexercise oxygen consumption in trained females: effect of exercise duration. Med Sci Sports Exerc 1994;26:908.)
factors likely account for the considerably larger oxygen debt than oxygen deficit in prolonged aerobic exercise and exhaustive anaerobic exercise. Body temperature, for example, rises about $3 \mathrm{C}(5.4 \mathrm{~F})$ during a long bout of intense aerobic exercise and can remain elevated for several hours in recovery. Elevated body temperature directly stimulates metabolism to increase recovery oxygen consumption.

Other factors also affect EPOC. Up to $10 \%$ of the recovery oxygen consumption reloads the blood returning to the lungs from the previously active muscles. An additional 2 to $5 \%$ restores oxygen dissolved in bodily fluids and bound to myoglobin within the muscle. Ventilation volumes in recovery from intense exercise remain 8 to 10 times above the resting requirement, a cost that can equal $10 \%$ of the EPOC. The heart also works harder and requires a greater oxygen supply during recovery. Tissue repair and redistribution of calcium, potassium, and sodium ions within muscle and other body compartments also require additional energy. The residual effects of the thermogenic hormones epinephrine, norepinephrine, and thyroxine and the glucocorticoids released in exercise keep metabolism elevated for a considerable time in recovery. In essence, all of the physiologic systems activated in exercise increase their own particular need for oxygen during recovery (Fig. 7.10). The recovery oxygen consumption, or EPOC, reflects two factors:

1. The level of anaerobic metabolism in previous exercise
2. The respiratory, circulatory, hormonal, ionic, and thermal adjustments that elevate metabolism during recovery


Figure 7.10 Factors that contribute to the excess postexercise oxygen consumption (EPOC) following exhaustive exercise.

## Implications of EPOC for Exercise and Recovery

Understanding the dynamics of EPOC provides a basis for structuring exercise intervals and optimizing recovery. No appreciable lactate accumulates either with steady-rate aerobic exercise or with brief 5 - to 10 -second bouts of all-out effort powered by the intramuscular high-energy phosphates. Consequently, recovery progresses rapidly and exercise can begin again with only a short rest period with passive recovery most desirable. ${ }^{18}$ In contrast, prolonged durations of anaerobic exercise produce considerable lactate buildup (in active muscles and blood), with disruption in various physiologic functions. In such cases, recovery oxygen consumption often requires considerable time to return to baseline. Prolonged recovery between exercise intervals would impair performance in basketball, hockey, soccer, tennis, and badminton. An athlete pushed to a high level of anaerobic metabolism may not fully recover during brief time-out periods or intermittent intervals of less-intense exercise.

Procedures for speeding recovery from exercise generally are either active or passive. In active recovery (often
termed cooling-down or tapering-off ), the individual performs submaximal exercise (with large muscle groups), believing that continued physical activity in some way prevents muscle cramps and stiffness and facilitates overall recovery. With passive recovery, the person usually lies down, presuming that total inactivity reduces the resting energy requirements and thus frees oxygen to fuel the recovery process. Modifications of passive recovery have included massage, cold showers, specific body positions, and consuming cold liquids.

## Optimal Recovery from Steady-Rate Exercise

Most individuals generally exercise in steady rate with little lactate accumulation at oxygen consumptions below 55 to $60 \%$ of $\mathrm{VO}_{2 \max }$. Recovery entails resynthesis of high-energy phosphates; replenishment of oxygen in the blood, bodily fluids, and muscle myoglobin; and a small energy cost to sustain elevated circulation and ventilation. Passive procedures facilitate recovery because any additional exercise under these circumstances only serves to elevate total metabolism and delay recovery.

## FOCUS ON RESEARCH

## A Challenge to Conventional Wisdom

## Brooks GA, et al. Glycogen synthesis and metabolism of lactic acid after exercise. Am J Physiol 1973; 224:1162.

> The early research of A. V. Hill and colleagues postulated that the elevated oxygen consumption $\left(\mathrm{VO}_{2}\right)$ in recovery from exercise (so-called oxygen debt) resulted from oxidation of about one-fifth of the lactate produced in exercise. Lactate oxidation provided the necessary energy to resynthesize the remaining lactate to glycogen. Subsequent research by Margaria (see Chapter 9, Focus on Research, p. 204 ) retained this traditional lactic acid interpretation of the elevated $\mathrm{VO}_{2}$ in recovery from exercise. Until the 1973 publication by Brooks and coworkers, few investigators had directly challenged the conventional wisdom that lactate produced in strenuous exercise caused significant glycogen resynthesis during the postexercise repayment of the oxygen debt.

Female rats served in two experiments to test the lactic acid oxygen debt theory. Experiment 1 placed animals into either a sedentary group or an exercise group that ran at intensities that produced considerable lactate buildup and a large postexercise $\mathrm{VO}_{2}$. Following exercise, the researchers periodically sacrificed some animals and measured glycogen, glucose, and lactate in muscle, liver, and blood during a 24-hour recovery. The top figure displays liver and muscle glycogen concentrations during recovery from exercise. Compared with sedentary controls (purple and blue squares) little glycogen remained in the muscles and liver at the end of exhaustive exercise ( 0 min ). Furthermore, no significant glycogen resynthesis occurred in the postexercise period; liver and muscle glycogen concentrations after 24 hours recovery did not exceed the immediate postexercise values. These findings did not support the hypothesis proposed by Hill and colleagues that the elevated postexercise $\mathrm{VO}_{2}$ largely related to glycogen resynthesis from lactate produced during exhaustive exercise.

In a parallel experiment (experiment 2 , bottom figure), the researchers infused ${ }^{14} \mathrm{C}$-labeled lactate into exerciseexhausted and pair-fasted sedentary control rats. Measurements included release of labeled $\mathrm{CO}_{2}$ in recovery to assess the fate of the infused ${ }^{14} \mathrm{C}$-labeled lactate. If lactate resynthesized to glycogen in recovery-as proposed by the lactic acid theory of oxygen debt -then little of the injected isotope should have appeared in expired $\mathrm{CO}_{2}$. Conversely, if oxidation explains the primary fate of lactate, then most of the labeled carbon in the infused lactate should indeed appear as ${ }^{14} \mathrm{CO}_{2}$ in expired air. The experiment produced unequivocal results: 70 to $90 \%$ of the isotope appeared as $\mathrm{CO}_{2}$.

Under the conditions of Brooks experiment, glycogen resynthesis from elevated lactate did not represent a predominant process to explain the oxygen debt proposed



$$
\square \text { Exercise - exhausted (liver) } \square \text { Pair - fasted controls }
$$

Experiment 1. Liver and muscle glycogen concentrations over time after exhaustive exercise in rats previously fasted for 10 to 12 hours. Experiment 2. Production of labeled $\mathrm{CO}_{2}$ after infusion of ${ }^{14} \mathrm{C}$-labeled lactate in exerciseexhausted and pair-fasted rats (bar graph, left ordinate). Expiration of labeled $\mathrm{CO}_{2}$ is also expressed as a cumulative percentage of ${ }^{14} \mathrm{C}$-labeled lactate (line graph, right ordinate).
by Hill and colleagues in the 1920s. Subsequent research by Brooks and other investigators continues to redefine and expand the biochemical and physiologic factors that affect recovery $\mathrm{VO}_{2}$.


Figure 7.11 Blood lactate concentration following maximal exercise using passive recovery and active recoveries at 35\%, $65 \%$, and a combination 35 and $65 \% \mathrm{VO}_{2 \max }$. The horizontal white line indicates the blood lactate level produced by exercise at $65 \% \mathrm{VO}_{2 \max }$ without previous exercise. The inset curve depicts the generalized relationship between exercise intensity and rate of lactate removal. (Adapted from Dodd S, et al. Blood lactate disappearance at various intensities of recovery exercise. J Appl Physiol: Respir Environ Exerc Physiol 1984;57:1462.)

## Optimal Recovery from Non Steady-Rate Exercise

When exercise intensity exceeds the maximum steadyrate level, lactate formation in muscle exceeds its removal rate, and blood lactate accumulates. With increasing exercise intensity, blood lactate levels rise sharply and the exerciser soon becomes exhausted. Although the precise mechanisms for exhaustion during anaerobic exercise remain unclear, blood lactate levels provide an objective indication of the relative strenuousness of exercise; they also reflect the adequacy of recovery. Because lactate anions induce a fatiguing effect on skeletal muscle (independent of associated reductions in
$\mathrm{pH}),{ }^{29}$ any procedure that accelerates lactate removal probably augments subsequent exercise performance. ${ }^{1}$

Performing aerobic exercise in recovery accelerates blood lactate removal. ${ }^{13,21}$ The optimal level of recovery exercise ranges between 30 and $45 \% \mathrm{VO}_{2 \text { max }}$ for bicycle exercise and 55 to $60 \% \mathrm{VO}_{2 \text { max }}$ when the recovery involves running. ${ }^{38}$ This difference between exercise modes reflects the more localized muscle involvement in bicycling that lowers the threshold for blood lactate accumulation.

Figure 7.11 illustrates blood lactate recovery patterns for trained men who performed 6 minutes of supermaximal exercise on a bicycle ergometer. Active recovery involved 40 minutes of continuous exercise at either 35 or $65 \%$

TABLE 7.2 Results of Classic Study with Intermittent Exercise

| Exercise <br> Rest <br> Periods | Total Distance Run (yards) | Average Oxygen Consumption $\left(\mathrm{L} \cdot \min ^{-1}\right)$ | Blood Lactate Level (mg • dL Blood $^{-1}$ ) |
| :---: | :---: | :---: | :---: |
| 4 min continuous | 1422 | 5.6 | 150 |
| $\begin{aligned} & 10 \text { s exercise } \\ & 5 \text { s rest } \end{aligned}$ | 7294 | 5.1 | 44 |
| 10 s exercise 10 s rest | 5468 | 4.4 | 20 |
| 15 s exercise 30 s rest | 3642 | 3.6 | 16 |

$\mathrm{VO}_{2 \text { max }}$. A combination of $65 \% \mathrm{VO}_{2 \text { max }}(7 \mathrm{~min})$ followed by $35 \% \mathrm{VO}_{2 \max }(33 \mathrm{~min})$ evaluated whether a higher-intensity exercise interval early in recovery would expedite lactate removal. The results indicated that moderate aerobic exercise $\left(35 \% \quad \mathrm{VO}_{2 \max }\right)$ performed in recovery facilitates lactate removal compared with passive recovery procedures. Combining higher-intensity followed by lower-intensity exercise provided no greater benefit than a single exercise level at moderate intensity. Performing recovery exercise above the lactate threshold $\left(65 \% \mathrm{VO}_{2 \max }\right)$ offers no advantage and may even prolong recovery by initiating lactate formation and accumulation. In a practical sense, if left to their own choice, most individuals select the optimal recovery exercise intensity.

The facilitated lactate removal with active recovery likely results from increased perfusion of blood through the lactate-using liver, heart, and inspiratory muscles, which may serve as net consumers of lactate during recovery from intense exercise. ${ }^{3,12}$ Increased blood flow through the muscles in active recovery also enhances lactate removal because this tissue readily oxidizes lactate via citric acid cycle metabolism.

## Intermittent (Interval) Exercise

One approach to performing exercise that normally produces exhaustion within several minutes if performed continuously requires exercising intermittently with preestablished spacing of exercise and rest intervals. The physical conditioning strategy of interval training characterizes this approach. This training regimen applies different work-to-rest intervals with supermaximal exercise to overload the energy transfer systems. For example, with all-out exercise of up to 8 second s duration, the intramuscular high-energy phosphates provide most of the energy with minimal reliance on the glycolytic pathway. This produces rapid recovery (alactic, fast component), enabling a subsequent bout of intense exercise to begin following a brief recovery.

Table 7.2 summarizes the results of a classic series of experiments that combined exercise and rest intervals. On one
day, the subject ran at a speed that would normally exhaust him within 5 minutes. The continuous run covered about 0.8 mile, and the runner attained a $\mathrm{VO}_{2 \max }$ of $5.6 \mathrm{~L} \cdot \min ^{-1}$. A high blood lactate level (last column of the table), owing to substantial anaerobic metabolism, verified a relative state of exhaustion. On another day, he ran at the same fast speed but intermittently with periods of 10 seconds of exercise and 5 seconds of recovery. During 30 minutes of intermittent exercise, the time running amounted to 20 minutes and the distance covered equaled 4 miles, compared with less than 5 minutes and 0.8 miles with a continuous run! The effectiveness of the intermittent exercise protocol becomes even more impressive considering that the blood lactate remained low, even though oxygen consumption averaged $5.1 \mathrm{~L} \cdot \min ^{-1}$ $\left(91 \% \mathrm{VO}_{2 \text { max }}\right.$ ) during the 30 -minute period. Thus, a relative balance existed between the energy requirements of exercise and aerobic energy transfer within the muscles throughout the exercise and rest intervals.

Manipulating the duration of exercise and rest intervals can effectively overload a specific energy-transfer system. When the rest interval increased from 5 to 10 seconds, oxygen consumption averaged $4.4 \mathrm{~L} \cdot \mathrm{~min}^{-1}$; 15-second work and 30 -second recovery intervals produced only a 3.6L oxygen consumption. For each 30 -minute bout of intermittent exercise, however, the runner achieved a longer distance and a substantially lower blood lactate level than when exercising continuously at the same intensity. Chapter 21 focuses on the specific application of the principles of intermittent exercise for aerobic and anaerobic training and sports performance.

## Summary

1. The relative contribution of the pathways for ATP production differs depending on exercise intensity and duration.
2. The intramuscular stores of ATP and PCr (immediate energy system) provide the energy for short-duration, intense exercise ( $100-\mathrm{m}$ dash, repetitive lifting of heavy weights).
3. For less intense exercise of longer duration (1 to 2 min ), the anaerobic reactions of glycolysis (shortterm energy system) generate most of the energy.
4. The aerobic system (long-term energy system) predominates as exercise progresses beyond several minutes.
5. Humans possess two distinct types of muscle fibers, each with unique metabolic and contractile properties: (1) low glycolytic high oxidative, slow-twitch fibers (type I) and (2) low oxidative high glycolytic, fast-twitch fibers (type II). Intermediate fibers of the fast-twitch type also exist with overlapping metabolic characteristics.
6. Understanding the energy spectrum of exercise makes it possible to train for specific improvement in each of the body s energy transfer systems.
7. A steady rate of oxygen consumption represents a balance between the energy requirements of the active muscles and aerobic ATP resynthesis.
8. Oxygen deficit defines the difference between the oxygen requirement of exercise and the oxygen consumed during exercise.
9. Maximum oxygen consumption $\left(\mathrm{VO}_{2 \max }\right)$ quantitatively defines a person $s$ maximum capacity to resynthesize ATP aerobically. This serves as an important indicator of physiologic functional capacity to sustain intense aerobic exercise.
10. Oxygen consumption remains elevated above the resting level following exercise. Recovery oxygen consumption reflects the metabolic demands of exercise and the exercise-induced physiologic imbalances that persist into recovery.
11. Moderate physical activity following intense exercise (active recovery) facilitates recovery compared with passive procedures.
12. Proper spacing of the work-to-rest intervals provides a way to augment exercise at an intensity that would normally prove fatiguing if performed continuously.

References are available online at http://thepoint.lww.com/mkk7e.

## CHAPTER



## Measurement of Human Energy Expenditure

## CHAPTER OBJECTIVES

> Define direct calorimetry, indirect calorimetry, closed-circuit spirometry, and open-circuit spirometry
> Diagram the closed-circuit spirometry system for oxygen consumption determinations
> Describe portable spirometry, bag technique, and computerized instrumentation systems of opencircuit spirometry
> Outline the basics of the micro-Scholander and Haldane techniques to chemically analyze expired air samples
> Discuss how the doubly labeled water technique estimates human energy expenditure and give advantages and limitations of the method
> Define respiratory quotient ( RQ ), and discuss its use to quantify energy release in metabolism and the composition of the food mixture metabolized during rest and steady-rate exercise
> Discuss the difference between RQ and respiratory exchange ratio (R) and factors that affect each

## MEASURING THE BODY S HEAT PRODUCTION

All of the metabolic processes within the body ultimately result in heat production. Thus, the rate of heat production (by cells, tissues, or even the whole body) operationally defines the rate of energy metabolism. The calorie (see Chapter 4) is the basic unit of heat measurement and the term calorimetry defines the measurement of heat transfer. Two different approaches, direct calorimetry and indirect calorimetry, accurately quantify human energy transfer, as illustrated in Figure 8.1.

## Direct Calorimetry

The early experiments of French chemist Antoine Lavoisier (1743 1794) and his contemporaries (http://scienceworld. wolfram.com/biography/Lavoisier.html) in the 1770s provided the impetus to directly measure energy expenditure during rest and physical activity. The idea, similar to that used in the bomb calorimeter described in Chapter 4 to determine food energy, provides a convenient (though elaborate) methodology to measure heat production in humans.

In the 1890s at Wesleyan University, professors W. O. Atwater (a chemist; 1844 1907) and E. B. Rosa (a physicist; 1861 1921) used the first human calorimeter of major scientific importance. ${ }^{1,30}$ Their pioneering and elegant calorimetric experiments relating energy input (food consumption) to energy expenditure verified the law of the conservation of energy and established the validity of indirect calorimetry.


Figure 8.1 The measurement of the body s rate of heat production gives a direct assesment of metabolic rate. Heat production (metabolic rate) can also be estimated indirectly by measuring the exchange of gases (carbon dioxide and oxygen) during the breakdown of the food macronutrients and the excretion of nitrogen.

The calorimeter, diagramed schematically in Figure 8.2, consisted of a chamber where a subject could live, eat, sleep, and exercise on a bicycle ergometer. The experiments lasted from several hours to 13 days, and some involved cycling exercise performed for up to 16 hours with total energy expenditure exceeding $10,000 \mathrm{kCal}$ ! A staff of 16 , working in teams for 8 - to 12 -hour shifts, operated the airtight, thermally insulated calorimeter. A known volume of water at a specified temperature circulated through a series of coils at the top of the chamber; this water absorbed the heat produced and radiated by the subject. Insulation surrounded the entire chamber so that any change in water temperature (measured in 0.01 C with a microscope mounted alongside a thermometer) reflected the subjects energy metabolism. For adequate ventilation, exhaled air continually passed from the room through chemicals that removed moisture and absorbed carbon dioxide. Oxygen was added to the air recirculated through the chamber.

In the 110 years since the publication of the seminal papers by Atwater and Rosa, other calorimetric methods have emerged for inferring energy expenditure from metabolic gas exchange (see next section) for extended periods in respiration chambers, and via metabolic and thermal balance with water flow and airflow calorimeters. ${ }^{5,8,13,19} 21$ The modern space suit worn by astronauts during extravehicular activities, for example, represents a suit calorimeter designed to maintain respiratory gas exchange, thermal balance, and protection from a potentially hostile ambient environment. These suits have application for performing extended work outside an orbiting space vehicle, on the lunar surface, and, eventually, while constructing space stations or returning astronauts to the Moon by 2020 to establish a manned lunar outpost and ultimately explore Mars. ${ }^{23}$

Over the years, various other heat-measuring devices have been developed, each based on a different principle of operation. In an airflow calorimeter, the temperature change in air that flows through an insulated space, multiplied by the airs mass and specific heat (including calculations for evaporative heat loss), determines heat production. A water flow calorimeter operates similarly, except that a change in temperature occurs in water flowing through coils that make up part of an environmentally self-contained body suit worn by astronauts. Gradient layer calorimetry measures body heat that flows from the subject through a sheet of insulating materials (with appropriate piping and cooler water flowing on the outside of the gradient). In storage calorimetry, the subject sits in an insulated tank surrounded by a known mass of water at a constant temperature. The heat given off by the subject changes the temperature of the surrounding water.

Direct measurement of heat production in humans has considerable theoretical implications but limited practical applications. Accurate measurements of heat production in the calorimeter require considerable time and expense and formidable engineering expertise. Thus, calorimeters remain inapplicable for energy determinations for most sport, occupational, and recreational activities.


Figure 8.2 A human calorimeter directly measures the body s rate of energy metabolism (heat production). In the Atwater-Rosa calorimeter, a thin sheet of copper lines the interior wall to which heat exchangers attach overhead and through which cold water passes. Water cooled to 2 C moves at a high flow rate, absorbing the heat radiated from the subject during exercise. As the subject rests, warmer water flows at a slower rate. In the original bicycle ergometer shown in the schematic, the rear wheel contacts the shaft of a generator that powers a light bulb. In later versions of ergometers, copper composed part of the rear wheel. The wheel rotated through the field of an electromagnet to produce an electric current for determining power output.

## Indirect Calorimetry

All energy-releasing reactions in humans ultimately depend on oxygen use. Measuring a persons oxygen consumption during physical activities provides researchers with an indirect yet highly accurate estimate of energy expenditure. Compared with direct calorimetry, indirect calorimetry remains simpler and less expensive.

Studies with the bomb calorimeter show the release of approximately 4.82 kCal of energy when a mixed-diet blend of carbohydrate, lipid, and protein burns with 1 L of oxygen. Even with large variations in the metabolic mixture, this calorific value for oxygen varies only slightly, generally within 2 to $4 \%$. A rounded value of 5.0 kCal per liter of oxygen consumed provides an appropriate conversion factor to estimate energy expenditure under steady-rate conditions of aerobic metabolism. This energy oxygen equivalent of 5.0 kCal per liter provides a suitable yardstick to express any aerobic physical activity in energy units (see Appendix C).

Indirect calorimetry yields results comparable to direct measurement in the human calorimeter. Closed-circuit
spirometry and open-circuit spirometry represent the two applications of indirect calorimetry.

## INTEGRATIVE QUESTION

What rationale underlies early experiments that quantified energy metabolism of small animals by measuring the rate that ice melted in a container that surrounded the animal?

## Closed-Circuit Spirometry

Figure 8.3 illustrates the technique of closed-circuit spirometry developed in the late 1800s and used in hospitals and research laboratories through the 1980s to estimate resting energy expenditure, but little used today. The simplicity of this method and its ability to directly measure oxygen consumption has considerable theoretical importance but limited practical applications. The subject breathes $100 \%$ oxygen from a prefilled container (spirometer). The equipment is a closed system because the subject rebreathes only the gas in


Figure 8.3 The closed-circuit method uses a spirometer prefilled with $100 \%$ oxygen. As the subject rebreathes from the spirometer, soda lime removes the expired air s carbon dioxide. The difference between the initial and final volumes of oxygen in the calibrated spirometer indicates oxygen consumption during the measurement interval.
the spirometer. A canister of potassium hydroxide (soda lime) placed in the breathing circuit absorbs the carbon dioxide in the exhaled air. A drum attached to the spirometer revolves at a known speed to record the oxygen removed (oxygen consumed) from changes in the systems total volume.

During exercise, closed-circuit spirometry measurement becomes problematic. The subject must remain close to the bulky equipment, the circuit offers considerable resistance to accommodate the large breathing volumes during exercise, and carbon dioxide removal lags behind its production rate during intense exercise. For these reasons, open-circuit spirometry remains the most widely used laboratory procedure to measure exercise oxygen consumption.

## Open-Circuit Spirometry

The open-circuit method provides a relatively simple way to measure oxygen consumption. A subject inhales ambient air with a constant composition of $20.93 \%$ oxygen, $0.03 \%$ carbon dioxide, and $79.04 \%$ nitrogen (includes a small quantity of inert gases). The changes in oxygen and carbon dioxide percentages in expired air compared with the percentages in inspired ambient air indirectly reflect the ongoing process of energy metabolism. Thus, analysis of two factorsthe volume of air breathed during a specified time and the

## IN A PRACTICAL SENSE

## Calculating Oxygen Consumption ( $\dot{V}_{2}$ ), Carbon Dioxide Production ( $\dot{\mathbf{V}} \mathrm{CO}_{2}$ ), and the Respiratory Quotient (RQ) Using Open-CircuitSpirometry

Because the percentage composition of inspired air remains relatively constant $\left(\mathrm{CO}_{2}=0.03 \%, \mathrm{O}_{2}=20.93 \%, \mathrm{~N}_{2}=79.04 \%\right)$, determining a person s oxygen consumption requires measuring the amount and composition of the expired air. Expired air always contains more $\mathrm{CO}_{2}$ (usually 2.5 to $5.0 \%$ ), less $\mathrm{O}_{2}$ (usually 15.0 to $18.5 \%$ ), and more $\mathrm{N}_{2}$ (usually 79.04 to $79.60 \%$ ) than the air inspired.

## NITROGEN EXCHANGE: THE HALDANE TRANSFORMATION

Nitrogen is inert in terms of energy metabolism; any change in its concentration in expired air reflects the fact that the number of oxygen molecules removed from inspired air are not replaced by the same number of carbon dioxide molecules produced in metabolism. This results in the volume of expired air ( $\mathrm{V}_{\mathrm{E}, \mathrm{STPD}}$ ) being unequal to the inspired volume $\left(V_{1, S T P D}\right)$. For example, if the respiratory quotient is less than 1.00 (i.e., less $\mathrm{CO}_{2}$ produced in relation to $\mathrm{O}_{2}$ consumed), and 3 liters (L) of air are inspired, less than 3 L of air will be expired. In this case, the nitrogen concentration is higher in the expired air than in the inspired air. This is not because nitrogen has been produced; rather, nitrogen molecules now represent a larger percentage of $\mathrm{V}_{\mathrm{E}}$ compared to $\mathrm{V}_{1} . \mathrm{V}_{\mathrm{E}}$ differs from $\mathrm{V}_{1}$ in direct proportion to the change in nitrogen concentration between the inspired and expired air volumes. Thus, $\mathrm{V}_{1}$ can be determined from $\mathrm{V}_{\mathrm{E}}$ using the relative change in nitrogen in an equation known as the Haldane transformation.

$$
\dot{V}_{1, S T P D}=\dot{V}_{E, S T P D} \times \frac{\% N_{2} \mathrm{E}}{\% \mathrm{~N}_{2} \mid}
$$

## Equation 1

where $\% \mathrm{~N}_{21}=79.04$ and $\% \mathrm{~N}_{21}=$ percent nitrogen in expired air computed from gas analysis as $\left[\left(100 \quad\left(\% \mathrm{O}_{2 \mathrm{E}}+\%_{2 \mathrm{CO}}^{2 \mathrm{E}}\right)\right]\right.$.

## CALCULATING $\mathrm{VO}_{2}$ USING EXPIRED AIR VOLUME

The following examples assume that all ventilation volumes are expressed as standard temperature, pressure, dry (STPD)—see How to Standardize Gas Volumes to Reference Conditions (STPD and BTPS) in Appendix D (http://thepoint.lww.com/mmk7e). The volume of $\mathrm{O}_{2}$ in inspired air per minute $\left(\mathrm{VO}_{21}\right)$ can be determined as follows:

$$
\mathrm{VO}_{21}=\mathrm{V}_{1} \times \% \mathrm{O}_{21}
$$

Equation 2
Using the Haldane transformation and substituting equation (1) for $V_{1}$,

$$
\mathrm{VO}_{21}=\mathrm{V}_{\mathrm{E}} \times \frac{\% \mathrm{~N}_{2} \mathrm{E}}{79.04 \%} \times \% \mathrm{O}_{21}
$$

Equation 3
where $\%_{2}=20.93 \%$.
The amount or volume of oxygen in the expired air $\left(\mathrm{VO}_{2 \mathrm{E}}\right)$ computes as

$$
\mathrm{VO}_{2 \mathrm{E}}=\mathrm{V}_{\mathrm{E}} \times \mathrm{O}_{2 \mathrm{E}} \quad \text { Equation } 4
$$

Where $\% \mathrm{O}_{2 \mathrm{E}}$ is the fractional concentration of oxygen in expired air determined by gas analysis (chemical or electronic methods).

## IN A PRACTICAL SENSE

The amount of $\mathrm{O}_{2}$ removed from inspired air each minute $\left(\mathrm{VO}_{2}\right)$ can then be computed as follows:

$$
\mathrm{VO}_{2}=\mathrm{V}_{1} \times \mathrm{O}_{21}-\mathrm{V}_{\mathrm{E}} \times \% \mathrm{O}_{2 \mathrm{E}}
$$

Equation 5
By substitution:

$$
\dot{\mathrm{VO}_{2}}=\left\langle\left[\left(\dot{\mathrm{V}}_{\mathrm{E}} \times \frac{\% \mathrm{~N}_{2} \mathrm{E}}{79.04 \%}\right) \times 20.93 \%\right]-\left(\dot{\mathrm{V}}_{\mathrm{E}} \times \mathrm{OO}_{2 \mathrm{E}}\right)\right\rangle
$$

Equation 6
where $\mathrm{VO}_{2}=$ volume of oxygen consumed per minute, expressed in mL or L , and $\mathrm{V}_{\mathrm{E}}=$ expired air volume consumed per minute, expressed in mL or L , and $\mathrm{V}_{\mathrm{E}}=$ expired air volume per minute, expressed in mL or L , STPD.

Equation 6 can be simplified to:

$$
\dot{\mathrm{VO}_{2}}=\dot{\mathrm{V}}_{\mathrm{E}}\left[\left(\frac{\% \mathrm{~N}_{2} \mathrm{E}}{79.04 \%} \times 20.93 \%\right)-\% \mathrm{O}_{2 \mathrm{E}}\right]
$$

Equation 7
After dividing 20.93 by 79.04 the final form of the equation becomes:

$$
\mathrm{VO}_{2}=\mathrm{V}_{\mathrm{E}}\left[\left(\% \mathrm{~N}_{2 \mathrm{E}} \times 0.265\right)-\% \mathrm{O}_{2 \mathrm{E}}\right]
$$

Equation 8
Equation 8 is the equation of choice to calculate $\mathrm{VO}_{2}$ when ventilation expired (STPD) is determined.

## True $\mathrm{O}_{2}$

The value obtained within the brackets in equations 7 and 8 is referred to as the True $\mathrm{O}_{2}$ and represents the oxygen extraction, or, more precisely, the percentage of oxygen consumed for any volume of air expired.

## CALCULATING $\dot{\mathrm{V}}_{2}$ USING INSPIRED AIR VOLUME

In situations where only $V_{1}$ is measured, the $V_{E}$ can be calculated from the Haldane transformation as:

$$
\dot{\mathrm{V}}_{\mathrm{E}}=\dot{\mathrm{V}}_{1} \frac{\% \mathrm{~N}_{21}}{\% \mathrm{~N}_{2 \mathrm{E}}}
$$

Equation 9
By substitution in equation (5), the computational equation becomes:

$$
\dot{\mathrm{VO}}_{2}=\dot{\mathrm{V}}_{\lfloor }\left[\% \mathrm{O}_{21}-\left(\frac{\% \mathrm{~N}_{21}}{\% \mathrm{~N}_{2 \mathrm{E}}} \times \% \mathrm{O}_{2 \mathrm{E}}\right)\right]
$$

Equation 10

Continued

## CALCULATING CARBON DIOXIDE PRODUCTION $\left(\dot{\mathrm{V}}_{2}\right)$

 The carbon dioxide production per minute $\left(\mathrm{VCO}_{2}\right)$ calculates as follows:$$
\mathrm{VCO}_{2}=\mathrm{V}_{\mathrm{E}}\left(\%_{2 \mathrm{CO}}^{2 \mathrm{E}} \quad \% \mathrm{CO}_{21}\right) \quad \text { Equation } 11
$$

where $\% \mathrm{CO}_{2 \mathrm{E}}=$ percent carbon dioxide in expired air determined by gas analysis, and $\% \mathrm{CO}_{21}=$ percent carbon dioxide in inspired air, which is essentially constant at $0.003 \%$.

The final form of the equation becomes:

$$
\mathrm{VCO}_{2 \mathrm{E}}=\mathrm{V}_{\mathrm{E}}\left(\% \mathrm{CO}_{2 \mathrm{E}}-0.003 \%\right)
$$

Equation 12

## CALCULATING THE RESPIRATORY QUOTIENT (RQ)

The respiratory quotient (RQ) calculates in one of two ways:

$$
\begin{aligned}
& \mathrm{RQ}=\frac{\dot{\mathrm{VCO}}{ }_{2}}{\dot{\mathrm{VO}}}{ }_{2} \\
& \text { or } \\
& \mathrm{RQ}=\frac{\% \mathrm{CO}_{2 \mathrm{E}}-0.03 \%}{\text { "True" } \mathrm{O}_{2}}
\end{aligned}
$$

Equation 13

## Example

Compute $\mathrm{VO}_{2}, \mathrm{VCO}_{2}$, and RQ from the following data:
a. $V_{E \text { STPD }}=60.0 \mathrm{~L}$
b. $\% \mathrm{O}_{2 \mathrm{E}}=16.86$ or (0.1686)
c. $\% \mathrm{CO}_{2 \mathrm{E}}=3.62$ or ( 0.0362 )
$\mathrm{VO}_{2}=\mathrm{V}_{\mathrm{E}}\left[\left(\% \mathrm{~N}_{2 \mathrm{E}} \times 0.265\right)-\% \mathrm{O}_{2 \mathrm{E}}\right] \quad$ Equation 8
$\mathrm{VO}_{2}=60.0[(1.00-(0.1686+0.0362)) \times 0.265-0.1686]$
$\mathrm{VO}_{2}=60.0[(0.7952 \times 0.265)-0.1686]$
$\mathrm{VO}_{2}=2.527 \mathrm{~L}$ min ${ }^{1}$

$$
\begin{aligned}
& \mathrm{VCO}_{2 \mathrm{E}}=\mathrm{V}_{\mathrm{E}}\left(\% \mathrm{CO}_{2 \mathrm{E}}-0.003 \%\right) \quad \text { Equation } 12 \\
& \mathrm{VCO}_{2 \mathrm{E}}=60.0(0.0362-0.003 \%)
\end{aligned}
$$

$\mathrm{VCO}_{2 \mathrm{E}}=1.992 \mathrm{~L}$ min ${ }^{1}$

$$
\left.\begin{array}{rl}
\mathrm{RQ} & =\frac{\dot{\mathrm{V} C O}}{2} \\
\dot{\mathrm{VO}} \\
2
\end{array}\right)\left(\begin{array}{l}
1.992 \\
\mathrm{RQ} \\
\mathrm{RQ}
\end{array}\right.
$$

$$
\text { Equation } 13
$$

composition of expired airprovides a practical way to measure oxygen consumption and infer energy expenditure.

Three common indirect calorimetry procedures measure oxygen consumption during physical activity:

1. Portable spirometry
2. Bag technique
3. Computerized instrumentation

## Portable Spirometry

Two German scientists in the early 1940s perfected a lightweight, portable system (first devised by German respiratory physiologist Nathan Zuntz [1847 1920] at the turn of the century) to determine energy expenditure indirectly during physical activity. ${ }^{15}$ The activities included war-related operations such as traveling over different terrain with full battle
gear, operating transportation vehicles including tanks and aircraft, and performing physical tasks that soldiers encounter during combat operations. With this system, the subject carries on the back the $3-\mathrm{kg}$ box-shaped apparatus shown in Figure 8.4. The subject inspires ambient air through a two-way breathing valve, while expired air exits through a gas meter. The meter measures the total expired air volume and simultaneously collects a small gas sample for later analysis of oxygen and carbon dioxide content. These values determine oxygen consumption and energy expenditure for the measurement period.

Carrying the portable spirometer allows considerable freedom of movement in physical activities as diverse as mountain climbing, downhill skiing, sailing, golf, and common household activities (Appendix C, http://thepoint.lww. com/mkk7e). The equipment becomes cumbersome during


Figure 8.4 Portable spirometer to measure oxygen consumption via the open-circuit method during golf and calisthenics exercise.
vigorous activity, and the meter begins to underrecord airflow volume during intense exercise with rapid breathing. ${ }^{17}$

## Bag Technique

Figure 8.5A and B depicts the classic bag technique. The subject in Figure 8.5A rides a stationary bicycle ergometer, wearing headgear attached to a two-way, high-velocity, lowresistance breathing valve. He breathes ambient air through one side of the valve and expels it through the other side. The expired air then passes into either large plastic or canvas Douglas bags (named for distinguished British respiratory physiologist Claude G. Douglas [1882 1963]) or rubber meteorological balloons or directly through a gas meter that continually measures expired air volume. The meter draws off an aliquot sample of expired air for subsequent analysis of $\mathrm{O}_{2}$


Figure 8.5 Measurement of oxygen consumption with open-circuit spirometry (classic bag technique) during (A) stationary cycle ergometer exercise and (B) box loading and unloading.
and $\mathrm{CO}_{2}$ composition. Figure 8.5 B illustrates oxygen consumption measured by the bag technique while the subject lifts boxes of different weights and sizes to evaluate the energy requirement of a specific occupational task. The technique also has determined energy expenditure during common household and garden tasks.

## Computerized Instrumentation

With advances in computer and microprocessor technology, the exercise scientist can rapidly measure metabolic and physiologic responses to exercise. A computer interfaces with at least three instruments: a system to continuously sample the subjects expired air, a flow-measuring device to record air volume breathed, and oxygen and carbon dioxide analyzers to measure the expired gas mixtures composition. The


Figure 8.6 Computer systems approach to collect, analyze, and monitor physiologic and metabolic data.
computer performs metabolic calculations based on electronic signals it receives from the instruments. A printed or graphic display of the data appears throughout the measurement period. More-advanced systems include automated blood pressure, heart rate, and temperature monitors, including preset instructions to regulate speed, duration, and exercise intensity with a treadmill, bicycle ergometer, stepper, rower, swim flume, or other exercise apparatus. Figure 8.6 depicts a typical computerized system to assess and monitor metabolic and physiologic responses during exercise.

Computerized systems offer advantages in ease of operation and speed of data analysis, but disadvantages also exist. ${ }^{4,10,32}$ These include the high cost of equipment and delays from system breakdowns. Regardless of the sophistication of a particular automated system, the output data still reflect the accuracy of the measuring devices. Therefore, accuracy and validity of measurement instruments require careful and frequent calibration that employs established reference standards.

## INTEGRATIVE QUESTION

Discuss the common energy basis to equate food intake and physical activity.

## Chemical Gas Analyzers for Calibration Purposes.

Figure 8.7 illustrates two of the classic chemical procedures to analyze gas mixtures for oxygen, carbon dioxide, and nitrogen and for calibrating and/or validating electronic analyzers. Before the conversion to electronic and computerized instrumentation, oxygen consumption determinations used either the Scholander or Haldane gas analysis methods. These methods involved hundreds of time-consuming separate analyses for a single experiment, with frequent duplicate measurements to verify results. This partly explains why energy metabolism studies from the early exercise physiology literature often only relied on one or two subjects and took so


Figure 8.7 General schematic for two common analytical procedures for gas analysis. Top. Micro-Scholander gas analyzer. $A$, Compensating chamber; $B$, reaction chamber; $C$, side arm for $\mathrm{CO}_{2}$ absorber; $D$, side arm for $\mathrm{O}_{2}$ absorber; $E$ and F, solid vaccine bottle stoppers; G, receptacle for stopcock; $H$, micrometer burette; I, leveling bulb containing mercury; J, handle for tilting apparatus; $K$, tube for storing the acid rinsing solution; $L$, pipette for the rinsing acid; $M$, transfer pipette. Bottom. Haldane gas analyzer. $A$, Water jacket surrounding the measuring burette; $B$, calibrated measuring burette containing a gas sample for measurement; $C$, vessel containing $\mathrm{CO}_{2}$ absorber (potassium hydroxide); $D$, vessel containing $\mathrm{O}_{2}$ absorber (pyrogallate); $E$, glass valve; $F$, entry for gas sample; $G$, mercury-leveling bulb. The gas introduced into the burette is exposed to the $\mathrm{O}_{2}$ and $\mathrm{CO}_{2}$ absorbers by alternately lowering and raising the mercury-leveling bulb. The $\mathrm{O}_{2}$ and $\mathrm{CO}_{2}$ gas volumes are determined by subtraction from the initial volume.
long to complete. When performed properly with attention to detail, these chemical analyzers produced highly accurate and reliable data.

The micro-Scholander technique measures oxygen and carbon dioxide concentration in expired air to an accuracy of $\pm 0.015 \mathrm{~mL}$ per 100 mL of gas. ${ }^{22}$ A skilled technician can perform one analysis of a $0.5-\mathrm{mL}$ microsample of the gas in about 10 minutes. The Haldane method provides another technique for gas analysis. ${ }^{11}$ It uses a larger air sample and requires between 10 and 15 minutes to complete one analysis.

## INTEGRATIVE QUESTION

Justify measuring only $\mathrm{CO}_{2}$ production to estimate energy expenditure during steady-rate exercise.

## Direct Versus Indirect Calorimetry

Comparisons of energy metabolism with direct and indirect calorimetry provide convincing evidence for the validity of the indirect method. Research in the early part of the 19th century compared the two methods of calorimetry over 40 days on three men who lived in a calorimeter similar to the one shown in Figure 8.2. Daily energy expenditure averaged 2723 kCal when measured directly by heat production and 2717 kCal when computed indirectly by closed-circuit oxygen consumption measures. Other experiments with animals and humans, using moderate (steady-rate) exercise, also showed close agreement between direct and indirect methods; in most instances, the difference averaged less than $\pm 1 \%$. In Atwater and Rosas calorimetry experiments, the error of the method averaged only $\pm 0.2 \%$. This remarkable achievement, using mostly handmade instruments, resulted from these scientists dedication to use precise calibration methods long before the availability of electronic instrumentation.

## DOUBLY LABELED WATER TECHNIQUE

The doubly labeled water technique provides an isotopebased method to safely estimate total (average) daily energy expenditure of groups of children and adults, in free-living conditions without the normal constraints imposed by laboratory procedures. ${ }^{7,24,25,27,33}$ Few studies routinely use this method, and subject number remains small because of the expense in using doubly labeled water and the need for sophisticated measurement equipment. Nevertheless, its measurement does serve as a criterion or standard to validate other methods that estimate total daily energy expenditure over prolonged periods. ${ }^{3,6,9,17,23,28}$

The subject consumes a quantity of water with a known concentration of the heavy, nonradioactive forms of the stable isotopes of hydrogen $\left({ }^{2} \mathrm{H}\right.$, or deuterium) and oxygen $\left({ }^{18} \mathrm{O}\right.$, or oxygen-18)hence the term doubly labeled water. The isotopes distribute throughout all bodily fluids. Labeled hydrogen
leaves the body as water $\left({ }^{2} \mathrm{H}_{2} \mathrm{O}\right)$ in sweat, urine, and pulmonary water vapor, while labeled oxygen leaves as both water $\left(\mathrm{H}_{2}{ }^{18} \mathrm{O}\right)$ and carbon dioxide $\left(\mathrm{C}^{18} \mathrm{O}_{2}\right)$ produced during macronutrient oxidation in energy metabolism. Differences between elimination rates of the two isotopes (determined by an isotope ratio mass spectrometer) relative to the bodys normal background levels estimate total $\mathrm{CO}_{2}$ production during the measurement period. Oxygen consumption is easily estimated on the basis of $\mathrm{CO}_{2}$ production and an assumed (or measured) respiratory quotient value of 0.85 (see next section).

Under normal circumstances, analysis of the subjects urine or saliva before consuming the doubly labeled water serves as the control baseline values for ${ }^{18} \mathrm{O}$ and ${ }^{2} \mathrm{H}$. Ingested isotopes require about 5 hours to distribute throughout the body water. The researchers then measure the enriched urine or saliva sample initially and then every day (or week) thereafter for the studys duration (usually up to 3 weeks). The progressive decrease in the sample concentrations of the two isotopes permits computation of the $\mathrm{CO}_{2}$ production rate. ${ }^{26}$ Accuracy of the doubly labeled water technique versus directly measured energy expenditure in controlled settings averages between 3 and 5\%. This magnitude of error probably increases in field studies, particularly among physically active individuals. ${ }^{31}$

The doubly labeled water technique provides an ideal way to assess total energy expenditure of individuals over prolonged periods including bed rest and extreme activities like climbing Mt. Everest, cycling the Tour de France, trekking across Antarctica, military activities, extravehicular activities in space, and endurance running and swimming. ${ }^{2,12,18,29}$ Drawbacks to the method include the cost of enriched ${ }^{18} \mathrm{O}$ and expense incurred in spectrometric analysis of both isotopes.

## RESPIRATORY QUOTIENT

Research in the early part of the 20th century discovered a way to evaluate the metabolic mixture metabolized during rest and exercise from measures of pulmonary gas exchange (see Focus on Research, p. 187). ${ }^{16}$ Because of inherent chemical differences in carbohydrate, fat, and protein composition, they require different amounts of oxygen for complete oxidation of each molecules carbon and hydrogen atoms to the carbon dioxide and water end products. Thus, carbon dioxide produced per unit of oxygen consumed varies with the type of substrate (carbohydrate, fat, protein) catabolized. The respiratory quotient ( $\mathbf{R Q}$ ) describes this ratio of metabolic gas exchange as follows:

$$
\mathrm{RQ}=\mathrm{CO}_{2} \text { produced } \div \mathrm{O}_{2} \text { consumed }
$$

The RQ provides a convenient guide to approximate the nutrient mixture catabolized for energy during rest and aerobic exercise. Also, because the caloric equivalents for oxygen differ somewhat depending on the nutrient oxidized, precise determination of the bodys heat production by indirect calorimetry requires measuring both RQ and oxygen consumption.

## RQ for Carbohydrate

The complete oxidation of one glucose molecule requires six oxygen molecules and produces six molecules of carbon dioxide and water as follows:

$$
\begin{aligned}
\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} & +6 \mathrm{O}_{2} \rightarrow 6 \mathrm{CO}_{2}+6 \mathrm{H}_{2} \mathrm{O} \\
\mathrm{RQ} & =6 \mathrm{CO}_{2} \div 6 \mathrm{O}_{2} \\
& =1.00
\end{aligned}
$$

Gas exchange during glucose oxidation produces a number of $\mathrm{CO}_{2}$ molecules equal to the number of $\mathrm{O}_{2}$ molecules consumed; therefore, the RQ for carbohydrate equals 1.00.

## RQ for Fat

The chemical composition of fats differs from carbohydrates because fats contain considerably more hydrogen and carbon atoms than oxygen atoms. Consequently, fat catabolism requires more oxygen in relation to carbon dioxide production. For example, palmitic acid, a typical fatty acid, oxidizes to carbon dioxide and water, producing 16 carbon dioxide molecules for every 23 oxygen molecules consumed. The following equation summarizes this exchange to compute the RQ:

$$
\begin{aligned}
\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2} & +23 \mathrm{O}_{2} \rightarrow 16 \mathrm{CO}_{2}+16 \mathrm{H}_{2} \mathrm{O} \\
\mathrm{RQ} & =16 \mathrm{CO}_{2} \div 23 \mathrm{O}_{2} \\
& =0.696
\end{aligned}
$$

Generally, a value of 0.70 represents the RQ for fat, with values ranging between 0.69 and 0.73 depending on the oxidized fatty acids carbon-chain length.

## RQ for Protein

Proteins do not simply oxidize to carbon dioxide and water during energy metabolism in the body. Rather, the liver first deaminates the amino acid molecule. The body then excretes the nitrogen and sulfur fragments in the urine, sweat, and feces. The remaining keto acid fragment oxidizes to carbon dioxide and water to provide energy for biologic work. To achieve complete combustion, these short-chain keto acids, as in fat catabolism, require more oxygen in relation to carbon dioxide produced. The protein albumin oxidizes as follows:

$$
\begin{gathered}
\mathrm{C}_{72} \mathrm{H}_{112} \mathrm{~N}_{2} \mathrm{O}_{22} \mathrm{~S}+77 \mathrm{O}_{2} \rightarrow 63 \mathrm{CO}_{2} \\
+38 \mathrm{H}_{2} \mathrm{O}+\mathrm{SO}_{3}+9 \mathrm{CO}\left(\mathrm{NH}_{2}\right)_{2} \\
\mathrm{RQ}=63 \mathrm{CO}_{2} \div 77 \mathrm{O}_{2} \\
=0.818
\end{gathered}
$$

The general value 0.82 characterizes the $R Q$ for protein.

## Nonprotein RQ

The RQ computed from the compositional analysis of expired air usually reflects the catabolism of a blend of carbohydrates, fats, and proteins. One can determine the precise contribution

## FOCUS ON RESEARCH

## Respiratory Gas Exchange Implies Metabolic Mixture

Krogh A, Lindhard J. The relative value of fat and carbohydrate as sources of muscular energy. Biochem J 1920;14:290.

> In this 73-page research report, Nobel laureate August Krogh (1874 1949) and colleague Johannes Lindhard (1870 1947) made 220 determinations of respiratory gas exchange on 6 subjects (including themselves) who consumed varied diets to determine macronutrient combustion during rest and exercise. For 2 days prior to testing, subjects maintained a high-carbohydrate, low-protein diet or a high-fat, low-protein diet. Krogh and Lindhard believed that different respiratory quotients (RQs) for the same exercise under different diets would indicate the preferential use of a particular fuel substrate.

The researchers made careful energy expenditure measurements during rest and 2 hours of cycling, with a closed-circuit air current flow-through apparatus common to that time. Subjects rode the stationary bicycle within the chamber, with appropriate tubing placed between the subject and a gas collection system outside the chamber (see figure). Typical of Kroghs research, extreme care in data collection ensured high accuracy and reliability of data. Respiratory gas exchange measurements achieved accuracy to within $\pm 1.0 \%$, a remarkable figure considering his equipment was handmade.

The major research finding was that the energy expended to perform a standard physical effort varied inversely with RQ. This meant that different energy values existed for fat and carbohydrate oxidation; specifically, fat released less energy than carbohydrate per liter of oxygen
consumed during exercise. Although subjects consumed exclusively either lipid or carbohydrate (with protein held constant), RQ values did not indicate combustion of fat only or carbohydrate only. This permitted quantifying the relationship between RQ and the relative amounts of fat and carbohydrate oxidized. The researchers discovered that the percentage of total energy derived from fat oxidation approximated a straight-line function of RQ.

In a second series of experiments performed on two trained athletes during rest and exercise, the proportion of carbohydrate to fat catabolized varied with the relative availability of the two substrates. Krogh and Lindhard hypothesized that neither fat nor carbohydrate exclusively supplied energy during exercise, but that a blend of the macronutrients served simultaneously as fuel sources.

Overall, this important 1920 experiment revealed the following:

1. Efficiency of constant-load exercise is higher with carbohydrate as the energy fuel than with fat.
2. Performance deteriorates in intense exercise when fat (not carbohydrate) serves as the preferential energy nutrient.
3. Preexercise nutrition influences the metabolic mixture during rest and exercise.
4. The RQ changes in the transition from rest to moderate exercise and increases with higher-intensity exercise, indicating greater reliance on carbohydrate oxidation.
5. Fat oxidation predominates during the latter portion of 1 hour of constant-intensity exercise.


Unique enclosed chamber containing a cycle ergometer and two fans. The gas collection apparatus, situated outside the chamber, connects to the chamber via small-bore tubing. The chamber sits in water to ensure an airtight seal.
of each of these nutrients to the metabolic mixture. For example, the kidneys excrete approximately 1 g of urinary nitrogen for every 5.57 (modern value) to 6.25 g (classic value) of protein metabolized for energy. ${ }^{14}$ Each gram of excreted nitrogen represents a carbon dioxide production of approximately 4.8 L and an oxygen consumption of about 6.0 L . Within this framework, the following example illustrates the stepwise procedure to calculate the elements in the nonprotein $\mathbf{R Q}$; that is, that portion of the respiratory exchange attributed to the combustion of only carbohydrate and fat but not protein.

This example considers data from a subject who consumes 4.0 L of oxygen and produces 3.4 L of carbon dioxide during a 15 -minute rest period. During this time, the kidneys excrete 0.13 g of nitrogen in the urine.

Step 1. 4.8 $\mathrm{L} \mathrm{CO}_{2}$ per g protein metabolized $\times 0.13 \mathrm{~g}=$ $0.62 \mathrm{~L} \mathrm{CO}_{2}$ produced in protein catabolism
Step 2. $6.0 \mathrm{~L} \mathrm{O}_{2}$ per g protein metabolized $\times 0.13 \mathrm{~g}=$ $0.78 \mathrm{~L} \mathrm{O}_{2}$ consumed in protein catabolism
Step 3. Nonprotein $\mathrm{CO}_{2}$ produced $=3.4 \mathrm{~L} \mathrm{CO}_{2}-0.62$ $\mathrm{LCO}_{2}=2.78 \mathrm{LCO}_{2}$
Step 4. Nonprotein $\mathrm{O}_{2}$ consumed $=4.0 \mathrm{~L} \mathrm{O}_{2}-0.78 \mathrm{~L}$ $\mathrm{O}_{2}=3.22 \mathrm{~L} \mathrm{O}_{2}$
Step 5. Nonprotein RQ $=2.78 \div 3.22=0.86$
Table 8.1 presents the thermal energy equivalents for oxygen consumption for different nonprotein RQ values and the percentage of fat and carbohydrate used for energy. For

TABLE 8.1 Thermal Equivalents of Oxygen for the Nonprotein RQ, Including Percentage Kilocalories and Grams Derived from Carbohydrate and Fat

| Nonprotein RQ | $\begin{gathered} \mathrm{kCal} \text { Per } \\ \mathrm{LO}_{2} \end{gathered}$ | Percentage kCal Derived from |  | Grams per $\mathrm{LO}_{2}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Carbohydrate | Fat | Carbohydrate | Fat |
| 0.707 | 4.686 | 0.0 | 100.0 | 0.000 | 0.496 |
| 0.71 | 4.690 | 1.1 | 98.9 | 0.012 | 0.491 |
| 0.72 | 4.702 | 4.8 | 95.2 | 0.051 | 0.476 |
| 0.73 | 4.714 | 8.4 | 91.6 | 0.090 | 0.460 |
| 0.74 | 4.727 | 12.0 | 88.0 | 0.130 | 0.444 |
| 0.75 | 4.739 | 15.6 | 84.4 | 0.170 | 0.428 |
| 0.76 | 4.750 | 19.2 | 80.8 | 0.211 | 0.412 |
| 0.77 | 4.764 | 22.8 | 77.2 | 0.250 | 0.396 |
| 0.78 | 4.776 | 26.3 | 73.7 | 0.290 | 0.380 |
| 0.79 | 4.788 | 29.9 | 70.1 | 0.330 | 0.363 |
| 0.80 | 4.801 | 33.4 | 66.6 | 0.371 | $0.347$ |
| 0.81 | 4.813 | 36.9 | 63.1 | $0.413$ | $0.330$ |
| 0.82 | 4.825 | $40.3$ | $59.7$ | $0.454$ | 0.313 |
| 0.83 | 4.838 | $43.8$ | 56.2 | $0.496$ | 0.297 |
| 0.84 | 4.850 | 47.2 | 52.8 | 0.537 | 0.280 |
| 0.85 | 4.862 | 50.7 | 49.3 | 0.579 | 0.263 |
| 0.86 | 4.875 | 54.1 | 45.9 | 0.621 | 0.247 |
| 0.87 | 4.887 | 57.5 | 42.5 | 0.663 | 0.230 |
| 0.88 | 4.899 | 60.8 | 39.2 | 0.705 | 0.213 |
| 0.89 | 4.911 | 64.2 | 35.8 | 0.749 | 0.195 |
| 0.90 | 4.924 | 67.5 | 32.5 | 0.791 | 0.178 |
| 0.91 | 4.936 | 70.8 | 29.2 | 0.834 | 0.160 |
| 0.92 | 4.948 | 74.1 | 25.9 | 0.877 | 0.143 |
| 0.93 | 4.961 | 77.4 | 22.6 | 0.921 | 0.125 |
| 0.94 | 4.973 | 80.7 | 19.3 | 0.964 | 0.108 |
| 0.95 | 4.985 | 84.0 | 16.0 | 1.008 | 0.090 |
| 0.96 | 4.998 | 87.2 | 12.8 | 1.052 | 0.072 |
| 0.97 | $5.010$ | $90.4$ | 9.6 | $1.097$ | $0.054$ |
| 0.98 | $5.022$ | 93.6 | 6.4 | $1.142$ | $0.036$ |
| 0.99 | $5.035$ | 96.8 | 3.2 | $1.186$ | $0.018$ |
| 1.00 | 5.047 | 100.0 | 0 | 1.231 | 0.000 |

[^20]
## IN A PRACTICAL SENSE

## The Weir Method to Calculate Energy Expenditure

In 1949, J. B. Weir, a Scottish physician and physiologist from Glasgow University, presented a simple method to estimate caloric expenditure $\left(\mathrm{kCal} \cdot \mathrm{min}^{-1}\right)$ from measures of pulmonary ventilation and expired oxygen percentage, accurate to within $\pm 1 \%$ of the traditional respiratory quotient (RQ) method.

## BASIC EQUATION

Weir showed that the following formula could calculate energy expenditure if total energy production from protein breakdown equaled $12.5 \%$ (a reasonable percentage for most people):

$$
\mathrm{kCal} \cdot \mathrm{~min}^{-1}=\mathrm{V}_{\mathrm{E}(\mathrm{STPD})} \times\left(1.044-0.0499 \times \% \mathrm{O}_{2 \mathrm{E}}\right)
$$

where $\mathrm{V}_{\mathrm{E}(\text { STPD })}$ represents expired minute ventilation $\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right.$ ) corrected to STPD conditions, and $\% \mathrm{O}_{2 \mathrm{E}}$ represents expired oxygen percentage. The value in parentheses ( $1.044-0.0499 \times \%_{\mathrm{O}_{2 \mathrm{E}}}$ ) represents the Weir factor. The table displays Weir factors for different $\% \mathrm{O}_{2 \mathrm{E}}$ values.

To use the table, locate the $\% \mathrm{O}_{2 \mathrm{E}}$ and corresponding Weir factor. Compute energy expenditure in $\mathrm{kCal} \cdot \mathrm{min}^{-1}$ by multiplying the Weir factor by $\mathrm{V}_{\mathrm{E}(\text { STPD })}$.

## EXAMPLE

A person runs on a treadmill and $\mathrm{V}_{\mathrm{E}(\text { STPD })}=50 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ and $\% \mathrm{O}_{2 \mathrm{E}}=16.0 \%$. Compute energy expenditure by the Weir method as follows:

$$
\begin{aligned}
\mathrm{kCal} \cdot \mathrm{~min}^{-1} & =\mathrm{V}_{\text {E(STPD) }} \times\left(1.044-\left[0.0499 \times \% \mathrm{O}_{2 \mathrm{E}}\right]\right) \\
& =50 \times(1.044-[0.0499 \times 16.0]) \\
& =50 \times 0.2456 \\
& =12.3
\end{aligned}
$$

Weir also derived the following equation to calculate $\mathrm{kCal} \cdot \mathrm{min}^{-1}$ from RQ and $\mathrm{VO}_{2}$ in $\mathrm{L} \cdot \mathrm{min}^{-1}$ :

$$
\mathrm{kCal} \cdot \mathrm{~min}^{-1}=([1.1 \times \mathrm{RQ}]+3.9) \times \mathrm{VO}_{2} .
$$

Weir Factors

| $\mathbf{\% O}_{\mathbf{2 E}}$ | Weir <br> Factor | $\mathbf{\% O}_{\mathbf{2 E}}$ | Weir <br> Factor |
| :---: | :---: | :---: | :---: |
| 14.50 | 0.3205 | 17.00 | 0.1957 |
| 14.60 | 0.3155 | 17.10 | 0.1907 |
| 14.70 | 0.3105 | 17.20 | 0.1857 |
| 14.80 | 0.3055 | 17.30 | 0.1807 |
| 14.90 | 0.3005 | 17.40 | 0.1757 |
| 15.00 | 0.2955 | 17.50 | 0.1707 |
| 15.10 | 0.2905 | 17.60 | 0.1658 |
| 15.20 | 0.2855 | 17.70 | 0.1608 |
| 15.30 | 0.2805 | 17.80 | 0.1558 |
| 15.40 | 0.2755 | 17.90 | 0.1508 |
| 15.50 | 0.2705 | 18.00 | 0.1468 |
| 15.60 | 0.2656 | 18.10 | 0.1408 |
| 15.70 | 0.2606 | 18.20 | 0.1368 |
| 15.80 | 0.2556 | 18.30 | 0.1308 |
| 15.90 | 0.2506 | 18.40 | 0.1268 |
| 16.00 | 0.2456 | 18.50 | 0.1208 |
| 16.10 | 0.2406 | 18.60 | 0.1168 |
| 16.20 | 0.2366 | 18.70 | 0.1109 |
| 16.30 | 0.2306 | 18.80 | 0.1068 |
| 16.40 | 0.2256 | 18.90 | 0.1009 |
| 16.50 | 0.2206 | 19.00 | 0.0969 |
| 16.60 | 0.2157 | 19.10 | 0.0909 |
| 16.70 | 0.2107 | 19.20 | 0.0868 |
| 16.80 | 0.2057 | 19.30 | 0.0809 |
| 16.90 | 0.2007 | 19.40 | 0.0769 |
|  |  |  |  |

If $\% \mathrm{O}_{2 \mathrm{E}}$ does not appear in the table, compute individual Weir factors as $1.044-0.0499 \times \% \mathrm{O}_{2 \mathrm{E}}$. From Weir JB. New methods for calculating metabolic rates with special reference to protein metabolism. J Physiol 1949;109:1.
the nonprotein RQ of 0.86 computed in the previous example, each liter of oxygen consumed liberates 4.875 kCal . Also, for this RQ, $54.1 \%$ of the nonprotein calories derive from carbohydrate, and $45.9 \%$ come from fat. The total 15 -minute heat production at rest attributable to fat and carbohydrate catabolism equals $15.70 \mathrm{kCal}\left(4.875 \mathrm{kCal} \cdot \mathrm{L}^{-1} \times 3.22 \mathrm{~L} \mathrm{O}_{2}\right)$; the energy from the breakdown of protein equals 3.51 kCal $\left(4.5 \mathrm{kCal} \cdot \mathrm{L}^{-1} \times 0.78 \mathrm{~L} \mathrm{O}_{2}\right)$. The total energy from the combustion of protein and nonprotein macronutrients during the 15 -minute period equals $19.21 \mathrm{kCal}(15.70 \mathrm{kCal}$ nonprotein +3.51 kCal protein).

Interestingly, if the thermal equivalent for a mixed diet $(R Q=0.82)$ had been used in the caloric transformation, or if RQ had been computed from total respiratory gas exchange and applied to Table 8.1 without considering the protein component, the estimated energy expenditure would be 19.3 kCal ( $4.825 \mathrm{kCal} \cdot \mathrm{L}^{-1} \times 4.0 \mathrm{~L} \mathrm{O}_{2}$; assuming a mixed diet). This corresponds to a difference of only $0.5 \%$ from the value obtained with the more elaborate and time-consuming method requiring urinary nitrogen analysis. In most cases, the gross metabolic nonprotein RQ calculated from pulmonary gas exchange and applied to Table 8.1 without measures of urinary
and other nitrogen sources introduces only minimal error because the contribution of protein to energy metabolism usually remains small.

## How Much Food Metabolizes for Energy?

The last two columns of Table 8.1 present conversions for the nonprotein RQ to grams of carbohydrate and fat metabolized per liter of oxygen consumed. For the subject with an RQ of 0.86 , this represents approximately 0.62 g of carbohydrate and 0.25 g of fat. For the 3.22 L of oxygen consumed during the 15 -minute rest period, this represents 2.0 g of carbohydrate (3.22 $\mathrm{L} \mathrm{O}_{2} \times 0.62$ ) and 0.80 g of fat $\left(3.22 \mathrm{~L} \mathrm{O}_{2} \times 0.25\right)$ metabolized for energy.

## RQ for a Mixed Diet

The RQ seldom reflects the oxidation of pure carbohydrate or pure fat during activities ranging from complete bed rest to mild aerobic exercise (walking or slow jogging). Instead, catabolism of a mixture of these nutrients occurs with an RQ intermediate between 0.70 and 1.00. For most purposes, assume an RQ of 0.82 (metabolism of a mixture of $40 \%$ carbohydrate and $60 \% \mathrm{fat}$ ) and apply the caloric equivalent of 4.825 kCal per liter of oxygen for energy transformations. In using 4.825, the maximum error possible in estimating energy expenditure from steady-rate oxygen consumption averages about $4 \%$. When requiring greater precision, one must compute the actual RQ and consult Table 8.1 to obtain the exact caloric transformation and percentage contribution of carbohydrate and fat to the metabolic mixture.

## INTEGRATIVE QUESTION

How have exercise physiologists determined that between 70 and $80 \%$ of the energy during the last phases of a marathon run comes from the combustion of fat?

## RESPIRATORY EXCHANGE RATIO

The RQ assumes that the exchange of oxygen and carbon dioxide measured at the lungs reflects gas exchange from macronutrient catabolism in the cell. This assumption remains reasonably valid during rest and steady-rate exercise conditions with little reliance on anaerobic metabolism. However, several factors other than food combustion spuriously alter the exchange of oxygen and carbon dioxide in the lungs. When this occurs, the ratio of gas exchange no longer reflects only the substrate mixture of energy metabolism. Respiratory physiologists refer to the ratio of carbon dioxide produced to oxygen consumed under such conditions as the respiratory exchange ratio ( $\mathbf{R}$, or RER). In this case, the pulmonary exchange of oxygen and carbon dioxide no longer reflects cellular oxidation of specific foods. One computes this exchange ratio in exactly the same manner as RQ.

For example, carbon dioxide elimination increases during hyperventilation because breathing increases to disproportionately higher levels compared with metabolic demands (see Chapter 14). Overbreathing decreases the bloods normal level of carbon dioxide because this nonmetabolic carbon dioxide blows off from the lungs in the expired air without a corresponding increase in oxygen consumption. This creates a rise in the respiratory exchange ratio (usually above 1.00) that does not reflect macronutrient oxidation.

Exhaustive exercise presents another situation in which R rises above 1.00 . Sodium bicarbonate in the blood buffers or neutralizes the lactate generated during anaerobic metabolism to maintain proper acid base balance (see Chapter 14). Lactate buffering produces carbonic acid, a weaker acid as follows:

$$
\mathrm{HLa}+\mathrm{NaHCO}_{3} \rightarrow \mathrm{NaLa}+\mathrm{H}_{2} \mathrm{CO}_{3}
$$

In the pulmonary capillaries, carbonic acid degrades to its component carbon dioxide and water molecules. Carbon dioxide readily exits the lungs in the reaction:

$$
\mathrm{NaHCO}_{3} \rightarrow \mathrm{H}_{2} \mathrm{O}+\mathrm{CO}_{2} \rightarrow \text { Lungs }
$$

The R increases above 1.00 because buffering adds extra nonmetabolic-created carbon dioxide to the expired air above the quantity normally released during energy metabolism. In rare instances, the exchange ratio exceeds 1.00 when a person gains body fat through excessive dietary carbohydrate intake. In this lipogenic situation, the conversion of carbohydrate to fat liberates oxygen as the excess calories accumulate in adipose tissue. The released oxygen then supplies energy metabolism; this reduces the lungs uptake of atmospheric oxygen despite the normal carbon dioxide production.

Relatively low R values can occur. Following exhaustive exercise, for example, the cells and bodily fluids retain carbon dioxide to replenish the sodium bicarbonate that buffered the accumulating lactate. This action to replenish alkaline reserve decreases the expired carbon dioxide level without affecting oxygen consumption and may cause the respiratory exchange ratio to go below 0.70 .

## Summary

1. Direct calorimetry and indirect calorimetry represent two methods to determine human energy expenditure.
2. Direct calorimetry measures heat production in an appropriately insulated calorimeter. Indirect calorimetry infers energy expenditure from oxygen consumption and carbon dioxide production, using either closed-circuit spirometry or open-circuit spirometry.
3. The doubly labeled water technique estimates energy expenditure in free-living conditions without the normal constraints imposed by laboratory procedures. It serves as a gold standard to validate other longterm energy expenditure estimates.
4. The complete oxidation of each macronutrient requires a different quantity of oxygen consumption
for comparable carbon dioxide production. The ratio of carbon dioxide produced to oxygen consumed, the respiratory quotient (RQ), quantifies the macronutrient mixture catabolized for energy.
5. The RQ averages 1.00 for carbohydrate, 0.70 for fat, and 0.82 for protein.
6. For each RQ, a corresponding caloric value exists per liter of oxygen consumed. The RQ kCal relationship can accurately determine energy expenditure during exercise.
7. The respiratory exchange ratio (R) reflects the pulmonary exchange of carbon dioxide and oxygen under differing physiologic and metabolic conditions; R does not fully mirror the gas exchange of the macronutrient mixture catabolized.

1, References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

The NASA Home Page
www.nasa.gov/
Antoine Lavoisier
http://scienceworld.wolfram.com/biography/Lavoisier.html

## CHAPTER



## Human Energy Expenditure During Rest and Physical Activity

## CHAPTER OBJECTIVES

> Define basal metabolic rate and list factors that affect it
$>$ Discuss three factors that affect total daily energy expenditure
> Outline two classification systems to rate the strenuousness of physical activity
$>$ Explain the role of body weight in the energy cost of different physical activities
> Present the rationale (including advantages and limitations) for using heart rate to estimate exercise energy expenditure


Figure 9.1 Components of total daily energy expenditure (TDEE).

Metabolism involves all of the chemical reactions of biomolecules within the body that encompass synthesis (anabolism) and breakdown (catabolism). Figure 9.1 illustrates the following three general factors that determine total daily energy expenditure (TDEE):

1. Resting metabolic rate, consisting of basal and sleeping conditions plus the added metabolic cost of arousal
2. Thermogenic effect of food consumed
3. Energy expended during physical activity and recovery

## Part 1 ENERGY EXPENDITURE AT REST

## BASAL AND RESTING METABOLIC RATE

Each individual requires a minimum level of energy to sustain vital functions in the waking state. This energy requirementtermed basal metabolic rate, or simply BMR (also referred to as basal energy expenditure [BEE])—reflects the body s total heat production. Measuring oxygen consumption under stringent conditions indirectly determines the BMR. For example, the person must rest in the postabsorptive state without food consumed for the 12 previous hours to avoid increases in metabolism from digestion, absorption, and assimilation of ingested nutrients. To reduce other calorigenic influences, the person cannot perform any physical activity for a minimum of 2 hours prior to the assessment. In the laboratory, the person rests supine for about 30 minutes in a
comfortable, thermoneutral environment before oxygen consumption is measured for a minimum of 10 minutes. Oxygen consumption values for BMR usually range between 160 and $290 \mathrm{~mL} \cdot \min ^{-1}\left(0.8\right.$ to $\left.1.43 \mathrm{kCal} \cdot \mathrm{min}^{-1}\right)$ depending on gender, age, overall body size (stature and body mass), and fat-free body mass (FFM).

Knowledge of BMR establishes the important energy baseline required to develop prudent weight control strategies through food restriction, regular exercise, or their combination. Basal values measured under controlled laboratory conditions fall only slightly below values for resting metabolic rate (RMR) measured 3 to 4 hours after a light meal without prior physical activity. For this reason, the term RMR is often substituted for and used interchangeably with BMR, but their differences need to be acknowledged (e.g., BMR is always slightly lower than RMR, depending on such factors as body size, amount of muscle mass, age, health/fitness status, hormonal status, and body temperature). When measured under standardized conditions, both BMR and RMR show high reproducibility and stability. ${ }^{8}$ Essentially, BMR and RMR refer to the sum of the metabolic processes of the active cell mass required to sustain normal regulatory balance and body functions during the basal, or less stringent, resting state. For the typical person, RMR accounts for about 60 to $75 \%$ of TDEE, whereas thermic effects from eating account for approximately $10 \%$, and physical activity for the remaining 15 to $30 \%$.

## METABOLIC SIZE CONCEPT

Experiments in the late 1800s showed that resting energy expenditure varied in proportion to the body s surface area. A series of careful experiments determined energy metabolism of a dog and a man over a 24 -hour period. The total heat generated by the larger man exceeded the energy metabolism of the dog by about $200 \%$. Expressing heat production in relation to surface area reduced the metabolic difference between man and dog to only about $10 \%$. This provided the basis for the common practice of expressing basal (or resting) metabolic rate (energy expenditure) by body surface area (in square meters) per hour $\left(\mathrm{kCal} \cdot \mathrm{m}^{-2} \cdot \mathrm{~h}^{-1}\right)$. This expression acknowledges the fundamental relationship between heat production and body size that has become known as the surface area law.

Further research in the 1920s provided solid evidence that the surface area formulation did not apply universally to all temperature-regulating species (homeotherms). To more fully describe the relationship between metabolic heat production and body size, the concept of metabolic size related basal metabolism to body mass raised to the 0.75 power (body mass ${ }^{0.75}$ ). BMR expressed relative to body mass ${ }^{0.75}$ holds true for humans and a wide variety of mammals and birds that differ considerably in size and shape. Figure 9.2 illustrates the logarithmic plot of body mass (range: 0.01 to $10,000 \mathrm{~kg}$ ) and metabolic rate expressed in watts $(\mathrm{W})$, where $1 \mathrm{~W}=0.01433 \mathrm{kCal} \mathrm{m} \mathrm{m}^{-2}$ (range: 0.1 to 1000 W ). The best-fitting straight line describing this relationship truly represents one of the more striking biologic


Figure 9.2 Metabolic rate (in watts) from mouse to elephant. Logarithmic plot of body mass and metabolic rate for a variety of birds and mammals differing considerably in body size and shape. Numerous experiments have confirmed the mouse-toelephant curve for metabolism using body mass to the 0.75 power, whereas metabolic rate relates to body surface area to the 0.67 power. The schematic inset figure compares the body size of the world s tallest male ( 2.89 m [ $9 \mathrm{ft} 53 / 4 \mathrm{in}$ ]) and female ( 2.48 m [8 ft $13 / 4 \mathrm{in}$ ]) with the world s largest land mammal (Baluchitherium, predecessor of the rhinoceros), whose body mass approximated 30 tons at a stature of $5.26 \mathrm{~m}(17 \mathrm{ft} 3 \mathrm{in}$ ). Comparisons between a microorganism (amoeba: mass, 0.1 mg ) and a 100-ton blue whale (Balaenoptera musculus) or the smallest Gabon dwarf shrew specimen, recently discovered in the Philippines, that weighed 1.4 g , one-tenth the size of a small mouse mammal or one-millionth the size of an elephant illustrate the importance of appropriate scaling procedures when relating oxygen consumption, heart size, and blood volume to body mass.
concepts related to animal size and metabolic and physiologic functions. Chapter 22 discusses the use of allometric scaling as a mathematical procedure to establish a proper relationship between a body size variable (e.g., stature, body mass, FFM) and some other variable of interest such as muscular strength or aerobic capacity. This correction permits comparisons among individuals or groups that exhibit large differences in body size.

Many subsequent studies have shown that indexing BMR or RMR to lean body mass (representing the nonadipose tissue component of the body) or the FFM (representing nonlipid mass) also can account for gender differences in energy expenditure (see inset Figure 9.3). For an individual or group of individuals of the same gender, body surface area provides as good an index of RMR as FFM because of the strong within-gender association between body surface area and FFM.

## COMPARING METABOLIC RATES IN HUMANS

Figure 9.3 presents BMR data for men and women over a wide range of age and body weight expressed as $\mathrm{kCal} \cdot \mathrm{m}^{-2} \cdot \mathrm{~h}^{-1}$. An individual s BMR (RMR) estimated from the curves generally falls within $\pm 10 \%$ of the value obtained from laboratory measurements. The inset figure illustrates the relatively strong association between FFM and daily RMR for men and women. The data reveal that females exhibit an average 5 to $10 \%$ lower rate than males of the same age. This does not necessarily reflect true sex differences in metabolic rates of specific tissues. Rather, it results largely because women possess more body fat (and less fat-free tissue) than men of similar size; fat tissue has lower metabolic activity than muscle. Changes in body composition, either a decrease in FFM and/or increase in body fat during adulthood, help to explain the 2 to


```
Females \square Males
```

Figure 9.3 Basal metabolic rate (BMR) as a function of age and gender. (Data from Altman PL, Dittmer D.
Metabolism. Bethesda, MD: Federation of American Societies for Experimental Biology, 1968.) Inset graph shows the relatively strong relationship between fat-free body mass (FFM) and resting metabolic rate (RMR) for men and women. (From Ravussin E, et al. Determination of 24 -hour energy expenditure in man. Methods and results using a respiratory chamber. J Clin Invest 1986;78:1568.)
$3 \%$ per decade BMR reduction observed for adult men and women. ${ }^{2,7,22}$ Some depression of the metabolic activity of the lean tissue components also may progress as one ages; ${ }^{19}$ this could contribute to an age-related increase in body fat.

## Effects of Regular Exercise

Similar BMR measures occur when comparing young and middle-aged endurance-trained men who showed no group difference for FFM. ${ }^{16}$ Moreover, resting metabolism increased by $8 \%$ when 50 - to 65 -year-old men increased their FFM with resistance training. ${ }^{23}$ An 8-week aerobic training program for older individuals produced a $10 \%$ increase in resting metabolism without a change in FFM. ${ }^{20}$ This suggests that regular exercise affects factors in addition to body composition to stimulate resting metabolism. Regular endurance and resistance exercise offsets the decrease in resting metabolism that usually accompanies aging. Each 1-pound gain in FFM increases RMR by 7 to 10 kCal daily.

The curves in Figure 9.3 can be used to estimate a person s resting metabolic rate. For example, between ages 20 and 40 years, the BMR of men averages about 38 kCal per $\mathrm{m}^{2}$ per hour, whereas for women the corresponding value equals 35 kCal . For greater precision, read the specific age-related value directly from the appropriate curve. To estimate total
metabolic rate per hour, multiply the BMR value by the person s calculated surface area. This hourly total provides important information for estimating the daily energy baseline requirement for caloric intake.

Accurate measurement of the body s surface area poses a considerable challenge. Experiments in the early 1900s provided the data to formulate Figure 9.4. The studies clothed 8 men and 2 women in tight whole-body underwear and applied melted paraffin and paper strips to prevent modification of the surface. The treated cloth was then removed and cut into flat pieces to allow precise measurements of body surface area (length $\times$ width). The close relationship between height (stature) and body weight (mass) and body surface area enabled derivation of the following empirical formula to predict body surface area (BSA):

$$
\mathrm{BSA}, \mathrm{~m}^{2}=\mathrm{H}^{0.725} \times \mathrm{W}^{0.425} \times 71.84
$$

where $\mathrm{H}=$ stature in cm and $\mathrm{W}=$ mass in kg . This formula yields results similar to the nomogram values in Figure 9.4.

To determine surface area from the nomogram, locate stature on scale I and body mass on scale II. Connect these two points with a straightedge; the intersection on scale III gives the surface area in square meters $\left(\mathrm{m}^{2}\right)$. For example, if stature equals 185 cm and body mass equals 75 kg , surface area from scale III on the nomogram equals $1.98 \mathrm{~m}^{2}$.


| Scale II <br> Body mass |  |
| :---: | :---: |
|  | lb kg |
| $\begin{array}{lc} \text { lb } & \mathrm{kg} \\ 310-F & 160 \end{array}$ |  |
| $320=150$ |  |
| $300=140$ |  |
| 280 |  |
|  |  |
| 240 |  |
| 220-105 |  |
|  |  |
| 200- 90 |  |
|  | 180-35 |
|  | $180-80$ |
| 170 素 75 |  |
| 160 |  |
| $150=-65$ |  |
|  |  |
| 130 |  |
| $120-55$ |  |
| 110 $=50$ |  |
| 100- -45 |  |
| 90 |  |
|  |  |
|  | 80 |
|  | 5 |
| $70-30$ |  |
|  | -30 |
| 60 |  |
|  | $-25$ |
| 50 |  |
|  |  |
| 40 |  |
|  |  |
|  | -15 |

Figure 9.4 Nomogram to estimate body surface area from stature and body mass. (Reproduced from Clinical spirometry, prepared by Boothby and Sandiford of the Mayo Clinic, through the courtesy of Warren E. Collins, Inc., Braintree, MA; based on the work of Dubois, EF. Basal metabolism in health and disease. Philadelphia: Lea \& Febiger, 1936.)

## Normalcy of BMR Values

Classical assessment of the normalcy of thyroid function compares a person s measured BMR with standard metabolic rates based on age and gender (Table 9.1 and Fig. 9.3). Any value within $\pm 10 \%$ of the standard represents a normal BMR. The following formula computes the deviation expressed as a percentage:

$$
\begin{aligned}
\Delta \mathrm{BMR}= & (\text { measured BMR }- \text { standard BMR }) \times 100 \\
& \div \text { standard BMR }
\end{aligned}
$$

For example, a BMR of $35 \mathrm{kCal} \cdot \mathrm{m}^{2} \cdot \mathrm{~h}^{-1}$ for a 19-yearold male, determined by indirect calorimetry, falls $10.7 \%$ below the standard BMR.

$$
\begin{aligned}
\Delta \mathrm{BMR} & =(35-39.2) \times 100 \div 39.2 \\
& =-10.7 \%
\end{aligned}
$$

## Estimating Resting Daily Energy Expenditure

To estimate a person s resting daily energy expenditure, multiply the appropriate BMR value in Table 9.1 by the surface area computed from stature and mass. For a 50 -year-old woman, for example, the estimated BMR equals 34 kCal per $\mathrm{m}^{2}$ per hour. For a surface area of $1.40 \mathrm{~m}^{2}$, the hourly energy expenditure equals 47.6 kCal per hour $\left(34 \mathrm{kCal} \times 1.40 \mathrm{~m}^{2}\right)$. On a daily basis, this amounts to an energy expenditure of 1142 kCal $(47.6 \mathrm{kCal} \times 24)$.

Table 9.2 provides an estimate of RDEE from FFM estimated from several indirect procedures described in Chapter 28. The data in the table were computed from the

TABLE 9.1 Standard Basal Metabolic Rates

| Age (Years) | $\mathrm{kCaI} \cdot \mathrm{M}^{-2} \cdot \mathrm{H}^{-1}$ |  | $\mathrm{kJ} \cdot \mathrm{M}^{-2} \cdot \mathrm{H}^{-1}$ |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Men | Women | Men | Women |
| 1 | 53.0 | 53.0 | 222 | 222 |
| 2 | 52.4 | 52.4 | 219 | 219 |
| 3 | 51.3 | 51.2 | 215 | 214 |
| 4 | 50.3 | 49.8 | 211 | 208 |
| 5 | 49.3 | 48.4 | 206 | 203 |
| 6 | 48.3 | 47.0 | 202 | 197 |
| 7 | 47.3 | 45.4 | 198 | 190 |
| 8 | 46.3 | 43.8 | 194 | 183 |
| 9 | 45.2 | 42.8 | 189 | 179 |
| 10 | 44.0 | 42.5 | 184 | 178 |
| 11 | 43.0 | 42.0 | 180 | 176 |
| 12 | 42.5 | 41.3 | 178 | 173 |
| 13 | 42.3 | 40.3 | 177 | 169 |
| 14 | 42.1 | 39.2 | 176 | 164 |
| 15 | 41.8 | 37.9 | 175 | 159 |
| 16 | 41.4 | 36.9 | 173 | 154 |
| 17 | 40.8 | 36.3 | 171 | 152 |
| 18 | 40.0 | 35.9 | 167 | 150 |
| 19 | 39.2 | 35.5 | 164 | 149 |
| 20 | 38.6 | 35.3 | 162 | 148 |
| 25 | 37.5 | 35.2 | 157 | 147 |
| 30 | 36.8 | 35.1 | 154 | 147 |
| 35 | 36.5 | 35.0 | 153 | 146 |
| 40 | 36.3 | 34.9 | 152 | 146 |
| 45 | 36.2 | 34.5 | 152 | 144 |
| 50 | 35.8 | 33.9 | 150 | 142 |
| 55 | 35.4 | 33.3 | 148 | 139 |
| 60 | 34.9 | 32.7 | 146 | 137 |
| 65 | 34.4 | 32.2 | 144 | 135 |
| 70 | 33.8 | 31.7 | 141 | 133 |
| 75+ | 33.2 | 31.3 | 139 | 131 |

From Fleish A. Le metabolisme basal standard et sa determination au moyen du Metabocalculator. Helv Med Acta 1951;18:23.

| TABLE 9.2 | Estimation of Resting Daily <br> Energy <br> Based on Fenditure (RDEE) <br> Mass (FFM) |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| FFM Body |  |  |  |  |  |
| (kg) | RDEE <br> (kCal $^{\text {a }}$ | FFM <br> (kg) | RDEE <br> (kCal) | FFM <br> (kg) | RDEE <br> (kCal) |
| 30 | 1018 | 58 | 1623 | 86 | 2228 |
| 31 | 1040 | 59 | 1644 | 87 | 2249 |
| 32 | 1061 | 60 | 1666 | 88 | 2271 |
| 33 | 1083 | 61 | 1688 | 89 | 2292 |
| 34 | 1104 | 62 | 1709 | 90 | 2314 |
| 35 | 1126 | 63 | 1731 | 91 | 2336 |
| 36 | 1148 | 64 | 1752 | 92 | 2357 |
| 37 | 1169 | 65 | 1774 | 93 | 2379 |
| 38 | 1191 | 66 | 1796 | 94 | 2400 |
| 39 | 1212 | 67 | 1817 | 95 | 2422 |
| 40 | 1234 | 68 | 1839 | 96 | 2444 |
| 41 | 1256 | 69 | 1860 | 97 | 2465 |
| 42 | 1277 | 70 | 1882 | 98 | 2487 |
| 43 | 1299 | 71 | 1904 | 99 | 2508 |
| 44 | 1320 | 72 | 1925 | 100 | 2530 |
| 45 | 1342 | 73 | 1947 | 101 | 2552 |
| 46 | 1364 | 74 | 1968 | 102 | 2573 |
| 47 | 1385 | 75 | 1990 | 103 | 2595 |
| 48 | 1407 | 76 | 2012 | 104 | 2616 |
| 49 | 1428 | 77 | 2033 | 105 | 2638 |
| 50 | 1450 | 78 | 2055 | 106 | 2660 |
| 51 | 1472 | 79 | 2076 | 107 | 2681 |
| 52 | 1493 | 80 | 2098 | 108 | 2703 |
| 53 | 1515 | 81 | 2120 | 109 | 2724 |
| 54 | 1536 | 82 | 2141 | 110 | 2746 |
| 55 | 1558 | 83 | 2163 | 111 | 2768 |
| 56 | 1580 | 84 | 2184 | 112 | 2789 |
| 57 | 1601 | 85 | 2206 | 113 | 2811 |
|  |  |  |  |  |  |

${ }^{a}$ Prediction equation for RDEE derived as the weighted mean of regression constants from studies of large samples of males and females. (V. Katch,
University of Michigan)
${ }^{b}$ To convert kCal to kJ, multiply by 4.18; to convert kCal to MJ, multiply by 0.0042 .
following generalized equation, applicable to males and females over a wide range of body weights:

$$
\operatorname{RDEE}(\mathrm{kCal})=370+21.6(\mathrm{FFM}, \mathrm{~kg})
$$

A male who weighs 90.9 kg at $21 \%$ body fat has an estimated FFM of 71.7 kg . Rounding to 72 kg translates to an RDEE of 1925 kCal or 8047 kJ ( 8.08 MJ ).

## Contribution of Diverse Tissues to Human Metabolism

Table 9.3 presents estimates of absolute and relative energy needs, expressed as oxygen consumption, of various

## TABLE 9.3 Oxygen Consumption of Various Body Tissues at Rest for a $65-\mathrm{kg}$ Man

| Organ | Oxygen <br> Consumption <br> $\left(\mathbf{m L} \cdot \mathbf{m i n}^{-\mathbf{1}}\right)$ | Percentage <br> of Resting <br> Metabolism |
| :--- | :---: | :---: |
| Liver | 67 | 27 |
| Brain | 47 | 19 |
| Heart | 17 | 7 |
| Kidneys | 26 | 10 |
| Skeletal muscle | 45 | 18 |
| Remainder | $\underline{48}$ | $\underline{19}$ |
|  | 250 | 100 |

organs and tissues of adults at rest. The brain and skeletal muscles consume about the same total quantity of oxygen, even though the brain weighs only $1.6 \mathrm{~kg}(2.3 \%$ of body mass), while muscle constitutes almost $50 \%$ of the body mass. For children, brain metabolism represents nearly $50 \%$ of total resting energy expenditure. This similarity in metabolism does not transfer to maximal exercise because the energy generated by active muscle increases nearly 100 times; the total energy expended by the brain increases only marginally.

INTEGRATIVE QUESTION
Discuss why middle-aged men and women should try to maintain or increase muscle mass for purposes of weight control.

## FACTORS THAT AFFECT ENERGY EXPENDITURE

Important factors that affect TDEE include physical activity, diet-induced thermogenesis, climate, and pregnancy and lactation.

## Physical Activity

Under typical circumstances, physical activity accounts for between 15 and $30 \%$ of a person s TDEE. As we discuss and illustrate throughout this text, physical activity exerts by far the most profound effect on human energy expenditure. World-class athletes nearly double their TDEE with 3 or 4 hours of intense training. Most persons can sustain metabolic rates 10 times the resting value during continuous big muscle exercise such as fast walking, running, bicycling, and swimming.

## IN A PRACTICAL SENSE

# Determining Basal Metabolic Rate from Body Mass, Stature, and Age 

Body mass, stature, and age contribute to individual differences in basal energy expenditure (BMR), making it possible to accurately estimate BMR using these variables. The method, validated in the early 1900 s by Drs. J.A. Harris and F.G. Benedict, used closed-circuit spirometry to carefully measure oxygen uptake in individuals who varied widely in body size and age. The Harris-Benedict method has become standard practice for estimating BMR.

EQUATIONS USING BODY MASS, STATURE, AND AGE

## Women

RDEE, $\left(\mathrm{kCal} \cdot 24 \mathrm{~h}^{-1}\right)=655+(9.6 \times$ body mass, kg$)+(1.85 \times$ stature, cm ) $-(4.7 \times$ age, y$)$

## Men

RDEE, $\left(\mathrm{kCal} \cdot 24 \mathrm{~h}^{-1}\right)=66.0+(13.7 \times$ body mass, kg$)+(5.0 \times$ stature, cm ) $-(6.8 \times$ age, y$)$

```
ExampleFemale
Data: Body mass = 62.7 kg; Stature = 172.5 cm; Age = 22.4 y.
RDEE = 655 + (9.6 < body mass, kg) + (1.85 × stature, cm) -
    (4.7 }\times\mathrm{ age, y)
RDEE = 655 + (9.6 < 62.7) + (1.85 < 172.5) - (4.7 × 22.4)
RDEE = 655 + 601.92 + 319.13-105.28
RDEE = 1471 kCal
```


## ExampleMale

```
Data: Body mass, 80 kg ; Stature, 189.0 cm ; Age, 30 y .
RDEE \(=66.0+(13.7 \times\) body mass, kg\()+(5.0 \times\) stature, cm\()-\) (6.8 \(\times\) age, y )
RDEE \(=66.0+(13.7 \times 80, \mathrm{~kg})+(5.0 \times 189.0, \mathrm{~cm})-(6.8 \times\) \(30.0, y)\)
RDEE \(=66.0+1096+945-204\)
RDEE \(=1903 \mathrm{kCal}\)
```

Reference: Harris, J.A., Benedict, F.G. A biometric study of basal metabolism in man. Publ. No. 279. Washington, DC: Carnegie Institute. 1919.

## Diet-Induced Thermogenesis

Food consumption generally increases energy metabolism.
Diet-induced thermogenesis (DIT; sometimes referred to as thermic effect of food [TEF]) consists of two components. One component, obligatory thermogenesis (formerly called specific dynamic action or SDA), results from the energy required to digest, absorb, and assimilate food nutrients. The second component, facultative thermogenesis, relates to the activation of the sympathetic nervous system and its stimulating influence on metabolic rate.

The first experiment on DIT, to our knowledge, was performed in 1891 using indirect calorimetry by the influential German nutritional scientist Max Rubner (1854 1932). This classic research established the 24 -hour energy expenditure of 742 kCal for a fasting dog. ${ }^{13}$ Rubner then fed the dog 2 kg of meat that contained 1926 kCal . Food consumption increased the dog s daily energy expenditure to 1046 kCal . Rubner attributed the $41 \%$ increase of 304 kCal to the chemical work of glands in metabolizing absorbed nutrients or the work of digestion. The increased metabolism represented $16 \%$ of the total energy ingested. Numerous subsequent experiments indicate that the meal s size and macronutrient composition, time elapsed since the previous meal, and nutritional and health status differentially affect the magnitude of DIT.

The thermic effect of food generally reaches maximum within 1 hour following a meal. Considerable variability exists among individuals; the magnitude of DIT usually varies between 10 and $30 \%$ of the ingested food energy, depending
on the quantity and type of food consumed. A meal of pure protein, for example, elicits a thermic effect nearly $25 \%$ of the meal s total caloric value. This large thermic effect results largely from activation of digestive processes. It also includes extra energy required by the liver to assimilate and synthesize protein and/or to deaminate amino acids and convert them to glucose or triacylglycerols.

Overweight individuals often have a blunted thermic response to eating that contributes to excess body fat accumulation. ${ }^{24}{ }^{26}$ Interestingly, the magnitude of DIT also may be lower in endurance-trained individuals than in untrained counterparts. ${ }^{11,21,28}$ Any training effect probably reflects a calorie-sparing adaptation to conserve energy and glycogen during periods of increased physical activity. Energy conservation in any form seems counterproductive to the potential of increased physical activity for weight control. For a physically active person, however, DIT represents only a small portion of TDEE compared with the energy expended through regular physical activity.

## Calorigenic Effect of Food on Exercise Metabolism

DIT has been compared in resting and exercising subjects after consuming meals of identical macronutrient composition and caloric content. In one study, six men performed moderate exercise on a bicycle ergometer before breakfast on one day; then on separate days, they performed exercise for 30 minutes after a breakfast containing either 350,1000 , or $3000 \mathrm{kCal} .^{3}$

## IN A PRACTICAL SENSE

# Predicting VO $_{2 \max }$ During Pregnancy from Submaximum Exercise Heart Rate and Oxygen Consumption 


#### Abstract

Authorities recommend that a woman participate in regular physical activity during an uncomplicated pregnancy. Most agree that an individualized exercise prescription should guide exercise because of concern for fetal well being. The exercise prescription typically specifies intensity, duration, and frequency of activity. Exercise intensity usually represents some percentage of the maximal oxygen consumption $\left(\% \mathrm{VO}_{2 \text { max }}\right)$ obtained from equations relating heart rate (HR) to $\% \mathrm{VO}_{2 \text { max }}$. The direct determination of $\mathrm{VO}_{2_{\text {max }}}$ requires that subjects perform near-exhaustive exercise, an unacceptable requirement for most pregnant women.


## PREDICTING $\mathrm{VO}_{2 \text { MAX }}$ FROM SUBMAXIMUM EXERCISE <br> Predicting $\mathrm{VO}_{2 \text { max }}$ during pregnancy involves a three-stage, submaximum cycle ergometer exercise test. Oxygen consumption $\left(\mathrm{VO}_{2}\right)$ and HR , measured toward the end of the final exercise stage, predict $\mathrm{VO}_{2 \text { max }}$ via regression analyses.

## SUBMAXIMUM CYCLE ERGOMETER TEST

Subject rests for 10 minutes and then performs a continuous threestage, 6-minute per stage, cycle ergometer test as follows:

Stage 1: 0 watts (W) (unloaded cycling)
Stage 2: $30 \mathrm{~W}\left(184 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}\right)$
Stage 3: $60 \mathrm{~W}\left(367 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}\right)$

## PREDICTION EQUATIONS

Measure $\mathrm{VO}_{2}\left(\mathrm{~L} \cdot \mathrm{~min}^{-1}\right.$ and $\mathrm{HR}\left(\mathrm{b} \cdot \mathrm{min}^{-1}\right)$ for each of the last 3 minutes of the final exercise stage. Average the three HR values to
predict $\% \mathrm{VO}_{2 \text { max }}$ in the following equation:

$$
\text { Predicted } \% \mathrm{VO}_{2 \max }=\left(0.634 \times \mathrm{HR}\left[\mathrm{~b} \cdot \min ^{-1}\right]\right)-30.79
$$

Use the predicted $\mathrm{VO}_{2 \text { max }}$ and the measured $\mathrm{VO}_{2}\left(\mathrm{~L} \cdot \mathrm{~min}^{-1}\right)$ during the last exercise stage to predict $\mathrm{VO}_{2 \text { max }}\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right)$ in the following equation:

$$
\text { Predicted } \mathrm{VO}_{2 \max }=\mathrm{VO}_{2} \div \text { predicted } \% \mathrm{VO}_{2 \max } \times 100
$$

## EXAMPLE

A woman 20 weeks pregnant, weighing 70.4 kg , performs the three-stage cycle ergometer test. The average value for final-stage exercise HR equals $155 \mathrm{~b} \cdot \mathrm{~min}^{-1}$; the average value for $\mathrm{VO}_{2}$ equals $1.80 \mathrm{~L} \cdot \mathrm{~min}^{-1}$.

$$
\begin{aligned}
\text { Predicted } & \% \mathrm{VO}_{2 \text { max }} \\
& =\left(0.634 \times \mathrm{HR}\left[\mathrm{~b} \cdot \min ^{-1}\right]\right)-30.79 \\
& =(0.634 \times 155)-30.79 \\
& =67.5 \% \\
\text { Predicted } & \mathrm{VO}_{2 \text { max }} \\
& =\mathrm{VO}_{2} \div \text { predicted } \% \mathrm{VO}_{2 \max } \times 100 \\
& =1.80 \div 67.5 \times 100 \\
& =2.67 \mathrm{~L} \cdot \mathrm{~min}^{-1}\left(2670 \mathrm{~mL} \cdot \mathrm{~min}^{-1}\right) \\
& =2670 \mathrm{~mL} \cdot \mathrm{~min}^{-1} \div 70.4 \mathrm{~kg} \\
& =37.9 \mathrm{~mL} \cdot \mathrm{~kg}^{1} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

Sady SP, et al. Prediction of $\mathrm{VO}_{2 \text { max }}$ during cycle exercise in pregnant women. J Appl Physiol 1988;65:657.

The results indicated that (1) breakfast increased resting metabolism by $10 \%$, (2) variations in the caloric value of the meal exerted no influence on the thermic effect, and (3) performing exercise following a meal of 1000 or 3000 kCal produced a larger energy expenditure than exercise without prior food. The calorigenic effect of food on exercise metabolism nearly doubled the food s thermic effect at rest. Apparently, exercise augments DIT. This agrees with previous findings in which the thermic response to a $1000-\mathrm{kCal}$ meal averaged $28 \%$ of the basal requirement at rest, yet increased to $56 \%$ of the basal requirement when subjects exercised following eating. ${ }^{17}$ The DIT of carbohydrate and protein is greater than for lipid. As with their response during rest, some obese men and women exhibit a depressed DIT when they exercise after eating (see Chapter 4, Focus on Research, p. 116). ${ }^{25,30}$ For most individuals, it seems reasonable to encourage moderate exercise after eating to possibly augment a diet-induced increase in caloric expenditure for weight control.

## Climate

Environmental factors influence resting metabolic rate. The resting metabolism of people in a tropical climate averages 5 to $20 \%$ higher than for counterparts living in more temperate
areas. Exercise performed in hot weather also imposes a small additional metabolic load; it causes about 5\% higher oxygen consumption compared to a thermoneutral environment. This probably results from the thermogenic effect of an elevated core temperature per se, including additional energy required for sweat gland activity and altered circulatory dynamics during work in the heat.

Cold environments can increase energy metabolism during rest and exercise. The magnitude of the effect depends largely on body fat content and effectiveness of the clothing ensemble. Metabolic rate increases up to fivefold at rest during extreme cold stress because shivering generates body heat to maintain a stable core temperature. Exercising in cold water serves as a good example of the effects of cold stress because of the difficulty in maintaining a stable core temperature in such a stressful thermal environment. ${ }^{27}$

## Pregnancy

One area of interest concerns the degree that pregnancy affects the metabolic cost and physiologic strain imposed by exercise. ${ }^{4}$ One investigation studied 13 women from the sixth month of pregnancy to 6 weeks after gestation. ${ }^{9}$ Physiologic
measures taken every 4 weeks included heart rate and oxygen consumption during bicycle and treadmill exercise. Heart rate and oxygen consumption during walking (weight-bearing exercise) increased progressively during the measurement period. Exercise heart rate and oxygen consumption remained unchanged during weight-supported bicycle exercise at a constant intensity. The added energy cost to weight-bearing locomotion such as walking, jogging, and stair climbing during pregnancy results primarily from the additional weight transported (and reduced economy of effort from encumbrance of fetal tissue) with a relatively small effect from the developing fetus per se. Chapter 21 more fully discusses the physiologic and metabolic impact of exercise on both mother and fetus during pregnancy.

## Summary

1. Total daily energy expenditure equals the sum of resting metabolism, thermogenic influences (e.g., thermic effect of food), and the energy generated in physical activity.
2. The BMR represents the minimum energy required to maintain vital functions in the waking state measured under controlled laboratory conditions. The BMR averages only slightly lower than the resting metabolic rate (RMR) and relates closely to body surface area.
3. RMR (like BMR) decreases with age from variations in fat-free body mass (FFM). The RMR for men generally exceeds values for women of similar body size. One can accurately predict RMR from FFM in men and women who vary considerably in body size.
4. Different organs expend different amounts of energy during rest and exercise. At rest, muscles generate about $20 \%$ of the body s total energy expenditure. During all-out exercise, the energy expended by skeletal muscles can increase more than 100 times above its resting value.
5. Five major factors affect a person s metabolic rate: body size, physical activity, dietary-induced thermogenesis, climate, and pregnancy, with physical activity exerting the greatest effect.

## Part 2 ENERGY EXPENDITURE DURING PHYSICAL ACTIVITY

## CLASSIFICATION OF PHYSICAL ACTIVITIES BY ENERGY EXPENDITURE

Most individuals have performed some type of physical work they would classify as exceedingly difficult. This might include walking up a long flight of stairs, shoveling snow for 60 minutes, running to catch a bus, digging a deep trench, skiing or snowshoeing through a blizzard, or hiking up steep terrain. Intensity and duration represent two important factors that
affect the strenuousness of a particular physical task. It requires about the same net number of calories to complete a 26.2 -mile marathon at various running speeds. One person might expend a considerable rate of energy expenditure running at maximum steady-rate pace (e.g., $80 \% \mathrm{VO}_{2 \max }$ ) and complete the distance in a little more than 2 hours. Another runner of equal fitness might select a slower, more comfortable pace (e.g., $55 \% \mathrm{VO}_{2 \max }$ ) and complete the run in 3 hours. In this example, the intensity of effort distinguishes the physical demands of the task. In another example, two persons of equal fitness may run at the same speed, but one person runs for twice as long as the other. In this case, exercise duration becomes the important consideration in classifying the strenuousness of physical effort.

Several classification systems rate sustained physical activity for its strenuousness. One system recommends classification of work by the ratio of energy required for the task to the resting energy requirement. ${ }^{1}$ This system uses the physical activity ratio (PAR). Light work for men elicits an oxygen consumption (or energy expenditure) up to 3 times the resting requirement. Heavy work encompasses physical activity requiring 6 to 8 times resting metabolism, whereas maximal work includes any task that requires metabolism to increase 9 times or more above rest. As a frame of reference, most industrial jobs and household tasks require less than 3 times resting energy expenditure. These work classifications (in multiples of resting metabolism) average slightly lower for women because of their generally lower aerobic capacity. Work classification based on the PAR model rates the strenuousness of occupational tasks at a somewhat lower level than typical classifications for general exercise. This is because occupational and industrial work usually extends for much longer periods than exercise training, often requiring the use of a small muscle mass performed under varying and stressful environmental conditions and physical constraints.

## THE MET

Table 9.4 presents a five-level classification system based on the energy ( kCal ) required by untrained men and women who perform different physical activities including a broad range of occupational tasks. ${ }^{6}$ Because 5 kCal equals approximately 1 L of oxygen consumed, one can transpose these values into liters of oxygen consumed per minute $\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right)$ or milliliters of oxygen per kilogram of body mass per minute $\left(\mathrm{mL} \cdot \mathrm{kg}^{-1}\right.$. $\mathrm{min}^{-1}$ ) or METs, defined as multiples of the resting metabolic rate. One MET equals resting oxygen consumption of about $250 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ for an average man and $200 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ for an average woman. Exercise performed at 2 METs requires twice the resting metabolism (about $500 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ for a man), 3 METs equals three times rest, and so on. For a different but usually more accurate classification that considers variations in body size, one should express the MET in terms of oxygen consumption per unit body mass: 1 MET equals $3.5 \mathrm{~mL} \cdot \mathrm{~kg}^{-1}$. $\mathrm{min}^{-1} ; 2$ METs equals $7.0 \cdot \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, and so on.

Table 9.5 presents a classification system for characterizing the intensity of leisure-time physical activity in absolute

TABLE 9.4 Five-Level Classification of Physical Activity Based on Energy Expenditure

| Level | Energy Expenditure ${ }^{a}$ |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
|  | $\mathrm{kCaI} \cdot \min ^{-1}$ | L $\cdot \mathbf{m i n}^{-1}$ | $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | METs |
| Men |  |  |  |  |
| Light | 2.04 .9 | 0.400 .99 | 6.115 .2 | 1.63 .9 |
| Moderate | 5.07 .4 | 1.001 .49 | 15.322 .9 | 4.05 .9 |
| Heavy | 7.59 .9 | 1.501 .99 | 23.030 .6 | 6.07 .9 |
| Very heavy | 10.012 .4 | 2.002 .49 | 30.738 .3 | 8.09 .9 |
| Unduly heavy | $\geq 12.5$ | $\geq 2.50$ | $\geq 38.4$ | $\geq 10.0$ |
| Women |  |  |  |  |
| Light | 1.53 .4 | 0.300 .69 | 5.412 .5 | 1.22 .7 |
| Moderate | 3.55 .4 | 0.701 .09 | 12.619 .8 | 2.84 .3 |
| Heavy | 5.57 .4 | 1.101 .49 | 19.927 .1 | 4.45 .9 |
| Very heavy | 7.59 .4 | 1.501 .89 | 27.234 .4 | 6.07 .5 |
| Unduly heavy | $\geq 9.5$ | $\geq 1.90$ | $\geq 34.5$ | $\geq 7.6$ |
| ${ }^{a} \mathrm{~L} \cdot \mathrm{~min}^{-1}$ based on 5 kCal per liter of oxygen; $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ based on $65-\mathrm{kg}$ man and $55-\mathrm{kg}$ woman; one MET equals the average resting oxygen consumption ( $250 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ for men, $200 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ for women). |  |  |  |  |

TABLE 9.5 Characterization of the Intensity of Leisure-Time Physical Activity Related to Age

|  | Relative Intensity <br> $\left(\% \mathbf{V O}_{\mathbf{2 m a x}}\right)$ | Young | Middle-Aged | Old | Very Old |
| :--- | :---: | :---: | :---: | :---: | :---: |
| Categorization | $<10$ | 1.0 | 1.0 | 1.0 | 1.0 |
| Rest | $<35$ | $<4.5$ | $<3.5$ | $<2.5$ | $<1.5$ |
| Light | $<50$ | $<6.5$ | $<5.0$ | $<3.5$ | $<2.0$ |
| Fairly light | $<70$ | $<9.0$ | $<7.0$ | $>5.0$ | $<2.8$ |
| Moderate | $>9.0$ | $>7.0$ | $>2.8$ |  |  |
| Heavy | 10 | 13.0 | 10.0 | 7.0 | 4.0 |
| Maximal | 100 |  |  |  |  |

From Bouchard C, et al. Exercise, fitness, and health: a consensus of current knowledge. Champaign, IL: Human Kinetics, 1990.
(METs) and relative ( $\% \mathrm{VO}_{2 \max }$ ) intensity by age categories. To account for the general aging effect on aerobic capacity, the categories for exercise intensity in METs adjust lower.

## DAILY RATES OF AVERAGE ENERGY EXPENDITURE

TABLE 9.6 shows averages for stature and body mass and daily energy expenditure for males and females living in the United States. The average man aged 19 to 50 years expends 2900 kCal per day, whereas the female expends 2200 kCal . The bottom of the table shows that these individuals spend nearly $75 \%$ of the day in activities that require only light energy expenditure. For most individuals, energy expenditure rarely rises substantially above the resting level, with walking the most common physical activity. The term homo sedentarius all too appropriately describes most of the world s population! This descriptor is
compelling, as physical inactivity in highly mechanized societies has become a pandemic despite the admonitions of scientists, educators, and governmental agencies. The Centers for Disease Control and Prevention (www.cdc.gov) estimates that physical inactivity and poor eating habits account for nearly 300,000 deaths yearly in the United States.

## ENERGY COST OF HOUSEHOLD, INDUSTRIAL, AND RECREATIONAL ACTIVITIES

Appendix C (available online at http://thepoint.lww.com/ mkk7e) lists examples of energy expenditures expressed by body mass for common household activities, selected industrial tasks, and popular recreational and sports activities. These data highlight the large variation in energy expenditure for diverse physical activities. The caloric values also represent

TABLE 9.6 Reference Heights, Weights, and Energy Expenditures of Children and Adults Living in the United States

| Gender | Age | Height, Weight, and Body Mass Index |  |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  | Median Body Mass Index ${ }^{\text {a }}$ | Reference Height (cm [in]) | Reference Weight, ${ }^{b}$ (kg [lb]) |
| Male, female | 26 mo | - | 64 (25) | 7 (16) |
|  | 711 mo | - | 72 (28) | 9 (20) |
|  | 13 y | - | 91 (36) | 13 (29) |
|  | 48 y | 15.8 | 118 (46) | 22 (48) |
| Male | 913 y | 18.5 | 147 (58) | 40 (88) |
|  | 1418 y | 21.3 | 174 (68) | 64 (142) |
|  | 1930 y | 24.4 | 176 (69) | 76 (166) |
| Female | 913 y | 18.3 | 148 (58) | 40 (88) |
|  | 1418 y | 21.3 | 163 (64) | 57 (125) |
|  | 1930 y | 22.8 | 163 (64) | 61 (133) |

${ }^{a}$ In kg per $\mathrm{m}^{2}$.
${ }^{b}$ Calculated from median body mass index and median heights for ages 4 to 8 years and older.
Adapted from Dietary reference intakes: a risk assessment model for establishing upper intake levels for nutrients. Food and Nutrition Board. Institute of Medicine. Washington, DC: National Academy Press, 1998.

| Gender, Age, and Energy Expenditure |  |  |
| :---: | :---: | :---: |
|  | Age (y) | Energy Expenditure (kCal) |
| Males | 1518 | 3000 |
|  | 1924 | 2900 |
|  | 2550 | 2900 |
|  | 51+ | 2300 |
| Females | 1518 | 2200 |
|  | 1924 | 2200 |
|  | 2550 | 2200 |
|  | 50+ | 1900 |
|  | Average Time Spent During the Day |  |
|  | vity | Time (h) |
|  | ng and lying down | 8 |
|  |  | 6 |
|  |  | 6 |
|  |  | 2 |
|  | ational activity | 2 |

Data from Food and Nutrition Board, National Research Council. Recommended dietary allowances, revised. Washington, DC: National Academy of Sciences, 1989.
averages, with values for an individual varying considerably depending on skill, pace, and fitness level.

The values listed in the column for body mass represent the activity s caloric cost for 1 minute. This equals the gross energy value (see Chapter 10, p. 207) because it includes the cost of rest for a 1-minute period. To estimate the total cost of performing an activity, multiply the caloric value in the table
by the number of minutes of participation. For example, if a $70-\mathrm{kg}$ man spends 30 minutes vacuuming (carpet sweeping), his total energy expenditure for this household task equals $102 \mathrm{kCal}(3.4 \mathrm{kCal} \times 30 \mathrm{~min})$. The same individual expends approximately 690 kCal during a 50 -minute judo workout, but only 90 kCal while sitting quietly watching television for 2 hours. Golf requires about 6.0 kCal each minute, or


Figure 9.5 Relationship between body mass and oxygen consumption measured during submaximal, brisk treadmill walking. (From Laboratory of Applied Physiology, Queens College, NY.)
$360 \mathrm{kCal} \cdot \mathrm{h}^{-1}$. The same person expends almost twice this energy, or $708 \mathrm{kCal} \cdot \mathrm{h}^{-1}$, while swimming backstroke. Viewed somewhat differently, 25 minutes of swimming backstroke requires about the same number of calories as playing golf for 1 hour. Increasing the pace of either the swim or the golf game proportionally increases the energy expenditure.

## Influence of Body Mass

Increases in body mass raise the energy expended in many physical activities (see Appendix C), particularly in weightbearing exercise like walking and running. Figure 9.5 clearly illustrates that the energy cost of walking increases directly with body mass (larger body mass requires greater energy expenditure). For persons with the same body mass, such a small variation in oxygen consumption exists that body mass accurately predicts the energy expended walking.

The influence of body mass on energy metabolism in weight-bearing exercise occurs whether the person gains weight naturally as body fat (or FFM) or as a short-term added load from sports equipment or a weighted vest on the torso. ${ }^{5,29}$ With weight-supported exercise (e.g., stationary cycling), the influence of body mass on energy cost decreases considerably. It averages only about $5 \%$ higher in stationary cycling among heavy people because of extra energy required to lift heavier lower limbs. ${ }^{10,12}$ This body weight effect during stationary cycling exercise slightly lowers energy cost values for women compared with men. For overweight persons desiring to use exercise for weight loss, weight-bearing exercise generates a
considerable caloric expenditure simply from the added cost of transporting a heavier body weight.

Appendix C also shows that the energy cost for crosscountry running ranges between 8.2 kCal per minute for a $50-\mathrm{kg}$ person and almost twice as much ( 16.0 kCal ) for a person who weighs 98 kg . Expressing the energy requirement by body mass as $\mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ attempts to eliminate this variation. In this case, energy cost averages about $0.164 \mathrm{kCal} \cdot$ $\mathrm{kg}^{-1} \cdot \min ^{-1}$. Expressing energy cost per kg of body mass reduces differences between individuals regardless of age, race, gender, and body mass. However, a heavier person still expends more total calories than a lighter person for an equivalent exercise period. This occurs because the activity mainly requires the transport of body mass-and this requires proportionately more energy.

## HEART RATE TO ESTIMATE ENERGY EXPENDITURE

For each person, heart rate and oxygen consumption relate linearly over a large range of exercise intensities. From this intrinsic relationship, the exercise heart rate provides an estimate of oxygen consumption (and thus energy expenditure) during aerobic exercise. This approach has proved useful when the oxygen consumption could not be measured during the actual activity.

Figure 9.6 presents data for two members of a women s basketball team during a laboratory treadmill running test. For each woman, heart rate increased linearly with oxygen


## $\square$ Player A $\square$ Player B

Figure 9.6 Linear relationship between heart rate and oxygen consumption for two women collegiate basketball players of different aerobic fitness levels. Measurements made during a graded exercise test on a motor-driven treadmill. (From Laboratory of Applied Physiology, Queens College, NY.)

## FOCUS ON RESEARCH

## Factors that Affect Recovery Oxygen Consumption

Margaria $R$, et al. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 1933;106:689.
$>$ A. V. Hill and colleagues had theorized that the increased oxygen consumption in recovery from exhaustive exercise (the so-called oxygen debt ) resulted largely from the delayed oxidation of a portion of the lactic acid (LA) that accumulated during exercise. Unfortunately, these researchers did not provide direct evidence to confirm their hypothesis by quantifying the relationship between the oxygen debt and LA accumulation.

Margaria and his group at the prestigious Harvard Fatigue Laboratory provided the first quantitative assessment of Hill s theory. The researchers determined the timecourse characteristics of LA removal, described as an exponential function of time. They also related LA removal rate to recovery oxygen consumption $\left(\mathrm{VO}_{2}\right)$. The $\mathrm{VO}_{2}$ recovery curve subdivided into two parts that the researchers attributed to distinctly different metabolic events during exercise. The terms alactacid and lactacid described these components of recovery $\mathrm{VO}_{2}$.

One subject, observed during 10-minute runs on different occasions at varied exercise intensities, provided the experimental data. LA, measured from the femoral vein and brachial artery at different times throughout exercise, indicated rapid and uniform LA diffusion throughout the body. Blood LA concentration varied directly with the body s total LA content. The figure illustrates the relationship between exercise blood LA concentration and the magnitude of recovery $\mathrm{VO}_{2}$. Note that the curve does not deviate from baseline LA until the oxygen debt reaches 3 to 4 L . This coincided with the subject s exercise $\mathrm{VO}_{2}$ of about $3.0 \mathrm{~L} \cdot \mathrm{~min}^{1}$. Blood LA concentration (and corresponding oxygen debt) then increased linearly with exercise intensity $\left(\mathrm{VO}_{2}\right)$. The researchers reasoned that when the total oxygen debt remained below 3.0 L , the LA mechanism in exercise remained inactive. They termed this level of exercise alactic to signify work production with-
out significant LA accumulation. Under these conditions, recovery $\mathrm{VO}_{2}$ proceeds rapidly to the resting level. LA began to accumulate with exercise at about $65 \%$ of the maximum aerobic metabolism $\left(\mathrm{VO}_{2 \text { max }}\right)$, accumulating rapidly thereafter. LA removal, a slow process, progressed at a velocity constant of 0.02 -one-half removed each 15 minutes.

Margaria and colleagues concluded that LA production became important only during strenuous exercise. They postulated that the total recovery $\mathrm{VO}_{2}$ consisted of the combined effects of two distinct components: (1) lactacid oxygen debt attributable to oxidation of LA produced in exercise and (2) alactacid oxygen debt, unrelated to LA accumulation and repaid early and rapidly in recovery. This important experiment in the early history of exercise physiology provided insight into why different $\mathrm{VO}_{2}$ recovery patterns emerged for different exercise intensities.


Relation between blood lactic acid concentration and oxygen debt (calculated after A. V. Hill) and oxygen consumption at various levels of exercise. Exercise duration equaled 10 minutes in each case.
consumption-a proportionate increase in exercise heart rate (HR) accompanied each increase in oxygen consumption $\left(\mathrm{VO}_{2}\right)$. Both $\mathrm{HR} \mathrm{VO}_{2}$ lines display linearity, but the same heart rate does not correspond to the same oxygen consumption for both women because the slopes (rate of change) of the lines differ. Heart rate for subject B increases less than that for subject A for a given increase in oxygen consumption.

Chapters 11,17 , and 21 discuss the significance of the difference in heart rate increase with exercise and its relation to cardiovascular fitness. For the current discussion, exercise heart rate estimates exercise oxygen consumption with reasonable accuracy. For player A, an exercise heart rate of $140 \mathrm{~b} \cdot \mathrm{~min}^{1}$ corresponds to an oxygen consumption of $1.08 \mathrm{~L} \cdot \min ^{1}$, whereas the same heart rate for player B corresponds to a
$1.60 \mathrm{~L} \cdot \min ^{1}$ oxygen consumption. Heart rates obtained by radiotelemetry during basketball competition were then applied to each player s $\mathrm{HR} \mathrm{VO}_{2}$ line to estimate energy expenditure under game conditions. ${ }^{15}$

Heart rate to estimate energy expenditure appears practical but has limited research applications because it has been validated for only a few general activities. One major problem concerns the degree of similarity between the laboratory exercise test to establish the $\mathrm{HR} \mathrm{VO}_{2}$ line and specific activities to which it applies. For example, factors other than oxygen consumption influence exercise heart rate response. These include environmental temperature, emotions, previous food intake, body position, muscle groups exercised, continuous or discontinuous (stop-and-go) exercise, or whether muscles act statically or more dynamically. In aerobic dance, for example, heart rates while dancing at a specific oxygen consumption exceed heart rates at the same oxygen consumption during treadmill exercise. ${ }^{18}$ Consistently higher heart rates occur in upper-body exercise; they are also higher when muscles act statically in straining-type exercises than in dynamic exercise at any submaximal oxygen consumption. Applying heart rate during upper-body or static-type exercise to a $\mathrm{HR} \mathrm{VO}_{2}$ line developed during running or cycling overpredicts the measured oxygen consumption. ${ }^{14}$

## INTEGRATIVE QUESTION

A high-tech computer company asks you to validate a wrist-mounted device to measure exercise energy expenditure. The person exhales one breath onto the top of the instrument while exercising. The devices electronic components and microprocessor analyze expired air to compute oxygen consumption and energy expenditure. Outline the steps to establish the instruments validity.

## Summary

1. Different classification systems rate the strenuousness of physical activities. These include ratings based on (1) ratio of the energy cost of the task to the resting energy requirement, (2) oxygen requirement in $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$, or (3) multiples of resting metabolism as METs.
2. Total daily energy expenditure averages 2900 kCal for men and 2200 kCal for women ages 19 to 50 years. Considerable variability among persons exists for daily energy expenditure, with the largest variation determined by one s physical activity level.
3. Daily energy expenditure provides a framework to classify different occupations. Within any classification, energy expended during leisure time recreational pursuits contributes considerable additional variability.
4. Heavier individuals expend more total energy in physical activity than lighter counterparts, particularly in weight-bearing walking and running activities.
5. Heart rate has only limited use to predict oxygen consumption and caloric expenditure for most physical activities.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

Centers for Disease Control and Prevention www.cdc.gov

## CHAPTER ?



# Energy Expenditure During Walking, Jogging, Running, and Swimming 

## CHAPTER OBJECTIVES

> Differentiate between gross energy expenditure and net energy expenditure
> Explain exercise economy and mechanical efficiency
> Describe differences in running economy between trained and untrained children and adults
> Graph the relationship between walking velocity and energy expenditure up to velocities achieved during competitive race-walking
> Discuss the influence of body mass, exercise surface, and footwear on energy expenditure during walking and running
> Describe advantages and disadvantages of ankle and handheld weights to increase energy expenditure during walking and running
> Graph the relationship between running velocity and energy expenditure
> Explain the association between running velocity and energy expenditure per unit distance traveled
> Outline the interactions between stride length and stride frequency and linear velocity during running versus competitive race-walking
> Quantify how drafting influences energy expenditure during running, swimming, and bicycling
> Identify factors that contribute to a lower exercise economy swimming compared with running

The following sections detail energy expenditure for walking, running, and swimming. These popular activities take on special significance to the general population for their roles in weight control, physical conditioning, and health maintenance and rehabilitation.

## GROSS VERSUS NET ENERGY EXPENDITURE

The following example illustrates the use of oxygen consumption to estimate the energy expenditure in swimming. A 25 -year-old man swimming for 40 minutes at a moderate, steady pace consumes oxygen at a rate of 2.0 L per minute for a total 80 L of oxygen consumed in the 40 -minute swim. To compute energy expenditure in $\mathrm{kCal} \cdot \min ^{-1}$ from oxygen consumption we use the calorific transformation of 5.0 kCal per liter of oxygen consumed (assuming carbohydrate as sole energy fuel; Chapter 8). Thus, the swimmer expends about $400 \mathrm{kCal}\left(80 \mathrm{~L} \mathrm{O}_{2} \times 5 \mathrm{kCal}\right)$ during the swim. This computation does not assess the energy expenditure of the swim per se because the 400 kCal (termed the gross energy expenditure) also includes energy that would have been expended if the person only rested and did not swim for 40 minutes. To obtain the true energy expenditure of only the 40 -minute swim (termed the net energy expenditure), one must subtract resting metabolism from the gross energy expenditure of the exercise as follows:

$$
\begin{aligned}
\text { Net energy expenditure }= & \text { Gross energy expenditure } \\
& \text { Resting energy expenditure } \\
& \text { (for equivalent time) }
\end{aligned}
$$

Knowing the swimmer s size (mass, 65 kg ; stature, 174 cm ) permits computation of the surface area of $1.78 \mathrm{~m}^{2}$ from the nomogram in Figure 9.4. Multiplying this value by the average basal metabolic rate (BMR) for young men, $38 \mathrm{kCal} \cdot \mathrm{m}^{-2} \cdot \mathrm{~h}^{-1}$ (Fig. 9.3), results in an estimated resting energy expenditure of 67.6 kCal per hour $\left(1.78 \mathrm{~m}^{2} \times 38 \mathrm{kCal}\right)$, or about 45 kCal for the 40 -minute swim. Thus, the net energy expended for the swim computes as gross energy expenditure ( 400 kCal ) minus the 40 -minute resting value ( 45 kCal ), resulting in a net energy expenditure of 355 kCal just for swimming.

In Figure 7.2 of Chapter 7, we show that oxygen consumption during constant-load light-to-moderate exercise rises rapidly during the first several minutes, then levels off and remains stable thereafter. This permits estimating total energy expenditure from only one or two oxygen consumption measures during steady-rate exercise. Activities with considerable variation in pace such as tennis, soccer, lacrosse, field hockey, or basketball require more frequent measures for accurate estimates of total energy expenditure. Strenuous exercise, when energy requirements considerably exceed aerobic energy transfer, derives considerable energy anaerobically with accompanying blood lactate accumulation. Estimating energy expenditure in such situations becomes problematic, often resulting in inaccurate values.

## ECONOMY OF HUMAN MOVEMENT AND MECHANICAL EFFICIENCY

The concept of human exercise efficiency (often referred to as mechanical efficiency) considers the ratio between the energy expenditure of exercise (calculated from the amount or rate of external work performed) and that fraction of energy expenditure that appears as external work (often called energy output). Efficiency of human movement relates the amount of energy required to perform a particular task to the actual energy requirement of the work accomplished. Movement economy, in contrast, refers to the energy required (usually inferred from oxygen consumption) to maintain a constant velocity of movement.

## Economy of Movement

Assessing economy of movement requires evaluation of the oxygen consumed during exercise at a constant power output or velocity. Movement economy determination only applies to steady-rate exercise where oxygen consumption closely mirrors energy expenditure. For example, at an established submaximal speed of running, cycling, or swimming, an individual with greater movement economy consumes less oxygen (lower steady-rate $\mathrm{VO}_{2}$ ). African women who balance heavy loads on their heads have mastered a subtle adjustment in walking technique that allows them to carry up to $20 \%$ of their body weight with no increase in energy expenditure. A group of Europeans, in contrast, exerted proportionately more effort (increased oxygen consumption) as the added weight on their head increased.

Economy of movement takes on added importance during longer duration exercise where success largely depends on the individual s aerobic capacity and ability to maintain the lowest oxygen consumption relative to the work rate. From age 21 to 28 years, a six-time Grand Champion of the Tour de France improved $8 \%$ in exercise economy (and thus power production when cycling at a given oxygen uptake), perhaps from changes in muscle myosin type stimulated from years of training intensely for 3 to 6 hours on most days. ${ }^{20,21}$ For children and adults, any training adjustment that improves economy of effort usually improves exercise performance. ${ }^{23,38}$ Figure 10.1 displays the strong association between running economy and endurance performance in elite athletes of comparable aerobic fitness. Clearly, athletes with greater running economies (lower oxygen consumption at a predetermined speed) achieve better race times. Variation in running economy among this homogeneous group explains approximately $64 \%$ of the total variation in $10-\mathrm{km}$ running performance.

Even among trained runners, notable variation in economy emerges at submaximal running speeds. ${ }^{55,58,74}$ In general, long-term programs of run training improve running economy, due partly to training-induced reductions in pulmonary ventilation during submaximal exercise. ${ }^{13,31,79}$ It remains unclear whether the first 6 weeks of run training affect running mechanics or economy despite improvements


Figure 10.1 Relationship between submaximal oxygen consumption running at $268 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ and $10-\mathrm{km}$ race time in elite male runners of comparable aerobic capacity. (From Morgan DW, Craib M. Physiological aspects of running economy. Med Sci Sports Exerc 1992;24:456.)
in performance and physiologic function. ${ }^{31,44}$ Short-term training emphasizing proper running technique (i.e., arm movements and body alignment) does not enhance running economy. ${ }^{40}$ In contrast, distance runners with an uneconomical stride-length pattern benefit from a short-term audiovisual feedback program that focuses on optimizing stride length, ${ }^{57}$ including biofeedback and relaxation psychophysiologic interventions. ${ }^{13}$ In addition, an 8-week program of heavy resistance training utilizing half squats improved running economy in well-trained male and female distance runners. ${ }^{78}$

No single biomechanical factor accounts for individual differences in running economy, although muscle structural and compositional factors probably play a role. ${ }^{43}$ Indirect evidence from studies of cyclists indicates that muscle fiber-type distribution in active muscles affects the economy of physical effort. During submaximal cycling, exercise economy of well-trained cyclists varies by $15 \% .{ }^{23}$ Cyclists with greater economy possessed a larger percentage of slow-twitch (type I) muscle fibers in their vastus lateralis muscle. Aerobic, type I muscle fibers act with greater mechanical efficiency than faster-contracting, highly anaerobic type II muscle fibers. ${ }^{22}$

## Mechanical Efficiency

Mechanical efficiency reflects the percentage of total chemical energy expended that contributes to external work, with the remainder lost as heat.

Mechanical efficiency (\%) = External work accomplished
$\div$ Energy expenditure $\times 100$
External work accomplished (energy output) equals force acting through a vertical distance ( $\mathrm{F} \times \mathrm{D}$ ), usually recorded as foot-pounds (ft-lb) or kilogram-meters (kg-m)
and then expressed in kCal units $(1 \mathrm{kCal}=3087 \mathrm{ft}-\mathrm{lb}$, or $426.4 \mathrm{~kg}-\mathrm{m}$ in a perfect machine without loss in efficiency). External work is easily determined during cycle ergometry or an exercise such as stair climbing or bench stepping-both require lifting the body mass a given distance (see In A Practical Sense, Chapter 5). One cannot compute mechanical efficiency during horizontal walking or running because technically no external work is accomplished; reciprocal arm and leg movements negate each other without a net gain in vertical distance. If a person walks or runs up a grade, the work component can be estimated from body mass and the vertical distance (lift) achieved during the movement. Total oxygen consumed provides the means to infer the denominator (energy expenditure) of the efficiency equation. During steady rate exercise, oxygen consumption converts to energy units-roughly $1.0 \mathrm{~L} \mathrm{O}_{2}=5.0 \mathrm{kCal}$ (see Table 8.1 for precise calorific transformations).

Suppose a 15 -minute ride on a stationary bicycle generates $13,300 \mathrm{~kg}-\mathrm{m}$ of work, with the net oxygen consumed to produce the work totaling $25 \mathrm{~L}(\mathrm{RQ}=0.88)$.

Convert oxygen consumed to kCal as follows:

1. For an RQ of 0.88 , each liter of oxygen consumed generates an energy equivalent of 4.9 kCal (Table 8.1).
2. 25 L of oxygen consumption during the 15 -minute ride generates 122.5 kCal of energy ( $25 \times 4.9 \mathrm{kCal}$ ).

Thus, the energy equivalent of $13,300 \mathrm{~kg}-\mathrm{m}$ of external work equals $31.19 \mathrm{kCal}(13,300 \mathrm{~kg}-\mathrm{m} \div 426.4 \mathrm{~kg}-\mathrm{m}$ per kCal ). Mechanical efficiency computes as follows:

$$
\text { Mechanical efficiency }=31.19 \mathrm{kCal} \div 122.5 \mathrm{kCal} \times 100
$$

$$
=25.5 \%
$$

As with all machines, the efficiency of the human body for mechanical work falls considerably below $100 \%$. The energy required to overcome internal and external friction represents the largest factor to affect mechanical efficiency. This constitutes wasted energy because it does not accomplish work; consequently, work input always exceeds work output.

On average, efficiency ranges between 20 and $25 \%$ for walking, running, and stationary cycling. Body size, gender, fitness level, and skill affect individual differences in efficiency. Mechanical efficiency falls below $20 \%$ for activities with substantial drag force that resists movement (e.g., road cycling, cross-country skiing, ice skating, rowing, and swimming). Competitors in these sports focus attention on reducing drag by improving aerodynamics and/or hydrodynamics through alterations in clothing, equipment, and technique. A small improvement in efficiency for an elite athlete increases the likelihood of success.

## Delta Efficiency

The calculation of delta efficiency provides an alternative approach to determine mechanical efficiency (not
affected by body mass or changes in body weight) as follows: ${ }^{5,63}$

$$
\text { Delta efficiency }=\frac{\Delta \text { Work production }}{\Delta \text { Energy expenditure }} \times 100
$$

where $\Delta$ work production equals the calculated difference in work output at two different exercise levels, and $\Delta$ energy expenditure equals the difference in the energy expenditure between the two exercise levels.

For example, suppose an individual initially cycles at 100 W at a $\mathrm{VO}_{2}$ of $1.50 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ with an RQ of 0.89 . Work intensity then increases to 200 W , with a corresponding $\mathrm{VO}_{2}$ of $2.88 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ and RQ of 0.95 . Delta efficiency computes as follows, where $1 \mathrm{~W}=0.014 \mathrm{kCal} \cdot \mathrm{min}^{-1}$; RQ of $0.89=$ $4.911 \mathrm{kCal} \cdot \mathrm{LO}_{2}^{-1} ; \mathrm{RQ}$ of $0.95=4.985 \mathrm{kCal} \cdot \mathrm{LO}_{2}^{-1}$ :

$$
\begin{aligned}
\text { Delta efficiency }= & 200 \mathrm{~W}-100 \mathrm{~W} \div 2.88 \mathrm{~L} \cdot \mathrm{~min}^{-1} \\
& -1.50 \mathrm{~L} \cdot \mathrm{~min}^{-1} \times 100 \\
= & (200 \times 0.014)-(100 \times 0.014) \\
& \div(2.88 \times 4.985)-(1.50 \times 4.911) \\
& \times 100 \\
= & 1.4 \mathrm{kCal} \cdot \mathrm{~min}^{-1} \div 6.99 \mathrm{kCal} \cdot \mathrm{~min}^{-1} \\
& \times 100 \\
= & 0.2003 \times 100 \\
= & 20.0 \%
\end{aligned}
$$

## ENERGY EXPENDITURE DURING WALKING

Walking represents the major daily physical activity for most persons. Figure 10.2 displays research from five countries on the energy expenditure of men who walked at speeds from 1.5 to $9.5 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ ( 0.9 to 5.9 mph ). The relationship between walking speed and oxygen consumption remains approximately linear between speeds of 3.0 and $5.0 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ (1.9 and 3.1 mph ); at faster speeds, walking economy decreases, and the relationship curves upward with a disproportionate increase in energy expenditure with increasing speed. This explains the reason why, per unit distance traveled,


Figure 10.2 Energy expenditure walking on a level surface at different speeds. The yellow line represents average values from various studies reported in the literature.
faster, less-efficient walking speeds require more total calories expended.

## Influence of Body Mass

One can accurately predict energy expenditure of horizontal walking at speeds between 3.2 and $6.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ ( 2.0 and 4.0 mph ) for men and women who differ in body mass, using an equation based on the combined data in Figure 10.2 and additional studies. ${ }^{1,29}$ These values, listed in Table 10.1, achieve accuracy to within $15 \%$ of the measured energy expenditure. On a daily basis, error estimates of energy expended in walking generally range from 50 to 100 kCal (assuming the person walks

TABLE 10.1 Prediction of Energy Expenditure ( $\mathrm{kCal} \cdot \mathrm{Min}^{-1}$ ) from Speed of Level Walking and Body Mass ${ }^{a}$

| Walking Speed |  | Body Mass |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| mph | $\mathrm{km} \cdot \mathrm{h}^{-1}$ | kg 36 <br> lb 80 | $\begin{gathered} 45 \\ 100 \end{gathered}$ | $\begin{gathered} 54 \\ 120 \end{gathered}$ | $\begin{gathered} 64 \\ 140 \end{gathered}$ | $\begin{gathered} 73 \\ 160 \end{gathered}$ | $\begin{gathered} 82 \\ 180 \end{gathered}$ | $\begin{gathered} 91 \\ 200 \end{gathered}$ |
| 2.0 | 3.22 | 1.9 | 2.2 | 2.6 | 2.9 | 3.2 | 3.5 | 3.8 |
| 2.5 | 4.02 | 2.3 | 2.7 | 3.1 | 3.5 | 3.8 | 4.2 | 4.5 |
| 3.0 | 4.83 | 2.7 | 3.1 | 3.6 | 4.0 | 4.4 | 4.8 | 5.3 |
| 3.5 | 5.63 | 3.1 | 3.6 | 4.2 | 4.6 | 5.0 | 5.4 | 6.1 |
| 4.0 | 6.44 | 3.5 | 4.1 | 4.7 | 5.2 | 5.8 | 6.4 | 7.0 |

[^21]
## TABLE 10.2 Effect of Different Terrain on the Energy Expenditure of Walking Between 5.2 and $5.6 \mathrm{~km} \cdot \mathrm{~h}^{-1}$

## Terrain

## Correction Factor ${ }^{a}$

Paved road (similar to grass track) 0.0
Plowed field 1.5
Hard snow
1.6

Sand dune 1.8
${ }^{a}$ The correction factor is a multiple of the energy expenditure for walking on a paved road or grass track. For example, the energy expenditure of walking in a plowed field equals 1.5 times that of walking on a paved road. Divide by 1.61 to convert to mph.
First entry from Passmore R, Durnin JVGA. Human energy expenditure. Physiol Rev 1955;35:801. Last three entries from Givoni B, Goldman RF. Predicting metabolic energy cost. J Appl Physiol 1971;30:429.

2 hours daily). Extrapolation for light ( $<36 \mathrm{~kg}$ ) and heavy individuals ( $>91 \mathrm{~kg}$ ) is possible, with some loss in accuracy.

## Terrain and Walking Surface

TABLE 10.2 summarizes the influence of terrain and different surfaces on the energy expenditure of walking. Similar economies exist for level walking on a grass track or paved surface. In contrast, walking in the sand requires almost twice the energy expenditure compared to walking on a hard surface because of sand $s$ hindering effects on the forward movement of the foot and the added force required by the calf muscle to compensate for foot slippage. Walking in soft snow triples energy expenditure compared with similar walking on a treadmill. ${ }^{77}$ A brisk walk (or run) along a beach or in freshly fallen snow provides excellent exercise stress to burn additional calories or improve physiologic fitness. ${ }^{75}$

Persons generate essentially the same energy expenditure walking on a firm, level surface or walking on a treadmill at an equivalent speed and distance. ${ }^{67}$ Such results lend support to laboratory data to quantify human energy expenditure in real-life situations.

## Downhill Walking

Walking the downhill portion of a mountain hike or golf course provides welcome relief compared with the uphill segment. Downhill walking (or running) represents a form of negative work because the body s center of mass moves in a downward vertical direction with each step cycle. At the same speed and elevation, it requires less energy to perform eccentric muscle actions (negative work) than the concentric actions of positive work.

Figure 10.3 illustrates the net oxygen consumption for both level and negative grade walking at constant speeds of


Walking speed=6.3 $\mathrm{km} \cdot \mathrm{h}^{-1} \quad \square$ Walking speed $=5.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$
Figure 10.3 Net oxygen consumption of level ( $0 \%$ grade) and downhill walking at grades between -3 and $-18 \%$ and speeds between 5.4 and $6.3 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. Percent grade reflects the vertical distance moved downward per unit horizontal distance traversed. (From Wanta DM, et al. Metabolic response to graded downhill walking. Med Sci Sports Exerc 1993;25:159.)
either 6.3 or $5.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. Compared with walking on level ground, progressive negative grade walking decreases oxygen consumption down to a $-9 \%$ grade for speeds of $5.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ and $-12 \%$ for speeds of $6.3 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. Energy expenditure begins to increase at the more severe negative grades. The additional energy expenditure to resist or brake the body from gravity s pull while trying to achieve a proper and safe walking rhythm increases the oxygen consumption for walking down the steeper grades.

## Footwear and Other Distal Leg Loads

It requires considerably more energy to carry weight on the feet or ankles than to carry the same weight on the torso. ${ }^{12} \mathrm{~A}$ weight equal to $1.4 \%$ of body mass placed on the ankles increases the energy expenditure of walking an average of $8 \%$ or nearly 6 times more than with the same weight on the torso. ${ }^{37}$ In a practical sense, wearing boots disproportionately increases the energy expenditure of walking and running compared with the energy expenditure wearing lighter running shoes. Adding an additional 100 g to each shoe increases oxygen consumption during moderate running by $1 \%$. In the design of running shoes, hiking and climbing boots, and work boots traditionally required in mining, forestry, fire fighting, and the military, small changes in shoe weight produce meaningful changes in movement economy and total energy expenditure. ${ }^{34}$ The cushioning properties and longitudinal bending stiffness of shoes also affect walking and running economy. A more flexible and softer-soled running shoe reduced the oxygen consumption (increased economy) of running at a moderate speed by $2.4 \%$ compared with a similar
shoe with a firmer cushioning system, even though the pair of softer-soled shoes weighed an additional $31 \mathrm{~g} .^{32,61,72}$

## Walking

Ankle weights increase the energy expenditure of walking to values usually observed for running. ${ }^{51}$ The effect benefits individuals who use only walking as a low-impact training modality yet require greater energy expenditures than during normal walking. Handheld weights, walking poles (simulating arm action in cross-country skiing), power belts (worn around waist with resistance cords with handles for arm action), weighted vests, and upper-body exercise (swinging the arms) increase the energy expenditure of walking. ${ }^{28,66,68,86}$

Handheld weights and walking poles may disproportionately increase exercise systolic blood pressure, perhaps from the blood pressure elevating effects of upper-body exercise (see Chapter 15, p. 318) and increased intramuscular tension from gripping the object. An augmented blood pressure response contraindicates handheld weights for individuals with existing hypertension or coronary heart disease.

## Running

Considering the relatively small increase in energy expenditure with hand or ankle weights in running, it seems more practical to simply increase the unweighted running speed or distance. This reduces the injury potential from the added impact force imparted by the weights and eliminates discomfort from carrying them. For individuals with orthopedic limitations, in-line skating offers a less-stressful alternative for an equivalent aerobic demand. ${ }^{45,50}$

## INTEGRATIVE QUESTION

What recommendations would you make for exercise mode specific physical activities for aerobic training of individuals with osteoarthritis of the knees?

## Competition Walking

For Olympic-caliber walkers, walking speed during competition averaged $13.0 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ (11.5 to $14.8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ [7.1 to $9.2 \mathrm{mph}]$ ) over distances from 1.6 to 50 km . This represents a relatively fast speed; the world record for the $20-\mathrm{km}$ walk (12.6-mile) for men of 1:17:16 (Vladimir Kanaikin of Russia, 2008; women, Olimpiada Ivanova of Russia, 2008:1:25:41) equals a speed of $15.53 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ ( 9.66 mph$)$ ! Figure 10.4 illustrates that the break point in the economy of locomotion between walking and running ranged between 8.0 and $9.0 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. These data, plus biomechanical evidence, indicate about the same crossover speed-when running becomes more economical than walking-for conventional and competitive styles of walking (Fig. 10.5). The preferred transition speed of 7.23 (nonrunners) and $7.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ (runners) is slower than the energetically optimal speed, and these speeds


## $\square$ Wakning Running

Figure 10.4 Relationship between oxygen consumption and horizontal velocity for walking and running in competition walkers. (Adapted from Menier DR, Pugh LGCE. The relation of oxygen intake and velocity of walking and running in competition walkers. J Physiol 1968;197:717.)
remain independent of training state or aerobic capacity. ${ }^{70}$ In addition, treadmill walking at competition speeds produced only slightly lower oxygen consumptions for race-walkers than their highest oxygen consumptions during treadmill running. A linear relationship existed between oxygen consumption and walking at speeds above 8 km per hour ( 5.0 mph ), but the slope of the line was twice as steep compared to running at the same speeds. The athletes could walk at velocities of nearly


Figure 10.5 Relationship between oxygen consumption and speed of horizontal walking and running in men and women. Different colored lines represent values from various research studies. (From Falls HB, Humphrey LD. Energy cost of running and walking in young women. Med Sci Sports 1976;8:9.)
$16 \mathrm{~km} \cdot \mathrm{~h}^{-1}(9.9 \mathrm{mph})$. The economy of walking faster than $8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ equaled only one-half the economy for running at the same speeds. The attainment of similar values for $\mathrm{VO}_{2 \text { max }}$ during race-walking and running by elite competitors further supports the model for aerobic training specificity because $\mathrm{VO}_{2 \text { max }}$ in untrained subjects during walking generally remains 5 to $15 \%$ below running values. ${ }^{33,48}$

Competition walkers achieve high yet uneconomical rates of movement, unattainable with conventional walking, with a distinctive modified walking technique that constrains the athlete to certain movement patterns regardless of walking speed. The athlete must maintain this gait despite progressive decreases in walking economy as exercise duration progresses and fatigue increases. ${ }^{10,11}$ Among elite race-walkers, variations in walking economy contribute more to successful performance than in competitive running. ${ }^{33}$

## ENERGY EXPENDITURE DURING RUNNING

Primary biomechanical factors that determine the energy expenditure of running related to velocity among mammals include the magnitude and rate of muscular force generation to counteract gravity and to operate the springlike properties of the muscle-tendon system. ${ }^{41}$ Energy expenditure for running has been quantified during performance of the actual activity and on a treadmill with precise control of speed and grade. The terms jogging and running reflect qualitative assessments related to speed and strenuousness. At identical submaximal speeds, an endurance athlete runs at a lower percentage of $\mathrm{VO}_{2 \text { max }}$ than an untrained person, even though both maintain similar oxygen consumption rates while running. The demarcation between a jog and a run relates more to the participant s fitness level; a jog for one person represents a run for another.

Independent of fitness, it becomes more economical from an energy expenditure standpoint to discontinue walking and begin running at speeds above about $8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. Figure 10.5 illustrates the relationship between oxygen consumption and horizontal walking and running for men and women at speeds between 4 and $14 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. For data depicted in purple and yellow, the lines relating oxygen consumption and speed intersect at a running speed of $8.0 \mathrm{~km} \cdot \mathrm{~h}^{-1}$; the breakpoint in locomotion economy for competition walkers (shown in red) occurs at about $8.7 \mathrm{~km} \cdot \mathrm{~h}^{-1}$.

## Economy of Running Fast or Slow

The data for running in Figure 10.5 illustrate an important principle about running speed and energy expenditure. The linear relationship between oxygen consumption and running speed signifies that the total energy requirement for running a given distance (in steady rate) is about the same regardless of speed at reasonable intensities. Simply stated, running a mile at 10 mph requires about twice the energy per minute as running a mile at 5 mph ; at the faster speed, completing the mile requires 6 minutes, but running at the slower speed takes
twice as long (about 12 minutes). As such, the net energy expenditure to traverse the mile remains about the same. ${ }^{69}$ Equivalent energy expenditure per mile (regardless of running speed) occurs for horizontal running and for running at a specific grade that ranges from -45 to $+15 \% .{ }^{24,46}$ During horizontal running, the net energy expenditure (i.e., excluding the resting requirement) per kilogram of body mass per kilometer traveled averages 1 kCal or $1 \mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~km}^{-1}$. Thus, the net energy expenditure running 1 km for individuals weighing 78 kg averages 78 kCal , regardless of running speed. Expressed in terms of oxygen consumption ( $5 \mathrm{kCal}=1 \mathrm{~L} \mathrm{O}_{2}$ ), this amounts to 15.6 L of oxygen consumed per kilometer ( $78 \mathrm{kCal} \cdot \mathrm{km}^{-1} \div 5 \mathrm{kCal} \cdot \mathrm{km}^{-1}$ ). Comparisons of net energy expenditure of locomotion per unit distance traveled for walking and running indicate greater energy expenditure when running a given distance. ${ }^{6}$

## INTEGRATIVE QUESTION

An elite 140-lb runner claims she consistently consumes $12,000 \mathrm{kCal}$ daily simply to maintain body weight owing to the strenuousness of her training. Using examples of exercise energy expenditures, discuss whether this level of intake reflects a plausible energy intake.

## Net Energy Expenditure Values

Table 10.3 presents values for net energy expenditure during running for 1 hour at various speeds-expressed in kilometers per hour, miles per hour, and the number of minutes required to complete 1 mile at a specific speed. Bolded values indicate net calories expended running 1 mile for a given body mass. As mentioned above, the energy requirement per mile remains fairly constant regardless of running speed. A person who weighs 62 kg requires approximately 2600 kCal (net) to run a 26.2-mile marathon regardless of whether the run takes just over 2 hours, 3 hours, or 4 hours!

Table 10.3 also reveals that the energy expenditure per mile increases proportionately with body mass. A $102-\mathrm{kg}$ person who runs 5 miles each day at a comfortable pace expends 163 kCal for each mile run or 815 kCal for 5 miles. The influence of body mass on exercise energy expenditure supports the role of weight-bearing exercise as an additional caloric stressor for the overly fat person who should increase daily energy expenditure for weight loss (see Focus on Research, p. 215). Increasing or decreasing the speed (within the broad range of steady-rate paces) simply alters the duration of the 5-mile run; it has little effect on the total energy ( $k C a l$ ) expended.

Table 10.4 summarizes data from various studies of energy expenditure for horizontal and grade walking and running on a firm surface. The energy requirement represents multiples of the resting metabolic rate or METs $(1 \mathrm{MET}=$ $3.5 \mathrm{~mL} \mathrm{O}_{2} \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ ).

## IN A PRACTICAL SENSE

## Predicting Energy Expenditure During Treadmill Walking and Running

An almost linear relationship exists between oxygen consumption (energy expenditure) and walking speeds between 3.0 and 5.0 km . $\mathrm{h}^{-1}$ ( 1.9 and 3.1 mph ), and running at speeds faster than 8.0 km . $\mathrm{h}^{-1}$ (5 to 10 mph ; see Fig. 10.5). Adding the resting oxygen consumption to the oxygen requirements of the horizontal and vertical components of the walk or run makes it possible to estimate total (gross) exercise oxygen consumption $\left(\mathrm{VO}_{2}\right)$ and energy expenditure.

## BASIC EQUATION

$\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)=$ Resting component (1 MET $\left[3.5 \mathrm{~mL} \mathrm{O}{ }_{2}\right.$ $\left.\left.\cdot \mathrm{kg}^{-1} \cdot \min ^{-1}\right]\right)+$ Horizontal component (speed, $\left[\mathrm{m} \cdot \min ^{-1}\right] \times$ oxygen consumption of horizontal movement) + Vertical component (percentage grade $\times$ speed $\left[\mathrm{m} \cdot \mathrm{min}^{-1}\right] \times$ oxygen consumption of vertical movement).
[To convert mph to $\mathrm{m} \cdot \mathrm{min}^{-1}$, multiply by 26.82; to convert $m \cdot \min ^{-1}$ to $m p h$, multiply by 0.03728.]

## Walking

Oxygen consumption of the horizontal component of movement equals $0.1 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, and $1.8 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ for the vertical component.

## Running

Oxygen consumption of the horizontal component of movement equals $0.2 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, and $0.9 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ for the vertical component.

## PREDICTING ENERGY EXPENDITURE OF TREADMILL WALKING

## Problem

A $55-\mathrm{kg}$ person walks on a treadmill at $2.8 \mathrm{mph}(2.8 \times 26.82=$ $75 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ ) up a $4 \%$ grade. Calculate (1) $\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1}\right.$. $\left.\mathrm{min}^{-1}\right)$, (2) METs, and (3) energy expenditure ( $\mathrm{kCal} \cdot \min ^{-1}$ ).
[Note: Express \% grade as a decimal value; i.e., $4 \%$ grade. $=0.04$ ]

## Solution

1. $\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)=$ Resting component + Horizontal
component + Vertical component
$\mathrm{VO}_{2}=$ Resting $\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)$
$+\left[\right.$ speed $\left.\left(\mathrm{m} \cdot \mathrm{min}^{-1}\right) \times 0.1 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}\right]$
$+\left[\%\right.$ grade $\times \operatorname{speed}\left(\mathrm{m} \cdot \mathrm{min}^{-1}\right)$
$\left.\times 1.8 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right]$
$=3.5+(75 \times 0.1)+(0.04 \times 75 \times 1.8)$
$=3.5+7.5+5.4$
$=16.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$

$$
\begin{aligned}
& \text { 2. } \begin{aligned}
\mathrm{METs}= & \mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right) \\
& \div 3.5 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1} \\
= & 16.4 \div \\
= & 4.5 \\
\text { 3. } \mathrm{kCaI} \cdot \mathrm{~min}^{-1}= & \mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right) \\
& \times{\mathrm{Body} \mathrm{mass}(\mathrm{~kg}) \times 5.05 \mathrm{kCal} \cdot \mathrm{LO}_{2}^{-1}}_{=} \\
& 16.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1} \\
& \times 55 \mathrm{~kg} \times 5.05 \mathrm{kCal} \cdot \mathrm{~L}^{-1} \\
= & 0.902 \mathrm{~L} \cdot \mathrm{~min}^{-1} \times 5.05 \mathrm{kCaI} \cdot \mathrm{~L}^{-1} \\
= & 4.6
\end{aligned} . \begin{aligned}
\\
\end{aligned} \\
&
\end{aligned}
$$

## PREDICTING ENERGY EXPENDITURE OF TREADMILL RUNNING

## Problem

A $55-\mathrm{kg}$ person runs on a treadmill at $5.4 \mathrm{mph}(5.4 \times 26.82=$ $145 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ ) up a $6 \%$ grade. Calculate (1) $\mathrm{VO}_{2}$ in $\mathrm{mL} \cdot \mathrm{kg}^{-1}$. $\min ^{-1}$, (2) METs, and (3) energy expenditure ( $\mathrm{kCal} \cdot \mathrm{min}^{-1}$ ).

## Solution

```
1. \(\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)=\) Resting component + Horizontal
    component + Vertical component
    \(\mathrm{VO}_{2}=\) Resting \(\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)\)
        \(+\left[\operatorname{speed}\left(\mathrm{m} \cdot \mathrm{min}^{-1}\right)\right.\)
        \(\left.\times 0.2 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right]\)
        \(+\left[\%\right.\) grade \(\times \operatorname{speed}\left(m \cdot \min ^{-1}\right)\)
        \(\left.\times 0.9 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right]\)
        \(=3.5+(145 \times 0.2)+(0.06 \times 145 \times 0.9)\)
        \(=3.5+29.0+7.83\)
        \(=40.33 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\)
2. \(\mathrm{METs}=\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\right)\)
            \(\times 3.5 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\)
    \(=40.33 \div 3.5\)
    \(=11.5\)
3. \(\mathrm{kCal} \cdot \min ^{-1}=\mathrm{VO}_{2}\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}\right)\)
        \(\times\) Body mass (kg)
        \(\times 5.05 \mathrm{kCal} \cdot \mathrm{LO}_{2}{ }^{-1}\)
        \(=40.33 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}\)
        \(\times 55 \mathrm{~kg} \times 5.05 \mathrm{kCal} \cdot \mathrm{L}^{-1}\)
        \(=2.22 \mathrm{~L} \cdot \mathrm{~min}^{-1} \times 5.05 \mathrm{kCal} \cdot \mathrm{L}^{-1}\)
        \(=11.2\)
```

The third option may seem obvious for increasing running speed, but several experiments have provided objective data concerning this alternative.

Research in 1944 evaluated the stride pattern for the Danish champion in 5 - and $10-\mathrm{km}$ running events. ${ }^{8}$ At a running speed of $9.3 \mathrm{~km} \cdot \mathrm{~h}^{-1}$, this athlete s stride frequency equaled 160 per minute, with a corresponding stride length of 97 cm . When running speed increased $91 \%$ to $17.8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$,

TABLE 10.3 Net Energy Expenditure Per Hour of Horizontal Running Related to Velocity and Body Mass ${ }^{a}$

| Body Mass |  | $\mathbf{k m} \cdot \mathbf{h}^{-1 b} \mathbf{m p h}$ min per mile $k C a l$ per mile | $\begin{gathered} 8 \\ 4.97 \\ 12: 00 \end{gathered}$ | $\begin{gathered} 9 \\ 5.60 \\ 10: 43 \end{gathered}$ | $\begin{gathered} 10 \\ 6.20 \\ 9: 41 \end{gathered}$ | $\begin{gathered} 11 \\ 6.84 \\ 8: 46 \end{gathered}$ | $\begin{gathered} 12 \\ 7.46 \\ 8: 02 \end{gathered}$ | $\begin{gathered} 13 \\ 8.08 \\ 7: 26 \end{gathered}$ | $\begin{gathered} 14 \\ 8.70 \\ 6: 54 \end{gathered}$ | $\begin{gathered} 15 \\ 9.32 \\ 6: 26 \end{gathered}$ | $\begin{gathered} 16 \\ 9.94 \\ 6: 02 \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| (kg) | (lb) |  |  |  |  |  |  |  |  |  |  |
| 50 | 110 | 80 | 400 | 450 | 500 | 550 | 600 | 650 | 700 | 750 | 800 |
| 54 | 119 | 86 | 432 | 486 | 540 | 594 | 648 | 702 | 756 | 810 | 864 |
| 58 | 128 | 93 | 464 | 522 | 580 | 638 | 696 | 754 | 812 | 870 | 928 |
| 62 | 137 | 99 | 496 | 558 | 620 | 682 | 744 | 806 | 868 | 930 | 992 |
| 66 | 146 | 106 | 528 | 594 | 660 | 726 | 792 | 858 | 924 | 990 | 1056 |
| 70 | 154 | 112 | 560 | 630 | 700 | 770 | 840 | 910 | 980 | 1050 | 1120 |
| 74 | 163 | 118 | 592 | 666 | 740 | 814 | 888 | 962 | 1036 | 1110 | 1184 |
| 78 | 172 | 125 | 624 | 702 | 780 | 858 | 936 | 1014 | 1092 | 1170 | 1248 |
| 82 | 181 | 131 | 656 | 738 | 820 | 902 | 984 | 1066 | 1148 | 1230 | 1312 |
| 86 | 190 | 138 | 688 | 774 | 860 | 946 | 1032 | 1118 | 1204 | 1290 | 1376 |
| 90 | 199 | 144 | 720 | 810 | 900 | 990 | 1080 | 1170 | 1260 | 1350 | 1440 |
| 94 | 207 | 150 | 752 | 846 | 940 | 1034 | 1128 | 1222 | 1316 | 1410 | 1504 |
| 98 | 216 | 157 | 784 | 882 | 980 | 1078 | 1176 | 1274 | 1372 | 1470 | 1568 |
| 102 | 225 | 163 | 816 | 918 | 1020 | 1122 | 1224 | 1326 | 1428 | 1530 | 1632 |
| 106 | 234 | 170 | 848 | 954 | 1060 | 1166 | 1272 | 1378 | 1484 | 1590 | 1696 |

${ }^{a}$ Interpret the table as follows: For a 50-kg person, the net energy expenditure for running for 1 hour at $8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ or 4.97 mph equals 400 kCal ; this speed represents a 12 -minute per mile pace. Thus, 5 miles would be run in 1 hour and 400 kCal would be expended. Increasing the pace to $12 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ expends 600 kCal during the hour of running.
${ }^{b}$ Running speeds are expressed as kilometers per hour $\left(\mathrm{km} \cdot \mathrm{h}^{-1}\right.$ ), miles per hour ( mph ), and minutes required to complete each mile (min per mile). The values in boldface type are net calories expended to run 1 mile for a given body mass, independent of running speed.

TABLE 10.4 Energy Requirements (METs) for Horizontal and Grade Walking and Running on a Solid Surface
Horizontal and Grade Walking

|  | mph | $\mathbf{1 . 7}$ | $\mathbf{2 . 0}$ | $\mathbf{2 . 5}$ | $\mathbf{3 . 0}$ | $\mathbf{3 . 4}$ | $\mathbf{3 . 7 5}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| \% Grade | $\mathbf{m} \cdot \mathbf{m i n}^{\mathbf{- 1}}$ | $\mathbf{4 5 . 6}$ | $\mathbf{5 3 . 7}$ | $\mathbf{6 7 . 0}$ | $\mathbf{8 0 . 5}$ | $\mathbf{9 1 . 2}$ | $\mathbf{1 0 0 . 5}$ |
| 0 |  | 2.3 | 2.5 | 2.9 | 3.3 | 3.6 | 3.9 |
| 2.5 |  | 2.9 | 3.2 | 3.8 | 4.3 | 4.8 | 5.2 |
| 5.0 |  | 3.5 | 3.9 | 4.6 | 5.4 | 5.9 | 6.5 |
| 7.5 |  | 4.1 | 4.6 | 5.5 | 6.4 | 7.1 | 7.8 |
| 10.0 |  | 4.6 | 5.3 | 6.3 | 7.4 | 8.3 | 9.1 |
| 12.5 |  | 5.2 | 6.0 | 7.2 | 8.5 | 9.5 | 10.4 |
| 15.0 |  | 5.8 | 6.6 | 8.1 | 9.5 | 10.6 | 11.7 |
| 17.5 |  | 6.4 | 7.3 | 8.9 | 10.5 | 11.8 | 12.9 |
| 20.0 |  | 7.0 | 8.0 | 9.8 | 11.6 | 13.0 | 14.2 |
| 22.5 |  | 8.2 | 9.7 | 10.6 | 12.6 | 14.2 | 15.5 |
| 25.0 |  |  |  |  |  | 13.6 | 15.3 |

Horizontal and Grade Jogging/Running

|  | $\mathbf{m p h}$ | $\mathbf{5}$ | $\mathbf{6}$ | $\mathbf{7}$ | $\mathbf{7 . 5}$ | $\mathbf{8}$ | $\mathbf{9}$ | $\mathbf{1 0}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| \% Grade | $\mathbf{m} \cdot \mathbf{m i n}^{\mathbf{1}}$ | $\mathbf{1 3 4}$ | $\mathbf{1 6 1}$ | $\mathbf{1 8 8}$ | $\mathbf{2 0 1}$ | $\mathbf{2 1 5}$ | $\mathbf{2 4 1}$ | $\mathbf{2 6 8}$ |
| 0 |  | 8.6 | 10.2 | 11.7 | 12.5 | 13.3 | 14.8 | 16.3 |
| 2.5 |  | 10.3 | 12.3 | 14.1 | 15.1 | 16.1 | 17.9 | 19.7 |
| 5.0 |  | 12.0 | 14.3 | 16.5 | 17.7 | 18.8 |  |  |
| 7.5 |  | 13.9 | 16.4 | 18.9 |  |  |  |  |
| 10.0 |  | 15.5 | 18.5 |  |  |  |  |  |

Modified from ACSM guidelines for exercise testing and prescription, 8th ed. Baltimore: Lippincott Williams \& Wilkins, 2010.

## FOCUS ON RESEARCH

## It Costs More Energy to Move More

Mahadeva $K$, et al. Individual variations in the metabolic cost of standardized exercises: the effects of food, age, sex and race. J Physiol 1953;121:225.
> Few early experiments in human energy metabolism dealt with energy requirements during exercise, particularly the influence of body size, age, gender, and skill. We now know that such contributing factors serve an important purpose for exercise prescription and estimating energy expenditure to adjust energy balance for weight loss and weight maintenance.

Mahadeva and colleagues conducted one of the first large-scale energy expenditure studies that focused attention on energy expenditure in two common exercise forms: stepping that produces measurable external work in raising body mass and walking on the level at a constant speed. The researchers made multiple observations on 50 men and women, aged 13 to 79 years, of diverse ethnic backgrounds, whose body mass ranged from 48 to 110 kg . Measurements included basal and resting metabolism with the Douglas bag method of open-circuit spirometry. Exercise studies used the portable spirometer (see Fig. 8.4). Subjects stepped to a metronome cadence of 15 up-and-down cycles per minute for 10 minutes on a $25.4-\mathrm{cm}$ stool and walked on an indoor track for 10 min utes at $4.8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$.

The two graphs show the relationship and corresponding prediction (regression) line between energy expenditure and body mass for each activity ( kCal , energy expenditure per 10 min ; $M$, body mass in kg ). Energy expenditure in walking and stepping varied directly with body mass. Separate analyses showed that age, gender, ethnicity, and previous diet contributed little to predicting energy expenditure of the activities. This pioneering work showed that body mass primarily determines the energy expended in nonskilled physical activities that require transporting one s body mass (i.e., weight-bearing
exercise). We now can accurately predict energy expenditure during steady-rate walking, running, and stepping exercise simply from knowledge of exercise intensity and body mass.


Walking $\lceil$ Stepping
Top. Energy expenditure in kilocalories per 10 minutes as a function of body mass during walking at 3 mph . Bottom. Energy expenditure in kilocalories per 10 minutes as a function of body mass during stepping. The dashed lines show twice the standard error of estimate.
stride frequency increased only $10 \%$, to 176 per minute, whereas stride length increased $83 \%$, to 168 cm . Figure 10.6A displays the interaction between stride frequency and stride length as running speed increases. Doubling speed from 10 to $20 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ increases stride length by $85 \%$, whereas stride frequency increases only about $9 \%$. Running at speeds above $23 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ occurs mainly by increasing stride frequency. As a general rule, running speed increases mainly by lengthening the stride: At faster speeds stride frequency becomes important. Relying on increasing length of the stroke cycle,
not frequency, to achieve rapid speeds in endurance performance also occurs among top-flight kayakers, rowers, crosscountry skiers, and speed skaters.

## Competition Walking

A competitive walker does not increase speed the same way as a runner. Figure 10.6B illustrates the stride length stride frequency relationship for an Olympic 10-km medal winner who walked at speeds from 10 to $14.4 \mathrm{~km} \cdot \mathrm{~h}^{-1}$.


Figure 10.6 A. Stride frequency and stride length as a function of running speed. B. Data for an Olympic walker during race-walking. (From Hogberg P. Length of stride, stride frequency, flight period and maximum distance between the feet during running with different speeds. Int Z Angew Physiol 1952;14:431.)

When walking speed increased within this range, stride frequency increased by $27 \%$ and stride length increased by $13 \%$. Faster speeds produced an even greater increase in stride frequency. Unlike running, in which the body glides through the air, competitive race-walking requires that the back foot remain on the ground until the front foot makes contact. Thus, lengthening the stride becomes a difficult and ineffective way to increase speed. Involving the trunk and arm musculature to move the leg forward rapidly requires additional energy expenditure; this explains the poorer economy for walking than running at speeds above 8 or $9 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ (see Fig. 10.4).

## Optimum Stride Length

Each person runs at a constant speed with an optimum combination of stride length and stride frequency. This optimum depends largely on the person s mechanics, or style, of running and cannot be determined from body measurements. ${ }^{16}$ Nevertheless, energy expenditure increases more for overstriding than for understriding. Figure 10.7 relates oxygen consumption to different stride lengths altered by a subject running at the relatively fast speed of $14 \mathrm{~km} \cdot \mathrm{~h}^{-1}$.

For this runner, a stride length of 135 cm produced the lowest oxygen consumption ( $3.35 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ ). When stride length decreased to 118 cm , oxygen consumption increased $8 \%$; lengthening the distance between steps to 153 cm increased oxygen consumption by $12 \%$. The inset graph shows a similar pattern for oxygen consumption when running speed increased to $16 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ and stride lengths varied between 135 and 169 cm . Decreasing this runner s stride length from the optimum of 149 cm to 135 cm increased oxygen con-
sumption by $4.1 \%$; lengthening the stride to 169 cm increased aerobic energy expenditure nearly $13 \%$. As one might expect, the stride length selected by the subject (marked in the figure by the solid red circle) produced the most economical stride length (lowest $\mathrm{VO}_{2}$ ). Lengthening the stride above the optimum produced a larger increase in oxygen consumption than a shorter-than-optimum length. Urging a runner who shows signs of fatigue to lengthen your stride! to maintain speed actually proves counterproductive in terms of economy of effort and exercise performance.

Well-trained runners should run at the stride length they have selected through years of running. In keeping with the concept that the body attempts to achieve a level of minimum effort, a self-selected stride length and frequency generally produce the most economical running performance. This reflects an individual s unique body size, inertia of limb segments, and anatomic development. ${ }^{15,52,53}$ No best style characterizes elite runners. Biomechanical analysis may help the athlete correct minor irregularities in movement patterns while running. For the competitive runner, any minor improvement in movement economy generally improves performance.

## Running Economy: Children and Adults, Trained and Untrained

Boys and girls are less economical runners than adults; they require 20 to $30 \%$ more oxygen per unit body mass to run at a particular speed..$^{2,40,60}$ Consequently, adult models to predict energy expenditure during weight-bearing locomotion fail to account for the increased (and changing) energy expenditures in children and adolescents. ${ }^{35,59}$


Figure 10.7 Oxygen consumption while running at $14 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ affected by different stride lengths. The inset graph plots oxygen consumption at a faster speed of $16 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. (From Hogberg P. Length of stride, stride frequency, flight period and maximum distance between the feet during running with different speeds. Int Z Angew Physiol 1952;14:431.)

Figure 10.8 illustrates the relationship between walking and running speeds (speeds between 2 and 8 mph ) and oxygen consumption (A) and energy expenditure (B) in male and female adolescent volunteers. Despite the higher oxygen consumption and energy expenditure values during walking and running for adolescents than in adults (depicted in Fig. 10.5), the shape of the curves for both groups remains remarkably similar.

Increased energy expenditure resulting in reduced economy among children and adolescents in weight-bearing exercise has been attributed to a larger ratio of surface area to body mass, greater stride frequencies, and shorter stride lengths and to differences in anthropometric variables and body mechanics that reduce movement economy. ${ }^{30,71}$ Figure 10.9B illustrates that running economy improves steadily during years 10 through 18 . Poor running economy among young children partly explains their inferior performance in distance running compared with adults, and their progressive performance improvement through adolescence, while aerobic capacity $\left(\mathrm{mL} \mathrm{O}_{2} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}\right.$; Fig. 10.9A) remains relatively unchanged throughout this period. Consequently, improvement during the growth years in weight-bearing exercise tests like the 1 -mile walk-run do not necessarily imply concomitant improvement in $\mathrm{VO}_{2 \max } .{ }^{23}$

## INTEGRATIVE QUESTION

Discuss the practical implications of knowing that children demonstrate lower economy for walking and running than adults.

Elite adolescent and adult endurance runners generally have lower oxygen consumptions when running at a particular speed than less trained or less successful age-matched counterparts. ${ }^{38,58}$ For trained runners, economy values and biomechanical characteristics during running remain fairly stable from day to day, even during high-intensity exercise, with probably no difference between genders. ${ }^{25,55,56}$

## Air Resistance

Anyone who has run into a headwind knows it requires greater energy to maintain a given pace than running in calm air or with wind at one s back. The effect of air resistance on energy expenditure of running varies with three factors:

1. Air density
2. Runner s projected surface area
3. Square of wind velocity

Depending on speed, overcoming air resistance requires 3 to $9 \%$ of the total energy expenditure of running in calm air. ${ }^{64}$ Running into a headwind creates an additional energy expense. Figure 10.10 shows that the oxygen consumption while running at $15.9 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ in calm conditions averaged $2.92 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. This increased $5.5 \%$ to $3.09 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ against a $16-\mathrm{km} \cdot \mathrm{h}^{-1}$ headwind, and further to $4.1 \mathrm{~L} \cdot \min ^{-1}$ when running against the strongest wind $\left(66 \mathrm{~km} \cdot \mathrm{~h}^{-1} ; 41 \mathrm{mph}\right)$ an additional $41 \%$ expenditure of energy to maintain running velocity!

Some have argued that the negative effects of running into a headwind are counterbalanced during the return with a tailwind. This does not occur because the energy expenditure



Girls walking Girls runningBoys walkingBoys running

Figure 10.8 Relationship between walking speed and running speed and oxygen consumption (A) and energy expenditure ( $B$ ) in adolescent boys ( $N=47$ ) and girls ( $\mathrm{N}=35$ ). The white line represents the curve of best fit for walking; the yellow line represents the best-fit line for running. (From Walker JL, et al. The energy cost of horizontal walking and running in adolescents. Med Sci Sports Exerc 1999;31:311.)


Figure 10.9 Effects of age during childhood and adolescence on (A) aerobic capacity and (B) submaximal oxygen consumption during running at $202 \mathrm{~m} \cdot \mathrm{~min}^{-1}$. (Adapted from Daniels J, et al. Differences and changes in $\mathrm{VO}_{2}$ among runners 10 to 18 years of age. Med Sci Sports 1978;10:200.)


Figure 10.10 Oxygen consumption as a function of the square of the wind velocity while running at $15.9 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ against various headwinds. (From Pugh LGCE. Oxygen intake and treadmill running with observations on the effect of air resistance. J Physiol 1970;207:823.)
of cutting through a headwind exceeds the reduced oxygen consumption with an equivalent wind velocity at one s back. Wind tunnel tests show that clothing modification or even trimming one s hair improves aerodynamics and reduces the effects of air resistance up to $6 \%$. A reduction of this magnitude translates into improved running performance, particularly for elite athletes. Wind velocity has less effect on energy expenditure at higher altitudes than at sea level because of the lower air density at higher elevations. Moderate altitude lowers the oxygen consumption of competitive ice skating at a given speed compared with sea level. ${ }^{3}$ An altitude effect also applies to the energy expenditure of running, cross-country skiing, and cycling.

## Drafting: A Wise Position

The negative effect of air resistance and headwind on the energy expenditure of running confirms the wisdom of athletes who choose to run in a more aerodynamically desirable position directly behind a competitor. This technique, called drafting, maintains a sheltered position for the person taking advantage of it. Running 1 m behind another runner at a speed of $21.6 \mathrm{~km} \cdot \mathrm{~h}^{-1}$, for example, decreases total energy expenditure by about $7 \% .^{63}$ The beneficial effect of drafting on economy of effort also occurs for cross-country skiing, short-track speed skating, and bicycling. ${ }^{7,27,73}$ Bicycling at $40 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ on a calm day requires generation of about $90 \%$ of the total exercise power simply to overcome air resistance. At this speed, energy expenditure decreases 26 to $38 \%$ when a competitor closely follows another cyclist. ${ }^{42}$

For elite speed skaters, drafting (within 1 m of the leader) during controlled-pace 4-minute skating trials lowers exercise heart rate and blood lactate concentration. ${ }^{73}$ A reduced level of exercise stress with drafting should theoretically give the competitor an additional energy reserve for the sprint to the finish. When triathletes draft during the cycling leg of a sprint-distance triathlon ( $0.75-\mathrm{km}$ swim, $20-\mathrm{km}$ bike, $5-\mathrm{km}$ run), oxygen consumptions, heart rates, and blood lactate concentrations remain lower than when the athletes cycle at the same speed without drafting. ${ }^{36}$ These physiologic benefits translate into improved subsequent performance as maximal running speed after biking in the drafting situation is faster than running performance in no-draft trials.

More modern equipment also plays a role. For elite cyclists, helmets now weigh 5.64 ounces, or less than a full can of soda. Helmet shape reduces drag by directing wind over the head and past the rider s back when leaning forward; adding dimples to the jersey reduces the drag, and the Dri-Fit microfiber polyester sucks moisture away from the body to facilitate a cooler and drier ride. When these economyenhancing and thermal-optimizing modifications to equipment combine with a physiologic capacity of a seven-time Tour de France Champion (oversized heart that pumps out nearly 34 L of blood per minute [versus 19 L for the average person], $\mathrm{VO}_{2 \max }$ of $83 \cdot \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, and exceptionally high blood lactate threshold), the ingredients exist for world-class performance. ${ }^{20}$

| TABLE 10.5 | Comparison of Average Metabolic Responses During Treadmill and Track Running |  |  |
| :---: | :---: | :---: | :---: |
| Measurement | Treadmill | Track | Difference |
| Submaximal Exercise |  |  |  |
| Oxygen consumption, $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \min ^{-1}$ | 42.2 | 42.7 | 0.5 |
| Respiratory exchange ratio | 0.89 | 0.87 | -0.02 |
| Running speed, $\mathrm{m} \cdot \mathrm{min}^{-1}$ | 213.7 | 216.8 | 3.1 |
| Maximal Exercise |  |  |  |
| Oxygen consumption, $\mathrm{L} \cdot \min ^{-1}$ | 4.40 | 4.44 | 0.04 |
| $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | 66.9 | 66.3 | -0.6 |
| Ventilation, $\mathrm{L} \cdot \mathrm{min}^{-1}$, BTPS | 142.5 | 146.5 | 4.0 |
| Respiratory exchange ratio | 1.15 | 1.11 | 20.04 |

Adapted from McMiken DF, Daniels JT. Aerobic requirements and maximum aerobic power in treadmill and track running. Med Sci Sports 1976;8:14.

## Treadmill Versus Track Running

The treadmill provides the primary exercise mode to evaluate the physiology of running. One might question the validity of this procedure for determining energy metabolism during running and relating it to competitive track performance. For example, does the energy required to run at a given treadmill speed equal that required to run on a track in calm weather? To answer this question, eight distance runners ran on a treadmill and track under calm air conditions at three submaximal speeds of $180 \mathrm{~m} \cdot \mathrm{~min}^{-1}, 210 \mathrm{~m} \cdot \mathrm{~min}^{-1}$, and $260 \mathrm{~m} \cdot \mathrm{~min}^{-1}$. Graded exercise tests determined possible differences between treadmill and track running on maximal oxygen consumption. TABLE 10.5 summarizes the results for one submaximal running speed and maximal exercise.

From a practical standpoint, no measurable differences emerged in the energy requirements of submaximal running (up to $286 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ ) on the treadmill and track, either on level or up grade, or between the $\mathrm{VO}_{2 \max }$ in both exercise modes. The possibility exists that at the faster speeds achieved by elite endurance runners, the impact of air resistance on a calm day increases the oxygen consumption in track running compared with stationary treadmill running at the same fast speed. This certainly occurs in activities requiring the athlete to move at high velocities in cycling and speed skating, in which the retarding effects of air resistance become considerable.

## Marathon Running

The current (as of June 2009) world marathon record is 2 h:03 min:59 s (H. Gebrselasse of Ethiopia, September 28, 2007). This average speed of 4 min:44 s per mile over the 26.2-mile course represents a truly outstanding achievement in human exercise capacity. Not only does this blistering pace require a steady-rate oxygen consumption that exceeds the
aerobic capacity of most male college students, it also demands that the marathoner sustain 80 to $90 \%$ of $\mathrm{VO}_{2 \max }$ for just over 2 hours!

Researchers measured two distance runners during a marathon to assess energy expenditure each minute and the total expenditure of the run. ${ }^{47}$ They determined oxygen consumption every 3 miles using open-circuit spirometry (Chapter 8). Marathon times were $2 \mathrm{~h}: 36 \mathrm{~min}: 34 \mathrm{~s}\left(\mathrm{VO}_{2 \max }=70.5 \mathrm{~mL}\right.$. $\left.\mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}\right)$ and $2 \mathrm{~h}: 39 \min : 28 \mathrm{~s}\left(\mathrm{VO}_{2 \max }=73.9 \mathrm{~mL} \cdot \mathrm{~kg}^{-1}\right.$. $\min ^{-1}$ ). The first runner maintained an average speed of $16.2 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ that required an oxygen consumption equal to $80 \%$ of $\mathrm{VO}_{2 \max }$. For the second runner, who averaged a slower speed of $16.0 \mathrm{~km} \cdot \mathrm{~h}^{-1}$, the aerobic component averaged $78.3 \%$ of maximum. For both men, the total energy required to run the marathon ranged between 2300 and 2400 kCal .

## SWIMMING

Swimming differs in several important aspects from walking or running. One obvious difference entails expenditure of energy to maintain buoyancy while simultaneously generating horizontal movement by using arms and legs, either in combination or separately. Other differences include requirements for overcoming the considerable drag forces that impede a swimmer s forward movement. The amount of drag depends on the fluid medium and the swimmer s size, shape, and velocity. These factors contribute to a mechanical efficiency in front-crawl swimming that ranges between only 5 and $9.5 \% .^{83}$ A considerably lower mechanical efficiency makes the energy expenditure during swimming a given distance average about four times more than the energy expenditure running the same distance.

## Methods of Measurement

Subjects need not breathe for short swims of 25 yards at different velocities. Oxygen consumption during a 20- to 40-minute recovery provides an estimate of energy expenditure. For longer swims, including 12- to 14 -hour endurance events, one can compute energy expenditure from oxygen consumption measured with open-circuit spirometry during portions of the swim. In studies conducted in the pool, pacer lights alongside the pool set swimming velocity, and the researcher walks alongside the swimmer and carries portable gas-collection equipment (Fig. 10.11D). ${ }^{39}$ For another form of swimming exercise illustrated in Figure 10.11A, the subject remains stationary while attached or tethered to a cable and pulley system by a belt worn around the waist. Periodic increases in the weight stack attached to the cable force the swimmer to exert greater effort to maintain a constant body position. Figure 10.11B and C show a swimmer in a flume or swimming treadmill. Water circulates at velocities varying from a slow swimming speed to near-record pace for a freestyle sprint. Aerobic capacity measurements using tethered, free, or flume swimming produce essentially identical values. ${ }^{9}$ Any of these modes of measurement objectively evaluate metabolic and physiologic dynamics and capacities during swimming.

## Energy Expenditure and Drag

The total drag force encountered by a swimmer consists of three components:

1. Wave drag caused by waves that build up in front of and form hollows behind the swimmer moving through the water. This component of drag does not significantly affect swimming at slow velocities, but its influence increases at faster swimming speeds.
2. Skin friction drag produced as water slides over the skin surface. Even at relatively fast swimming velocities, the quantitative contribution of skin friction drag to the total drag remains small. Research supports the common practice of swimmers shaving down to reduce skin friction drag and thereby decrease energy expenditure. ${ }^{76}$
3. Viscous pressure drag caused by the pressure differential created in front of and behind the swimmer, which substantially counters propulsive efforts at slow velocities. Viscous pressure drag forms adjacent to the swimmer from separation of a thin sheet of water or boundary layer. Its effect is reduced for highly skilled swimmers who learn to streamline stroke mechanics. This reduces the separation region by moving it closer to the trailing edge of the water, akin to an oar slicing through water with the blade parallel rather than perpendicular to the water flow.

## Ways to Reduce Effects of Drag Force

Figure 10.12 depicts a curvilinear relationship between body drag and velocity when towing a swimmer through the water. As velocity increases above $0.8 \mathrm{~m} \cdot \mathrm{~s}^{-1}$, drag decreases by supporting the legs with a flotation device that places the body in a more hydrodynamically desirable horizontal position. Generally, drag force averages 2 to 2.5 times more during swimming than passive towing. ${ }^{81}$

Variations in swim suit designs tend to reduce overall drag, with positive effects noted for suits that cover the shoulder to either the ankle or knee and for those that cover only the lower body compared to a conventional suit. ${ }^{17,54}$ Wet suits worn by triathletes during swimming reduce body drag by about $14 \%$, thus lowering oxygen consumption at a given speed. ${ }^{82,84}$ Improved swimming economy largely explains the faster swim times of triathletes who use wet suits. As in running, cross-country skiing, and cycling, drafting in swimming (following up to 50 cm behind the toes of a lead swimmer) reduces drag force, metabolic cost (by 11 to $38 \%$ ), and physiologic demand, ${ }^{4,19}$ and also improves economy in a subsequent cycling session. ${ }^{26}$ This effect enables an endurance swimmer (e.g., triathlete or ocean racer) to conserve energy and possibly improve performance toward the end of competition. Triathletes swimming 400 m swam the total distance $3 \%$ faster in a drafting position with lower blood lactate levels and stroke rates than in the lead position. ${ }^{18}$ Performance changes were related to large reductions in passive drag force in the drafting position; faster and leaner


Figure 10.11 A. Measurement of energy expenditure during tethered swimming. B. and C. Swimming treadmill. An environmental chamber surrounding the swimming treadmill controls atmospheric pressure (and other environmental conditions) during swimming. Using the swimming treadmill, researchers conduct physiologic and biomechanical experiments during swimming that simulate actual performance conditions. The underwater viewing area provides a convenient means for directly observing swimming performance related to stroke mechanics. D. Open-circuit spirometry (bag technique) to measure oxygen consumption during front-crawl swimming. (Schematic and photos of the swimming treadmill courtesy of the United States Swimming International Center for Aquatic Research, Colorado Springs, CO.)
swimmers showed the greatest drag force reduction and performance improvement.

In the 2004 Athens Summer Olympic Games, swimmers wore neck-to-ankle body suits for the first time. Proponents maintain that the technology-driven approach to competitive swimming maximizes swimming economy and allows swimmers to achieve 3\% faster times than those with standard swimsuits.

Kayaking. The energy demands of kayaking largely reflect the resistance provided by the water to the forward movement of the craft. Consequently, drafting (wash riding) behind the leader reduces the energy requirements of paddling between 18 and $32 \% .{ }^{62}$ The assist to forward movement provided by the wash generated by the lead boat improves kayaking economy. This effect decreases resistance and water pressure through which the boat moves.


Figure 10.12 Drag force in three different prone positions related to towing velocity. (From Holm rI. Energy cost of arm stroke, leg kick, and the whole stroke in competitive swimming styles. Eur J Appl Physiol 1974;33:105.)

## Energy Expenditure, Swimming Velocity, and Skill

Elite swimmers swim a particular stroke at a given velocity with lower oxygen consumption (greater economy) than relatively untrained or recreational swimmers. Highly skilled swimmers use more of the energy they generate per stroke to overcome drag forces. Consequently, they cover a greater distance per stroke than less skilled swimmers who waste considerable energy ineffectively moving water. Figure 10.13A compares the oxygen consumptions and velocities for breaststroke, back crawl, and front crawl at three levels of swimming ability. One subject, a recreational swimmer, did not participate in swim training; the trained subject, a top Swedish swimmer, swam on a daily basis; the elite swimmer was a European champion. Except during the breaststroke, the elite swimmer had a lower oxygen consumption at a given speed than trained and untrained swimmers. Figure 10.13B illustrates that the breaststroke required greater oxygen consumption for the trained swimmers at any speed, followed by the backstroke, with the front crawl being the least expensive of the three strokes. The marked accelerations and decelerations within each stroke cycle cause energy expended for the butterfly and breaststroke to nearly double that for
front and back crawl at the same speeds. ${ }^{80}$ At comparable speeds sustained aerobically, the energy expenditure of surface swimming with fins was about $40 \%$ lower than swimming without them. ${ }^{85}$

## Effects of Water Temperature

Relatively cold water places the swimmer under thermal stress. Swimming in colder water initiates different metabolic and cardiovascular adjustments than swimming in warmer water. These responses primarily maintain a stable core temperature by compensating for considerable heat loss from the body, particularly at water temperatures below $25 \mathrm{C}(77 \mathrm{~F})$. Body heat loss occurs most readily in lean swimmers, who lack benefits from the insulatory effects of subcutaneous fat accumulation.

Figure 10.14 illustrates oxygen consumption during breaststroke swimming at water temperatures of 18,26 , and 33 C. Regardless of swimming speed, the highest oxygen consumptions occurred in cold water. The body begins to shiver in cold water to regulate core temperature; this accounts for the higher energy expenditure swimming in lower water temperatures. For individuals of average body composition, optimal water temperature for competitive swimming ranges between 28 and 30 C ( 82 to 86 F ). Within this range, the metabolic heat generated during exercise transfers readily to the water. However, the heat flow gradient from the body is not large enough to stimulate increased energy metabolism (shivering) or reduce core temperature from cold stress.

## Effects of Buoyancy: Men Versus Women

Women of all ages possess, on average, a higher body fat percentage than men. Because fat floats and muscle and bone sink in water, the average woman gains a hydrodynamic lift and expends less energy to stay afloat than the average man. More than likely, gender differences in percentage body fat and thus body buoyancy partially explain the greater swimming economy for women. For example, women swim a given distance at about a $30 \%$ lower total energy expenditure than men. Expressed another way, women achieve higher swimming velocities than men at the same energy expenditure.

Women also show a greater peripheral body fat distribution. This causes their legs and arms to float relatively high in water, making them more streamlined. In contrast, the leaner legs of men tend to swing down and float lower in the water. ${ }^{14}$ Lowering the legs to a deeper position increases body drag and reduces swimming economy (see Fig. 10.12). Enhanced flotation and the females smaller body size, which also reduces drag, contribute to the gender difference in swimming economy. ${ }^{80,81}$ The potential hydrodynamic benefits that women possess become evident during longer distance ocean swims because swimming economy and body insulation contribute to success. For example, the woman s record for swimming the 21-mile English Channel from England to France equals $7 \mathrm{~h}: 25 \mathrm{~min}: 15 \mathrm{~s}$ (Yvetta Hlavacova; Czech Republic, 2006). The men s record (Peter Stoychev; Bulgaria, 2007) equals $6 \mathrm{~h}: 57 \mathrm{~min}: 50 \mathrm{~s}$, a difference of only


Figure 10.13 A. Oxygen consumption related to swimming velocity for the breaststroke, front crawl, and back crawl in subjects at three levels of skill ability. B. Oxygen consumption for two trained swimmers during three competitive strokes. (From Holm r I. Oxygen uptake during swimming in man. J Appl Physiol 1972;33:502.)
6.6\% (http://www.channelswimming.com/swim-list.htm). In several instances, women swam faster than men. In fact, the first woman to swim the Channel (1926) swam $35 \%$ faster than the first male to complete the swim (1875).

## Endurance Swimmers

Distance swimming in ocean water poses a severe metabolic and physiologic challenge. A study of nine English Channel
swimmers included measurements taken under race conditions in a saltwater pool at swimming speeds that ranged from 2.6 to $4.9 \mathrm{~km} \cdot \mathrm{~h}^{-1} .{ }^{65}$ During the race, competitors maintained a constant stroke rate and pace until the last few hours when fatigue set in. From detailed observations of one male subject, the average speed of $2.85 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ during a 12-hour swim required an average oxygen consumption of $1.7 \mathrm{~L} \mathrm{O}_{2} \cdot \mathrm{~min}^{-1}$, or an equivalent energy expenditure of $8.5 \mathrm{kCal} \cdot \mathrm{min}^{-1}$. The gross caloric expenditure for the 12 -hour swim was about 6120 kCal


Figure 10.14 Energy expenditure for the breaststroke at three water temperatures related to swimming velocity. (From Nadel ER, et al. Energy exchanges of swimming man. J Appl Physiol 1974;36:465.)
$(8.5 \mathrm{kCal} \times 60 \mathrm{~min} \times 12 \mathrm{~h})$. The net energy expenditure of swimming the English Channel, assuming a resting energy expenditure of $1.2 \mathrm{kCal} \cdot \mathrm{min}^{-1}\left(0.260 \mathrm{~L} \mathrm{O}_{2} \cdot \mathrm{~min}^{-1}\right)$, exceeded 5200 kCal , or approximately twice the number of calories expended running a marathon.

## INTEGRATIVE QUESTION

Discuss whether swim training improves swimming economy more than run training improves running economy.

## Summary

1. Total or gross energy expenditure includes the resting energy requirement; net energy expenditure represents the energy expenditure of the activity excluding the resting value.
2. Economy of movement refers to the oxygen consumed during steady-rate exercise; mechanical efficiency evaluates the relationship between work accomplished and energy expended doing the work.
3. Walking, running, and cycling produce mechanical efficiencies between 20 and $25 \%$. Efficiencies decrease below $20 \%$ for activities with considerable resistance to movement (drag).
4. A linear relationship exists between walking speed and oxygen consumption at normal walking speeds.

Walking on sand requires about twice the energy as walking on firm surfaces. A proportionately larger energy expenditure exists for heavier persons during such weight-bearing exercises.
5. Running becomes more economical than walking at speeds that exceed $8 \mathrm{~km} \cdot \mathrm{~h}^{-1}$.
6. Handheld and ankle weights can increase the energy expenditure of walking to values similar for running.
7. The total caloric expenditure of running a given distance at steady-rate oxygen consumption remains about the same independent of running speed.
8. Net energy expenditure during horizontal running approximates $1 \mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~km}^{-1}$.
9. Shortening running stride and increasing stride frequency to maintain a constant running speed requires less energy than lengthening stride and reducing frequency.
10. An individual subconsciously selects the combination of stride length and frequency to favor optimal economy of movement (i.e., a level of minimum effort).
11. Energy expended to overcome air resistance accounts for 3 to $9 \%$ of the energy expenditure of running in calm air. This percentage increases considerably when a runner maintains pace while running into a brisk headwind.
12. Children generally require more oxygen to transport their body mass while running than do adults. A relatively lower running economy accounts for the poorer endurance performance of children compared with adults of similar aerobic capacity.
13. Running a given distance or speed on a treadmill requires about the same energy as running on a track under identical environmental conditions.
14. A person expends about four times more energy to swim a given distance than to run the same distance. This occurs because the swimmer expends considerable energy to maintain buoyancy and overcome drag forces that impede forward movement.
15. Elite swimmers expend fewer calories to swim a given stroke at any velocity than less skilled counterparts.
16. Significant gender differences exist in body drag, mechanical efficiency, and net oxygen consumption during swimming. Women swim a given distance at about a $30 \%$ lower energy expenditure than men.

References are available online at
http://thepoint.lww.com/mkk7e.

## On the Internet

Swim Lists: Lists of Successful Solo \& Relay English Channel Swims
http://www.channelswimming.com/swim-list.htm


## CHAPTER ${ }^{11}$

## Individual Differences and Measurement of Energy Capacities

## CHAPTER OBJECTIVES

> Explain specificity and generality applied to exercise performance and physiologic functions
> Outline the anaerobic-to-aerobic exercise energy transfer continuum
> Describe two practical field tests to evaluate power output capacity of the immediate energy system
> Describe a common test to evaluate power output capacity of the short-term energy system
> Explain how motivation, buffering, and exercise training influence the glycolytic energy pathway
> Define maximal oxygen consumption and its physiologic significance
> Differentiate between maximal oxygen consumption and peak oxygen consumption
> Define graded exercise test and list criteria that indicate attainment of a true $\mathrm{VO}_{2 \text { max }}$ during graded exercise testing
> Outline three common treadmill protocols to assess $\mathrm{VO}_{2 \text { max }}$
> Indicate the influence of each of the following six factors on $\mathrm{VO}_{2 \text { max }}$ : mode of exercise, heredity, state of training, gender, body composition, and age
> Describe a walking field test to predict $\mathrm{VO}_{2 \text { max }}$
$>$ List three assumptions when predicting $\mathrm{VO}_{2 \text { max }}$ from submaximal exercise heart rate

## SPECIFICITY VERSUS GENERALITY OF METABOLIC CAPACITY AND EXERCISE PERFORMANCE

The body derives useful energy from anaerobic and aerobic energy metabolic pathways, but the capacity for each form of energy transfer varies considerably among individuals. This between-person variability underlies the concept of individual differences in metabolic capacity. A high $\mathrm{VO}_{2 \max }$ in running, for example, does not necessarily ensure a similarly high $\mathrm{VO}_{2 \max }$ using different muscle groups required in swimming and rowing. That some individuals with high aerobic power in one activity possess above average aerobic power in other activities illustrates the generality principle of metabolic function. The nonoverlapped areas in Figure 11.1 represent specificity of metabolic function, while the three overlapped portions represent generality. In the broadest sense, specificity indicates a low likelihood for an individual to excel in each of a particular sport s sprint, middle-distance, and long-distance competitions. In a more narrow definition of metabolic and physiologic specificity, most individuals do not possess an equally high energy-generating capacity for aerobic activities as different as running (lower-body) and swimming or arm-crank (upper-body) exercises.

Based on the exercise specificity concept, training to achieve a high aerobic power $\left(\mathrm{VO}_{2 \max }\right)$ contributes little to one s capacity to generate energy anaerobically, and vice versa. Ahigh degree of specificity also exists for the effects of exercise training on neuromuscular patterning and demands. Terms such as speed, power, and endurance must be applied precisely within the context of the specific movement patterns and specific metabolic and physiologic requirements of the activity.


Figure 11.1 - Specificity generality of the three systems for energy transfer. When considering only two systems, their overlap represents generality and the remainder specificity.

This chapter evaluates the capacity of the three energytransfer systems discussed in Chapters 6 and 7, with emphasis on individual differences, specificity, and appropriate measurement.

INTEGRATIVE QUESTION
Explain why it is important that a triathlete train in each of the sport s three events.

## OVERVIEW OF ENERGY-TRANSFER CAPACITY DURING EXERCISE

The immediate and short-term energy systems predominantly power all-out exercise for up to 2 minutes. Both systems operate anaerobically. A greater reliance on anaerobic energy exists for fast, short-duration movements or when increasing resistance to movement at a given speed. Figure 11.2 illustrates the relative activation of anaerobic and aerobic energytransfer systems for different durations of all-out exercise. When movement begins at either fast or slow speed, intramuscular high-energy phosphates adenosine triphosphate (ATP) and phosphocreatine ( PCr ) provide immediate energy to power muscle action. Following the first few seconds of movement, glycolytic pathways generate an increasingly greater percentage of energy for ATP resynthesis. Continued exercise places progressively greater demands on the longterm system of aerobic metabolism. All physical activities and sports lend themselves to classification on an anaerobic-to-aerobic continuum. Some activities rely predominantly on


[^22]Figure 11.2 - Three systems of energy transfer and percentage use of their total capacity during all-out exercise of different durations.
a single system of energy transfer, whereas most require activation of more than one energy system, depending on exercise intensity and duration. Performing at a higher intensity but shorter duration of effort requires a markedly increased demand on anaerobic energy transfer.

## ANAEROBIC ENERGY TRANSFER: THE IMMEDIATE AND SHORT-TERM ENERGY SYSTEMS

## Evaluation of the Immediate Energy System: Performance Tests

Football, weightlifting and other short-duration, maximaleffort physical activities that require rapid energy release rely nearly exclusively on energy from the intramuscular highenergy phosphates. Performance tests that maximally activate the ATP PCr energy system serve as practical field tests to evaluate the capacity for immediate energy transfer. Two assumptions underlie use of performance test scores to infer the power-generating capacity of the high-energy phosphates:

1. All ATP at maximal power output regenerates via ATP PCr hydrolysis.
2. Adequate ATP and PCr exist to support maximal performance for about 6 seconds duration.
The term power test generally describes these measures of brief, maximal exercise capacity. Power in this context refers to the time-rate of accomplishing work computed as follows:

$$
P=(F D) \div T
$$

where $F$ equals force generated, $D$ equals distance the force moves, and $T$ represents exercise time or duration. Power is expressed in watts- 1 watt equals $0.73756 \mathrm{ft}-\mathrm{lb} \cdot \mathrm{s}^{-1}$, $0.01433 \mathrm{kCal} \cdot \mathrm{min}^{-1}, 1.341 \times 10^{3} \mathrm{hp}$ (or 0.0013 hp ), or $6.12 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$.

## Stair-Sprinting Power Tests

Researchers have evaluated high-energy phosphate power output by the time required to run up a staircase as fast as possible, taking three steps at a time (Fig. 11.3). External work accomplished consists of total vertical distance traversed up the stairs; this distance for six stairs usually equals 1.05 m . For example, the power output of a $65-\mathrm{kg}$ woman who traverses six steps in 0.52 second computes as follows:

$$
\begin{aligned}
F & =65 \mathrm{~kg} \\
D & =1.05 \mathrm{~m} \\
T & =0.52 \mathrm{~s} \\
\text { Power } & =(65 \mathrm{~kg} \times 1.05 \mathrm{~m}) \div 0.52 \mathrm{~s} \\
& =131.3 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{~s}^{-1}(1287 \text { watts })
\end{aligned}
$$

Body mass influences power in stair-sprinting tests; a heavier person who achieves the same speed as a lighter counterpart necessarily achieves a higher power score. This implies that the heavier person possesses a more highly developed immediate energy system. Unfortunately, no direct evidence justifies this conclusion, thus one must use care


Figure 11.3 - Stair-sprinting power test. The subject begins at point $A$ and runs as fast as possible up a flight of stairs, taking three steps at a time. Electric switch mats placed on the steps record the time needed to cover the distance between stairs 3 and 9 to the nearest 0.01 second. Power output equals the product of the subject s body mass $(F)$ and vertical distance covered ( $D$ ), divided by the time ( $T$ ).
interpreting differences in stair-sprinting power scores and inferring individual differences in ATP PCr energy-transfer capacity among individuals who differ in body weight. The test should be used with individuals of similar body mass or the same individuals before and after specific training designed to develop leg power output from the immediate energy system (assuming no change in body mass).

## INTEGRATIVE QUESTION

Considering training specificity, describe how to test the power output capacity of the immediate energy system of volleyball players, swimmers, and soccer players.

## Jumping-Power Tests

Jump tests, such as the popular Sargent jump-and-reach test or a standing broad jump, often appear in physical fitness test batteries as measures of immediate energy outout. The Sargent jump score reflects the difference between a person s standing reach and maximum vertical jump-and-touch height. The broad jump score consists of the horizontal distance traversed in a leap from a semi-crouched position. Both tests purport to measure leg power, but they probably fail to achieve this goal. For example, jump tests generate power to propel the body from the crouched position only while the feet maintain contact with the surface. This extremely brief period of muscle activation probably does not adequately


Figure 11.4 - Ten consecutive broad-jump performances (with and without arm swing) of collegiate soccer players. Prior to testing, subjects stretched for 3 minutes and performed light calisthenics. Subjects were exhorted to make a maximal effort in all jumps. Improvement for the standing broad jump averaged $7.0 \%$ from trial 1 to trial 10 with arm swing and $15.5 \%$ without arm swing. (Standing long-jump data courtesy of Frank Katch, Human Performance Laboratory, Exercise Science Department, University of Massachusetts, Amherst, 1996.)
evaluate a person s ATP and PCr energy transfer capacity. Also, we are aware of no data to show a relationship between jump-test scores and actual ATP PCr levels or depletion patterns in the primary muscles activated during the jump.

Figure 11.4 displays data for subjects who performed 10 standing broad jumps with and without an arm swing, with a 1-minute rest between jumps. An underestimation of peak power occurs using the scores from only the first 2 or 3 jumps. Whether the progressive increase in power with repeated jumps results from a warming-up effect or improved neuromuscular activation has not been established. From a testing perspective, the important consideration requires administering enough trials to establish a person s true power score. This is best achieved by averaging 2 or 3 jumps after the performance curve plateaus.

## Other Power Performance Tests

Figure 11.2 suggests that any all-out exercise of 6 to 8 seconds probably reflects a person s capacity for immediate power from the high-energy phosphates in the specific muscles activated. Other tests include sprint running or cycling, brief shuttle runs, and localized movements produced by arm cranking.

## Interrelationships Among Power Performance Tests

If the various power tests measure the same general metabolic capacity, then individuals who perform best on one test should rank correspondingly high on a second or third

TABLE 11.1 - Correlations Among Tests Purported to Measure Immediate Anaerobic Power Output from the Intramuscular High-Energy Phosphates ATP and PCr

| Variable | Jump and Reach | Stair-Sprinting |
| :--- | :---: | :---: |
| 40-yard dash | $-0.48^{a}$ | $-0.88^{a}$ |
| Jump and reach | - | $-0.31^{a}$ |

From the Applied Physiology Laboratory, University of Michigan ( $n=31$ males).
${ }^{a}$ Negative correlations mean faster times (lower scores) associate with higher jumps or greater power outputs.
different test. Unfortunately, this does not usually occur to any great extent. Although some individuals who score well on one power performance test tend to score well on another test, a poor relationship generally exists. ${ }^{86}$ Table 11.1 shows the interrelationship (expressed statistically as a correlation coefficient) between several tests purported to measure immediate energy power output. The relationship ranges from poor to good, depending on the test. This indicates some commonality among tests for measuring the immediate energy system. The fairly strong relationship between stair-sprinting power test scores and 40-yard dash scores ( $r=-0.88$ ) indicates that one can obtain almost the same information on short-term power performance through sprint running on a track as the more elaborate procedures required in the stair sprint.

Several factors explain relatively low relationships among the other test scores. First, human exercise performance remains highly task specific. From a metabolic and performance perspective, this means that the best sprint runner does not necessarily rank as the best sprint swimmer, sprint cyclist, stair sprinter, or arm cranker. Although identical metabolic reactions generate energy to power each performance, these reactions occur within the specific muscles activated by exercise. Each specific test also requires different neuromuscular and skill components that introduce variability and specificity into test scores.

Power tests offer an excellent means for self-testing and motivation. The tests also can serve as exercise for training the immediate energy system. For example, football coaches use the 40-yard dash for power training and as a criterion to evaluate movement speed for football. Forty-yard dash test scores may provide relevant information concerning speed in football, even though no data exist to quantify how a 40 -yard sprint in a straight line relates to all of the complex skills and movements involved in game performance, let alone some general factor of overall football ability. A run test of shorter distance (up to 20 yd ) and/or with multiple changes in direction and pacing probably would provide a more appropriate, task-specific performance to assess the likelihood of football success.

## Evaluation of the Immediate Energy System: Physiologic Tests

Several physiologic and biochemical measures evaluate energy-generating capacity of the immediate energy system. These include the following:

1. Size of the intramuscular ATP PCr pool
2. Depletion rates of ATP and PCr in all-out, shortduration exercise

The oxygen deficit computed from the initial phase of the exercise oxygen consumption curve has also been used as an estimate of the immediate energy system. Because it is not a physiologic measure and because of recent understandings of exercise energetics, its use is less common.

ATP and PCr depletion rates provide the most direct estimate and correlate highly with physical performance assessments of the immediate energy system. For example, one experiment determined muscle PCr depletion at different intervals of a $100-\mathrm{m}$ sprint, using the muscle biopsy technique. ${ }^{34}$ Compared with resting values ( $22 \mathrm{mmol} \cdot \mathrm{kg}$ wet weight ${ }^{-1}$ ), PCr decreased by $60 \%$ during the first $40 \mathrm{~m}(<6 \mathrm{~s})$ and only another $20 \%$ for the remainder of the sprint. It remains nearly impossible with current technology to readily obtain precise biochemical data during all-out exercise of brief duration. Researchers must rely on the face validity of the various specific performance measures as satisfactory markers to evaluate capacity for ATP PCr energy transfer in exercise.

## Evaluation of the Short-Term Energy System

Figure 11.2 showed that when all-out exercise continues for longer than a few seconds, the short-term energy system (anaerobic glycolysis) generates increasingly more of the energy for ATP resynthesis. This does not mean that aerobic metabolism is unimportant at this stage of exercise or that oxygen-consuming reactions have not switched on. To the contrary, the contribution of aerobic energy transfer increases early in exercise (Fig. 11.2). ${ }^{82}$ During short-duration maximal exercise, the energy requirement greatly exceeds energy generated by hydrogen oxidation in the respiratory chain. Consequently, anaerobic glycolysis predominates, with large quantities of lactate accumulating in active muscle and ultimately in blood. Blood lactate level provides the most common indicator of activation of the short-term energy system.

Unlike tests for maximal oxygen consumption, no specific criteria exist to indicate that a person has attained maximal anaerobic effort. More than likely, self-motivation and testing environment greatly influence performance on such tests. ${ }^{103}$ Performance test scores show good reproducibility from day to day, particularly under standardized conditions., ${ }^{4,50,62}$

## Anaerobic Power Performance Tests

Performances that activate the short-term energy system require maximal exercise for up to 3 minutes. All-out runs and
stationary cycling have usually assessed anaerobic power, as have shuttle runs and repetitive weightlifting of a certain percentage of maximum capacity. The influence of age, gender, skill, motivation, and body size creates difficulty selecting a suitable criterion test or developing appropriate norms to evaluate anaerobic power. Above-normal intramuscular glycogen levels do not affect exercise test performance or final level of blood lactate accumulation. ${ }^{90}$ Based on the principle of exercise specificity, one should not use a test that requires maximal activation of the leg musculature to assess short-term anaerobic capacity for an upper-body activity like rowing or swimming. The performance test must closely resemble the activity that requires energy capacity assessment. In most cases, the activity itself best serves as the performance test.

In 1973, the Katch test of all-out stationary cycling of short duration estimated the power of the anaerobic energy systems. ${ }^{41}$ Subsequent extension of this work created a stationary bicycle test with frictional resistance against the flywheel preset at a high load ( 6 kg for men; 5 kg for women). Subjects turned as many revolutions as possible in 40 sec onds, with pedal rate continuously recorded with a microswitch assembly. Peak cycling power during any portion of the test (properly reported in watts) represented the subject s anaerobic power, whereas total work accomplished indicated anaerobic capacity (properly reported in joules). A later modification, the Wingate test, involves 30 seconds of supermaximal exercise on either an arm-crank or leg-cycle ergometer. ${ }^{4,106}$ Body mass determines resistance to pedaling (originally set to 0.075 kg per kg body mass but now can exceed 0.12 kg in athletes) applied within 3 seconds after overcoming the initial inertia and unloaded frictional resistance of the ergometer. Peak power represents the highest mechanical power generated during any 3- to 5 -second period of the test; relative power represents peak power divided by body mass. Anaerobic fatigue is the percentage decline in power output during the test and anaerobic capacity is the total work accomplished over the 30 seconds. Rate of fatigue represents the decline in power in relation to the peak value. The Katch and Wingate tests assume that peak power output reflects the energy-generating capacity of the high-energy phosphates, while average power reflects glycolytic capacity.

Confusion regarding use of the the terms power and capacity emerges with use of these tests. Originally, the desire was to create measures of anaerobic exercise performance, similar to aerobic exercise performance, as a power measurement. However, some authors incorrectly use the term capacity to infer total work (joules) but use power scores (joules • $\mathrm{s}^{-1}=$ watts) to represent this entity. The term capacity, in this context to represent anaerobic power, needs to be a power score (much like $\mathrm{VO}_{2 \max }$ ) and not a work score; thus, the correct expression is watts. The joule is used to compute total anaerbobic work.

In a Practical Sense, on page 230, provides the procedures to determine anaerobic power and capacity on the Wingate cycle ergometer test. Table 11.2 presents normative standards for average and peak power outputs in young,

## IN A PRACTICAL SENSE

## Determining Anaerobic Power and Capacity: The Wingate Cycle Ergometer Test

The Wingate cycle ergometer test represents the most popular test to assess anaerobic capacity. Developed at the Wingate Institute in Israel in the 1970s, test scores can reliably determine peak anaerobic power and anaerobic fatigue.

## THE TEST

A mechanically braked bicycle ergometer serves as the testing device. After warming up ( 3 to 5 min ), the subject begins pedaling as fast as possible, without resistance. Within 3 seconds, a fixed resistance is applied to the flywheel; the subject continues to pedal all out for 30 seconds. An electrical or mechanical counter continuously records flywheel revolutions in 5-second intervals. Total work during the 30 seconds computes in joules and power computes as joules • $\mathrm{s}^{-1}$, or watts.

## RESISTANCE

Flywheel resistance equals 0.075 kg per kg body mass. For a $70-\mathrm{kg}$ person, the flywheel resistance would equal 5.25 kg ( $70 \mathrm{~kg} \times$ 0.075 ). Resistance often increases to 0.10 kg per kg body mass or higher (up to 0.12 kg ) when testing power- and sprint-type athletes. The Wingate test was originally designed using the Swedish Monarch cycle ergometer. The unit of resistance was the former standard Swedish unit of force called the kilopond. Measurement of the kilopond (kp) was a cleverly engineered system comprised of a basket containing a weight representing the braking force applied to the flywheel, equal to the weight of the basket and its contents. The standard corresponded to the weight of a 1 kg mass; hence, 1 kp has come to represent 1 kg . The proper unit of force when using the Monarch bike should be kp-m $\cdot \mathrm{min}^{-1}$, not $\mathrm{kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$. When Sweden joined the European Union, they switched to the SI unit of force, the Newton (N). [One kp corresponds to the force exerted by Earth s gravity ( $9.80665 \mathrm{~m} \cdot \mathrm{~s}^{-2}$ ) on 1 kilogram of mass; thus, one kilogram-force equals 9.80665 Newtons (N).]

## TEST SCORES

1. Peak power output (PP) -The highest power output, observed during the first 5 -second exercise interval, indicates the energy-generating capacity of the immediate energy system (intramuscular high-energy phosphates ATP and PCr). PP, expressed in watts ( $1 \mathrm{~W}=6.12 \mathrm{kp}-\mathrm{m} \cdot \min ^{-1}$ ), computes as Force in Newtons (kp resistance $\times$ acceleration due to gravity) $\times$ Distance (number of revolutions $\times$ distance per revolution) $\div$ Time in minutes ( $5 \mathrm{~s}=0.0833 \mathrm{~min}$ ).
2. Relative peak power output (RPP)—Peak power output (W) relative to body mass: PP $\div$ Body mass (kg).
3. Anaerobic fatigue (AF)—Percentage decline in power output during the test; AF is thought to represent the total capacity to produce ATP via the immediate and short-term energy systems. AF computes as (Highest 5 -second PP - Lowest 5 -second PP) $\div$ Highest 5 -second PP $\times 100$.
4. Anaerobic work (AW)—Total work accomplished in watts for duration of the test ( 30 s ).

## EXAMPLE

A male weighing 73.3 kg performs the Wingate test on a Monark cycle ergometer ( 6.0 m traveled per pedal revolution) with an applied resistance (force) of 5.5 kp ( $73.3-\mathrm{kg}$ body mass $\times 0.075=$ 5.497 , rounded to 5.5 kg ); pedal revolutions for each 5 -second interval equal 12, 10, 8, 7, 6, and 5 ( 48 total revolutions in 30 s).

## CALCULATIONS

1. Peak power output

$$
\begin{aligned}
\mathrm{PP} & =\text { Force } \times \text { Distance } \div \text { Time } \\
& =\left(5.5 \mathrm{kp} \times 9.8 \mathrm{~m} \cdot \mathrm{~s}^{-2}\right) \cdot(12 \mathrm{rev} \cdot 6 \mathrm{~m} / \mathrm{rev}) / 5 \mathrm{~s} \\
& =776.8 \mathrm{~kg} \cdot \mathrm{~m}^{2} \cdot \mathrm{~s}^{-3} \\
& =776.8 \mathrm{~N} \cdot \mathrm{~m} \cdot \mathrm{~s}^{-2} \\
& =776.8 \mathrm{~W}
\end{aligned}
$$

2. Relative peak power output

RPP $=\mathrm{PP} \div$ Body mass, kg
$=776.8 \mathrm{~W} \div 73.3 \mathrm{~kg}$
$=10.6 \mathrm{~W} \cdot \mathrm{~kg}^{-1}$
3. Anaerobic fatigue

AF $=($ Highest PP - Lowest PP $) \div$ Highest PP $\times 100$
[Highest PP $=$ Force $\times$ Distance $\div$ Time: $=5.5 \mathrm{kp} \times 9.8 \mathrm{~m} \cdot \mathrm{~s}^{-2}$ ) $\times(12 \mathrm{rev} \times 6 \mathrm{~m}) \div 0.0833 \mathrm{~min}$
$=4753.9 \mathrm{kp}-\mathrm{m} \cdot \mathrm{min}^{-1}$, or 776.8 W ]
[Lowest PP $=$ Force $\times$ Distance $\div$ Time: $=\left(5.5 \mathrm{kp} \times 9.8 \mathrm{~m} \cdot \mathrm{~s}^{-2}\right)$
$\times(5 \mathrm{rev} \times 6 \mathrm{~m}) \div 0.0833 \mathrm{~min}$
$=1980.8 \mathrm{kp}-\mathrm{m} \cdot \mathrm{min}^{-1}$, or 323.7 W ]
$A F=776.8 \mathrm{~W}-323.7 \mathrm{~W} \div 776.8 \mathrm{~W} \times 100$
$=58.3 \%$
4. Anaerobic work
$\mathrm{AW}=$ Force $\times$ Total Distance (in 30 s )
$=\left(5.5 \mathrm{~kg} \times 9.8 \mathrm{~m} \cdot \mathrm{~s}^{-2}\right) \times[(12 \mathrm{rev}+10 \mathrm{rev}+8 \mathrm{rev}$
$+7 \mathrm{rev}+6 \mathrm{rev}+5 \mathrm{rev}) \times 6 \mathrm{~m}]$
$=15,523$ joules, or 15.5 kJ

criteria. ${ }^{64,99}$ Elite volleyball and ice hockey players have achieved some of the highest Wingate power scores.

Figure 11.5 A and B present the relative contributions of each energy system during three cycle ergometer anaerobic

TABLE 11.2 - Percentile Norms for Average Power and Peak Power for Physically Active Young Adult Men and Women

| \% | Average Power <br> Watts (W) |  | Peak Power <br> Watts (W) |  |
| :---: | :---: | :---: | :---: | :---: |
| Rank | Male | Female | Male | Female |
| 90 | 662 | 470 | 822 | 560 |
| 80 | 618 | 419 | 777 | 527 |
| 70 | 600 | 410 | 757 | 505 |
| 60 | 577 | 391 | 721 | 480 |
| 50 | 565 | 381 | 689 | 449 |
| 40 | 548 | 367 | 671 | 432 |
| 30 | 530 | 353 | 656 | 399 |
| 20 | 496 | 336 | 618 | 376 |
| 10 | 471 | 306 | 570 | 353 |


|  | W $\cdot \mathrm{kg} \mathrm{BM}^{-1 a}$ |  | $\mathrm{~W} \cdot \mathrm{~kg} \mathrm{BM}^{-1}$ |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Male | Female | Male | Female |
| 90 | 8.24 | 7.31 | 10.89 | 9.02 |
| 80 | 8.01 | 6.95 | 10.39 | 8.83 |
| 70 | 7.91 | 6.77 | 10.20 | 8.53 |
| 60 | 7.59 | 6.59 | 9.80 | 8.14 |
| 50 | 7.44 | 6.39 | 9.22 | 7.65 |
| 40 | 7.14 | 6.15 | 8.92 | 6.96 |
| 30 | 7.00 | 6.03 | 8.53 | 6.86 |
| 20 | 6.59 | 5.71 | 8.24 | 6.57 |
| 10 | 5.98 | 5.25 | 7.06 | 5.98 |

From Maud PJ, Schultz BB. Norms for the Wingate anaerobic test with comparisons in another similar test. Res Q Exerc Sport 1989;60:144. ${ }^{a} \mathrm{~W} \cdot \mathrm{~kg} \mathrm{BM}{ }^{-1}$, watts per kilogram of body mass.
power tests of different durations. The lower figure (B) gives estimated kilojoules of total energy; the upper figure presents the percentage contribution of each system to total work accomplished. Note the progressive change in the percentage contribution of each energy system as a function of increasing duration of effort.

Lower in Children. The reason for the relatively poor performance of children compared with adolescents and young adults on the Wingate test remains unclear. Possible explanations include children s relatively lower intramuscular glycogen concentrations, poorer motivation, and their slower rate of glycogen hydrolysis during exercise.

Gender Differences. Large gender differences exist in anaerobic power when comparing test scores on an absolute basis. ${ }^{21,75}$ These observations, as with most physiologic and exercise performance tests, seem readily explained by the clear gender differences in factors that affect absolute anaerobic power-output-body mass, active muscle mass, and fat-free


Figure 11.5 - Relative contribution of each energy system to total work accomplished in three short-duration exercise tests.
A. Percentage of total work output. B. Total kilojoules of energy. Test results based on Katch test protocol (see p. 229). (Data from Applied Physiology Laboratory, University of Michigan, Ann Arbor.)
body mass (FFM). Expressing power output capacity relative to a component of body mass or composition should minimize or even eliminate the gender difference in anaerobic capacity. This adjustment should offer insight into whether true gender effects exist in a muscle s capacity to generate energy anaerobically.

Gender differences in body composition, physique, muscular strength, or neuromuscular factors do not fully explain the lower anaerobic performance of women. ${ }^{51,65}$ For a given fat-free leg volume, the peak oxygen deficit (considered by some a measure of anaerobic power) ${ }^{3,56}$ during supermaximal cycling remained higher in men than in women. ${ }^{100}$ These differences averaged about $20 \%$, even when adjusting for the estimated difference in active muscle mass between genders. Similar gender differences in anaerobic performance exist for children and adolescents. ${ }^{63,75}$ The gender effect among adolescents remains apparent for the lower body musculature even
when considering differences in body composition. ${ }^{65}$ Males greater relative muscle area and metabolic capacity of the fasttwitch fiber type and larger catecholamine response to exercise may help to explain their larger anaerobic performance.

Available evidence indicates a biologic gender difference in anaerobic exercise capacity. Physical testing that focuses on this fitness component would inflate typically observed performance differences between men and women. Even adjusting the performance score to body size or body composition does not eliminate this difference. In occupational settings, the justifiable concern when using all-out anaerobic exercise to predict job performance relates to the potential to exacerbate gender differences in performance scores and magnify any adverse impact on females. Females maximal anaerobic performance remains unaffected by variations in menstrual cycle phase. ${ }^{29}$

## Maximally Accumulated Oxygen Deficit

Determination of the maximally accumulated oxygen deficit (MAOD) provides another indirect measure of anaerobic metabolic capacity. ${ }^{56,57,78,97}$ MAOD determination relies on an extrapolation procedure using the linear exercise intensity oxygen consumption relationship established from several levels of submaximal treadmill exercise. From these data, a regression line predicts the individual s supramaximal oxygen consumption, usually set at $125 \%$ of the subject s directly measured $\mathrm{VO}_{2 \max }$. MAOD calculates as the difference between the predicted supramaximal oxygen consumption from the exercise intensity oxygen consumption relationship and oxygen consumption measured during a 2 - to 3 -minute all-out treadmill run to fatigue. The measure correlates positively with Wingate test, sprint running, and stair climbing anaerobic performance test scores; it demonstrates independence from aerobic energy estimates, differentiates between aerobically and anaerobically trained individuals, and remains unchanged with high-intensity exercise of varying durations.

## Biologic Indicators for Anaerobic Power

## Blood Lactate Levels

Physiologists have traditionally interpreted the appearance of excess lactate in muscle and blood following exercise to indicate contributions of anaerobic metabolism to the exercise energy requirement. Measurements of muscle or venous blood lactate routinely verified steady-rate exercise or magnitude of glycolytic activity consequent to non steady-rate exercise. This view now appears overly simplified in light of research showing lactate s role as a metabolic intermediate rather than a metabolic dead end whose only fate involves reconversion to pyruvate. Lactate serves as an important substrate in energy-storing and energy-generating pathways in different tissues. Lactate measured during or following exercise does not necessarily reflect absolute levels of anaerobic energy transfer via glycolysis. ${ }^{11,18,30,31}$ With increasing
exercise intensity, including near-maximal and supramaximal levels, greater lactate production reflects increasing ATP resynthesis from anaerobic pathways. ${ }^{83}$ Anaerobic glycolysis and PCr degradation provides about $70 \%$ of the total energy yield for 30 seconds of all-out exercise, with aerobic pathways generating the remaining energy (see Fig. 11.5).

## INTEGRATIVE QUESTION

Explain why females score poorly when using absolute scores for average power and peak power on the Wingate leg-cycle ergometer test.

## Glycogen Depletion

The pattern of glycogen depletion reveals the glycolytic contribution to exercise because glycogen stored in specific muscles activated by exercise powers the short-term energy system. Figure 11.6 illustrates the close connection between glycogen depletion rate in the quadriceps femoris muscle during bicycle exercise and exercise intensity. During prolonged but relatively light exercise $\left(30 \% \quad \mathrm{VO}_{2 \max }\right)$, a considerable muscle glycogen reserve remains even after


Figure 11.6 - Glycogen depletion from the vastus lateralis of the quadriceps femoris muscles during bicycle exercise of different intensities and durations. Exercise at $31 \%$ of $\mathrm{VO}_{2 \text { max }}$ (the lightest workload) caused some depletion of muscle glycogen, but the most rapid depletion occurred during exercise between 83 and $150 \%$ of $\mathrm{VO}_{2 \text { max }}$. (Adapted from Gollnick PD. Selective glycogen depletion pattern in human muscle fibers after exercise of varying intensity and at varying pedaling rates. J Physiol 1974;241:45.)

180 minutes. Relatively large quantities of fatty acids provide fuel for exercise at this intensity, with only minimal reliance on stored glycogen. The two intense supermaximal workloads produced the most rapid and pronounced glycogen depletion. This outcome makes sense from a metabolic standpoint: Glycogen provides the most rapid phosphorylation of ATP of the three macronutrients, and glycogen serves as the only stored macronutrient that anaerobically resynthesizes ATP.

Changes in total muscle glycogen, like those illustrated in Figure 11.6, do not necessarily indicate precise amounts of glycogen catabolism in specific fibers within active muscle. Depending on exercise intensity, glycogen depletion progresses selectively in either fast- or slow-twitch muscle fibers. Fast-twitch fibers provide most of the power requirements for all-out exercise (e.g., repeated 1-min sprints on a bicycle ergometer at an intense load). The glycogen content of these fibers becomes almost totally depleted because of the exercise $s$ anaerobic nature. In contrast, during moderately intense but more prolonged aerobic exercise, slow-twitch muscle fibers become glycogen depleted first. Specificity in glycogen use (and depletion) by specific fiber types makes it difficult to evaluate the anaerobic involvement of distinct fibers from changes in a muscle $s$ total glycogen content before and after exercise.

## Individual Differences in Anaerobic Energy-Transfer Capacity

Three factors contribute to differences among individuals in capacity to generate short-term anaerobic energy:

1. Effects of previous training
2. Capacity to buffer acid metabolites
3. Motivation

## Effects of Training

Figure 11.7 compares biochemical factors related to anaerobic metabolism for sprint-trained athletes and untrained subjects. Trained subjects always exhibit higher levels of muscle and blood lactate and greater depletion of muscle glycogen following short-term maximal bicycle ergometer exercise. Such cross-sectional comparisons suggest that training for short-term, all-out exercise enhances capacity to generate energy from anaerobic sources.

Figure 11.7 - Depletion of the anaerobic substrates (ATP, PCr , and glycogen) and increases in muscle and blood lactate during short-term maximal exercise by sprint-trained athletes and untrained subjects. Trained subjects exhibited a greater increase in anaerobic metabolism (higher lactate levels) and more pronounced muscle glycogen depletion; reductions in the intramuscular high-energy phosphates remained essentially the same as for the nontrained subjects. (From Karlsson J, et al. Muscle metabolites during submaximal and maximal exercise in man. Scand J Clin Invest 1971;26:382.)


[^23]
## Buffering of Acid Metabolites

Buffering capacity refers to how well different substances resist increases in free hydrogen ion concentration by binding free protons to prevent a decrease in pH . When anaerobic energy transfer predominates, lactate accumulates and muscle and blood acidity increase to negatively affect the intracellular environment and the contractile capacity of active muscles. Anaerobic training might enhance short-term energy capacity by improving the body s alkaline reserve for buffering. Such a training adaptation would theoretically enable greater lactate production through more effective buffering. This reasoning seems appealing, yet athletes have only a slightly larger alkaline reserve than sedentary counterparts. Additionally, no appreciable change in alkaline reserve occurs following intense physical training. Exercise training most likely confers a buffering capability within the range expected for healthy untrained individuals. Chapter 23 discusses the potential ergogenic effects of preexercise-induced alkalosis.

## Motivation

Individuals with a higher pain tolerance, toughness, or ability to push beyond the discomforts of intense, fatiguing exercise can accomplish more work anaerobically. This coincides with higher blood lactate concentrations and greater glycogen depletion. Motivational factors prove difficult to categorize or quantify yet undoubtedly play an integral role in achieving superior performance at most levels of competition.

## AEROBIC ENERGY: THE LONG-TERM ENERGY SYSTEM

Figure 11.8 illustrates that athletes who excel in endurance sports generally have a superior capacity for aerobic energy transfer. The maximal oxygen consumption of elite distance runners, swimmers, bicyclists, and cross-country skiers exceeds that of sedentary men and women by almost twofold. This does not mean that $\mathrm{VO}_{2 \text { max }}$ provides the sole determinant of endurance performance. Other factors, principally those at the local tissue level, include improved capillary density, enzymes, mitochondrial size and number, and muscle fiber type. These intrinsic qualities strongly influence a muscle s capacity to sustain a high level of aerobic exercise. ${ }^{35}$ The $\mathrm{VO}_{2 \text { max }}$ does provide important information about the capacity of the longterm energy system. This measure also conveys important physiologic meaning because attaining a high $\mathrm{VO}_{2 \text { max }}$ requires integration of high levels of pulmonary, cardiovascular, and neuromuscular function (see Fig. 7.5 and Focus on Research on p. 236). This makes $V O_{2 \text { max }}$ a fundamental measure of physiologic functional capacity for exercise.

## Assessment of Maximal Oxygen Consumption

Over the past 70 years, considerable research effort has standardized methodology to assess maximal aerobic power. Normative standards exist related to age, gender, state of training, and body size.


Figure 11.8 - Maximal oxygen consumption of male and female Olympic-caliber athletes in different sport categories compared with healthy sedentary subjects. (Adapted from Saltin B, strand PO. Maximal oxygen consumption in athletes. J Appl Physiol 1967;23:353.)

## Criteria for Maximal Oxygen Consumption

The plot in Figure 11.9 relates oxygen consumption and exercise intensity during progressive increases in treadmill
effort. The test terminated when the subject would not complete the full duration of a particular exercise interval. The highest oxygen consumption (average of 18 subjects) occurred before subjects attained their maximum exercise level. Demonstration of a leveling off or peaking over in oxygen consumption with increasing exercise intensity generally provides assurance that a person has reached maximum aerobic metabolism (i.e., achieved true $\mathrm{VO}_{2 \max }$; see
Focus on Research on p. 236). Agreement on a precise standard for the criterion remains controversial. ${ }^{20,36,81}$ Less stringent criteria, besides failure for oxygen consumption to increase in graded exercise, also establish attainment of $\mathrm{VO}_{2 \text { max }}$. Oxygen consumption that fails to increase by the value expected on the basis of previous observations with the specific test protocol often serves as an appropriate criterion. ${ }^{1,36,85}$

Oxygen consumption at the higher exercise levels does not readily plateau, particularly among children, ${ }^{73}$ except in treadmill running. The term peak oxygen consumption, or $\mathbf{V O}_{2 \text { peak }}$, applies when leveling off does not occur or maximum performance appears limited by local muscular factors rather than central circulatory dynamics. $V O_{2 \text { peak }}$ refers to the highest value of oxygen consumption measured during a graded exercise test. The highest oxygen consumption value often occurs in the last minute of exercise. Secondary criteria that objectify $\mathrm{VO}_{2 \text { peak }}$ include attainment of the age-predicted maximum heart rate (see Figs. 21.17 and 21.18) or a respiratory exchange ratio ( R ) that exceeds 1.15 . Some also argue that to accept an oxygen consumption value as near maximum, blood lactate should attain 70 or 80 mg per dL of blood (8 to 10 mmol ) or above. ${ }^{20}$

## Maximal Oxygen Consumption Tests

A variety of exercise tests that activate the body s large muscle groups can determine $\mathrm{VO}_{2 \text { max }}$ provided exercise intensity and duration maximize aerobic energy transfer. Usual exercise modes include treadmill running or walking, bench stepping, and stationary cycling. In accord with exercise test and training specificity, other forms of testing employ free, tethered, and flume swimming ${ }^{6,46}$; swim-bench ergometry ${ }^{28}$; inline skating ${ }^{94}$; roller skiing ${ }^{74}$; simulated arm leg climbing ${ }^{10}$; rowing ${ }^{14}$; ice skating ${ }^{23}$; and arm-crank and wheelchair exercise. ${ }^{77,89,91}$ Such performance tests remain substantially unaffected by a subject s strength, speed, body size, and skill, with the exception of specialized tests that measure aerobic capacity in sport-specific activities.

The $\mathrm{VO}_{2 \text { max }}$ test may require a single, continuous 3- to 5-minute supramaximal effort. In most cases, the test usually consists of progressive increments in effort (graded exercise) until the subject simply refuses to continue exercising. Some researchers term this end point exhaustion. However, the person exercising terminates the test-a decision often influenced by motivational factors that do not necessarily reflect true physiologic strain. Bringing the subject to the point of acceptable criteria for either $\mathrm{VO}_{2 \text { max }}$ or $\mathrm{VO}_{2 \text { peak }}$ often requires considerable urging and prodding. ${ }^{93}$ Practical experience indicates that attaining a plateau in oxygen consumption during a graded exercise test requires a high level of anaerobic energy output. This poses some difficulty for untrained and elderly persons who normally do not perform strenuous exercise with its associated discomforts and potential health concerns.


Figure 11.9 - Peaking over in oxygen consumption with increasing treadmill exercise intensity. Each point represents the average oxygen consumption of 18 sedentary males. The region where oxygen consumption fails to increase the expected amount or even decreases slightly with increasing exercise intensity represents the $\mathrm{VO}_{2 \text { max }}$. (Data from the Applied Physiology Laboratory, University of Michigan, Ann Arbor.)

## FOCUS ON RESEARCH

## AN IMPORTANT MEASURE OF CARDIORESPIRATORY FUNCTIONAL CAPACITY


#### Abstract

Mitchell JH, et al. The physiological meaning of the maximal oxygen intake test. J Clin Invest 1958; 37:538.


> In the 1920s, A. V. Hill and colleagues-and in latter years other researchers-considered maximal oxygen consumption $\left(\mathrm{VO}_{2 \text { max }}\right)$ the single best measure of cardiorespiratory capacity. Hill asserted that $\mathrm{VO}_{2 \max }$ was physiologically restricted owing to the limitation of the circulatory and respiratory systems. This assertion, however, had not been tested experimentally because the interplay among physiologic parameters had not yet been established. Mitchell and coworkers directly examined the relationships among $\mathrm{VO}_{2 \text { max }}$ and various cardiovascular pulmonary measures to objectify the physiologic significance of $\mathrm{VO}_{2 \text { max }}$.

Sixty-five men performed graded, discontinuous treadmill exercise to $\mathrm{VO}_{2 \text { max }}$. Subgroups ran in several different protocols to volitional exhaustion. Measurements included cardiac output and $a-\bar{v} \mathrm{O}_{2}$ difference by the dye dilution technique, blood gas pressures, and central blood volume. Two significant findings emerged that related to test methodology. First, $\mathrm{VO}_{2 \text { max }}$ provides a highly reproducible measure of aerobic capacity if rigid criteria for determining the point at which the maximal value has been attained are applied. The reproducibility of test scores for 15 subjects was $r=0.92$, with a standard error of measurement of $\pm 7 \%$ for the maximal values. Second, a peaking over or plateauing criterion (when relating $\mathrm{VO}_{2}$ to exercise intensity) provided an important conceptual standard to establish attainment of $\mathrm{VO}_{2 \text { max }}$ in diverse forms of exercise as follows:

Plots of oxygen intake against workload for the entire material showed that, until a maximal value was attained, oxygen intake rose $142 \pm 44 \mathrm{~mL}$ with each increase in workload. If the rise was less than 142 minus 88 (twice the standard deviation), or 54 mL , the final value was accepted as the maximal oxygen intake, the assumption being that the subject had attained his true maximal value or had reached the beginning of a plateau and could not increase his intake very much more.

Findings from this study supported the view that the $\mathrm{VO}_{2 \text { max }}$ depended almost exclusively on the functional capacity of the cardiovascular system (cardiac output and $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff) and not accommodation of left ventricular output by the peripheral vascular bed. No significant change occurred in arterial oxygen pressure from rest to intense
exercise; the slight arterial desaturation often observed in intense exercise resulted from a blood pH decrease and the resulting Bohr effect on hemoglobin saturation. Maintenance of high arterial oxygen pressures during intense exercise argued against the possibility that pulmonary factors provided a weak link in limiting $\mathrm{VO}_{2 \text { max }}$. The researchers maintained that in healthy individuals an adequate arterial oxygen diffusion gradient always exits from the alveoli to the blood and from the blood to active tissues.

This study confirmed the importance of $\mathrm{VO}_{2 \text { max }}$ to indicate central circulatory function (cardiac capacity) and capacity of peripheral or local factors reflected by the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference. This and subsequent research firmly established $\mathrm{VO}_{2 \text { max }}$ as a benchmark to quantify cardiovascular functional capacity and aerobic fitness.


Magnitude of changes in cardiovascular dynamics (arteriovenous oxygen difference [ $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff], heart rate, oxygen consumption, stroke volume, and blood volume) in 15 normal subjects between rest and maximal exercise.

INTEGRATIVE QUESTION
Explain why $V O_{2 \text { max }}$ provides important insights about the functional capacities of different physiologic systems.

## Test Comparisons

There are two popular maximal oxygen consumption test protocols:

1. Continuous-progressively increasing exercise increments without recovery or rest intervals
2. Discontinuous-progressively increasing exercise increments interspersed with recovery intervals
Both test protocols yield similar $\mathrm{VO}_{2 \text { max }}$ values. ${ }^{20}$ The data in Table 11.3 reveal a systematic comparison of $\mathrm{VO}_{2 \text { max }}$ scores measured using six common continuous and discontinuous treadmill and bicycle protocols. Only an 8 -mL difference in $\mathrm{VO}_{2 \text { max }}$ ocurred between the continuous and discontinuous bicycle tests, but $\mathrm{VO}_{2 \text { max }}$ during cycling averaged 6.4 to $11.2 \%$ below treadmill values. The largest difference among the three treadmill running tests equaled only $1.2 \%$. In contrast, the walking test elicited $\mathrm{VO}_{2 \text { max }}$ scores nearly $7 \%$ higher than values on the bicycle, but $5 \%$ lower than the three running tests.

Subjects commonly complained of intense local discomfort in the thigh muscles during intense exercise (limiting their ability to continue) in both continuous and discontinuous bicycle tests. They experienced discomfort in the lower back and calf muscles during treadmill walking, notably at higher treadmill elevations. Running tests rarely produced local discomfort; subjects complained more of general fatigue usually categorized as feeling winded. For ease of administration, the continuous treadmill run provides a practical test of aerobic capacity for most healthy individuals. The total time to administer the test should average between 8 and $10 \mathrm{~min}-$ utes for moderately to highly trained individuals, compared with 65 minutes for the discontinuous running test. Subjects tolerate the continuous test well and prefer the shorter time. ${ }^{105}$ Achievement of $\mathrm{VO}_{2 \text { max }}$ also occurs with a continuous protocol that increases exercise intensity progressively in 15 -second intervals. ${ }^{22}$ Total test time for either bicycle or
treadmill exercise with this approach averages only about 5 minutes.

Common Treadmill Protocols. Figure 11.10 summarizes six common treadmill protocols to assess aerobic capacity in normal individuals and cardiac patients. Manipulation of exercise duration and treadmill speed and grade share common features. The Harbor treadmill test (example F), referred to as a ramp test, depicts a unique application. With this protocol, treadmill grade increases by a constant amount (between 1 and $4 \%$ ) each minute for up to 10 minutes, depending on the person $s$ fitness. This relatively quick proce-dure-well tolerated by both healthy subjects and cardiac patients-elicits a linear increase in oxygen consumption up to maximum. ${ }^{12,17,68,96}$

INTEGRATIVE QUESTION
Discuss why training studies should objectively demonstrate attainment of true $\mathrm{VO}_{2 \text { max }}$ in both pre- and posttest measures. How can this goal be verified?

## Factors That Affect Maximal Oxygen Consumption

The six most important factors that influence the maximal oxygen consumption score include:

1. Mode of exercise
2. Heredity
3. State of training
4. Gender
5. Body size and composition
6. Age

## Mode of Exercise

Variations in $\mathrm{VO}_{2 \max }$ with different forms of exercise generally reflect variations in the quantity of muscle mass activated. Treadmill exercise usually produces the highest values among diverse exercise modes. Bench stepping produces $\mathrm{VO}_{2 \text { max }}$ scores similar to treadmill values and higher

TABLE 11.3 - Average $\mathrm{VO}_{2 \max }$ for 15 Male College Students During Continuous and Discontinuous Tests on the Treadmill and Bicycle Ergometer ${ }^{a}$

| Variable | Bike, Discontinuous | Bike, Continuous | Treadmill, Discontinuous Run-Walk | Treadmill, Continuous Walk | Treadmill, Discontinuous Run | Treadmill, Continuous Run |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{mL} \cdot \mathrm{min}^{-1}$ | $3691 \pm 453$ | $3683 \pm 448$ | $4145 \pm 401$ | $3944 \pm 395$ | $4157 \pm 445$ | $4109 \pm 424$ |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | $50.0 \pm 6.9$ | $49.9 \pm 7.0$ | $56.6 \pm 7.3$ | $53.7 \pm 7.6$ | $56.6 \pm 7.6$ | $55.5 \pm 6.8$ |

[^24]

Figure 11.10 - Six commonly used treadmill protocols to assess $\mathrm{VO}_{2 \text { max }}$. A. Naughton protocol. Three-minute exercise periods of increasing intensity alternate with 3 minutes of rest. Exercise periods vary in $\%$ grade and speed. B. strand protocol. Constant speed at 5 mph . After 3 minutes at $0 \%$ grade, the grade increases $2^{1}{ }_{2} \%$ every 2 minutes. C. Bruce protocol. Grade and/or speed change every 3 minutes. Omit the $0 \%$ and $5 \%$ grades for healthy subjects. D. Balke protocol. After 1 minute at $0 \%$ grade and 1 minute at $2 \%$ grade, the grade increases $1 \%$ per minute; speed is maintained at 3.3 mph . E. Ellestad protocol. Initial grade of $10 \%$ and later grade of $15 \%$, while speed increases every 2 or 3 minutes. F. Harbor protocol. After 3 minutes of walking at a comfortable speed, the grade increases at a constant preselected amount each minute: $1 \%, 2 \%, 3 \%$, or $4 \%$, so that the subject achieves $\mathrm{VO}_{2 \max }$ in approximately 10 minutes. (From Wasserman K, et al. Principles of exercise testing and interpretation. 2nd ed. Philadelphia: Lea \& Febiger, 1994.)
than values on a cycle ergometer. ${ }^{38}$ During arm-crank exercise, aerobic capacity averages only about $70 \%$ of the treadmill score. ${ }^{89}$ For skilled but untrained swimmers, the $\mathrm{VO}_{2 \max }$ during swimming usually equals about $80 \%$ of treadmill values. ${ }^{46,54}$ A definite test specificity emerges for this form of exercise because trained collegiate swimmers achieve $\mathrm{VO}_{2 \text { max }}$ values swimming only $11 \%$ below treadmill values. ${ }^{52}$ Some elite swimmers equal or even exceed their treadmill scores during swimming tests. ${ }^{46}$ Similarly, a distinct exercise specificity exists for competitive race-walkers who achieve similar $\mathrm{VO}_{2 \max }$ values during treadmill walking and treadmill
running. ${ }^{58}$ When competitive cyclists pedal at the rapid frequencies of competition, they too achieve $\mathrm{VO}_{2 \max }$ values equivalent to treadmill $\mathrm{VO}_{2 \max }$ scores. ${ }^{32,84}$

Treadmill exercise proves highly desirable for determining $\mathrm{VO}_{2 \max }$ in healthy subjects in the laboratory. One can easily quantify and regulate exercise intensity. Compared with other forms of exercise, the treadmill allows subjects to more readily meet one or more of the criteria to attain $\mathrm{VO}_{2 \max }$ or $\mathrm{VO}_{2 \text { peak }}$. In field experiments (outside the laboratory setting), bench stepping and cycle ergometry remain suitable alternatives.

## Heredity

The interaction between inherited factors (DNA sequence variation; see Section 8, A Look to the Future ) and exercise enhances our understanding of individual variations in training responsiveness, including anticipated health-related benefits from regular physical activity. ${ }^{7,33,61,72}$ Frequent questions concern the relative contribution of natural endowment (genotype) to physiologic function, neuromuscular coordination, and exercise performance (phenotype). ${ }^{26,45,60,71,102}$ For example, to what extent does heredity determine the extremely high aerobic capacities of the endurance athletes in Figure 11.8? Do these exceptionally high levels of functional capacity simply reflect intensive training? How does familial aggregation affect skeletal muscle capillary density and enzyme activity and their response to training?

In general, most physical fitness characteristics demonstrate high heritability. Early research focused on 15 pairs of identical twins (monozygous; same heredity from a single fertilized ovum) and 15 pairs of fraternal twins (dizygous; like ordinary siblings, derived from two separate fertilized ovum) raised in the same city and with parents of similar socioeconomic backgrounds. Heredity alone accounted for up to $93 \%$ of observed differences in $\mathrm{VO}_{2 \text { max }}$. The capacity of the shortterm glycolytic energy system indicated a genetic determination of approximately $81 \%$, while maximum heart rate showed approximately $86 \%$ genetic determination. ${ }^{43}$ In larger groups of brothers, fraternal twins, and identical twins, a smaller effect of inherited factors occurred for aerobic capacity and endurance performance. ${ }^{8,9}$ Figure 11.11 presents data


## $\square$ monozygous twins $\square$ Dizygous twins

Figure 11.11 - Maximal oxygen consumptions $\left(\mathrm{VO}_{2 \max }\right)$ for pairs of monozygotic (identical) and dizygotic (fraternal) twin brothers. (From Bouchard C, et al. Aerobic performance in brothers, dizygotic and monozygotic twins. Med Sci Sports Exerc 1986;18:639.)

## TABLE 11.4 • Estimated Genetic Contribution to Individual Differences in Important Components of HealthRelated Physical Fitness

Fitness Component
Genetic Contribution

| $\mathrm{VO}_{2 \text { max }}$ | $2030 \%$ |
| :--- | ---: |
| Submaximal exercise response | $2030 \%$ |
| Muscular fitness | $2030 \%$ |
| Blood lipid profile | $3050 \%$ |
| Resting blood pressure | $30 \%$ |
| Total body fat | $25 \%$ |
| Regional fat distribution | $30 \%$ |
| Habitual activity level | $30 \%$ |

Modified from Bouchard C, Perusse L. Heredity, activity level, fitness, and health. In: Physical activity, fitness, and health. Champaign, IL: Huma Kinetics, 1994.
for $\mathrm{VO}_{2 \max }$ for identical twin and fraternal twin brothers. The least variation in aerobic capacity between brother pairs emerged for identical twins with identical genetic constitutions. Chapter 21 and On the Horizon, the final chapter in this book, discuss the potential contribution of genetic makeup to one s responsiveness to aerobic exercise training.

Researchers estimate the genetic effect at about 20 to $30 \%$ for $V O_{2 \max }, 50 \%$ for maximum heart rate, and $70 \%$ for physical working capacity. ${ }^{7,8,67}$ Combining the estimated effects of genetics and familial environment raises the upper limit of genetic determination to about $50 \%$ for $\mathrm{VO}_{2 \max }$ when adjusted for age, gender, and body mass and/or body composition. ${ }^{9}$ Identical twins have similar muscle fiber type composition, whereas fiber type varies widely between fraternal twins and brothers. ${ }^{44}$ Between 15 and $40 \%$ of the variation in muscular strength among individuals probably results from genetic factors. ${ }^{66,88}$ TABLE 11.4 summarizes estimations of the genetic contribution to some important health-related physical fitness components. Future research may determine a precise upper limit of genetic determination; at this time, we can assume that inherited factors contribute considerably to physiologic function, exercise performance, training responsiveness, and specific components of health-related physical fitness. ${ }^{25,45,70,72}$

## State of Training

A person s state of aerobic training contributes substantially to the $\mathrm{VO}_{2 \text { max }}$, which normally varies between 5 and $20 \%$ depending on a person s fitness at the time of testing. Chapter 21 further discusses the influence of training on aerobic capacity.

## Gender

Women typically achieve $V_{2 \max }$ scores 15 to $30 \%$ below values of male counterparts. ${ }^{80,92}$ Even among trained
endurance athletes, the gender difference ranges between 15 and $20 \% .^{5}$ These differences remain considerably larger for $\mathrm{VO}_{2 \text { max }}$ expressed in absolute units $\left(\mathrm{L} \cdot \min ^{-1}\right)$ rather than to body mass $\left(\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}\right) .{ }^{98}$ Among world-class crosscountry skiers, for example, a $43 \%$ lower $\mathrm{VO}_{2 \max }$ absolute value for women ( 6.54 vs. $3.75 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ ) becomes $15 \%$ lower when expressed relative to body mass ( 83.8 vs. 71.2 $\mathrm{mL} \mathrm{kg}{ }^{-1} \cdot \min ^{-1}$ ).

Differences in body composition (discussed in the next section) and hemoglobin concentration usually explain the gender difference in $\mathrm{VO}_{2 \text { max. }}$. Untrained young adult women generally average about $25 \%$ body fat, whereas men average $15 \%$. The average male generates more total aerobic energy simply because he possesses more muscle mass and has less fat than the average female. Trained athletes have lower percentages of fat than average individuals, yet trained women still possess more body fat than male counterparts. Perhaps because of higher testosterone levels, men also have a 10 to $14 \%$ greater hemoglobin concentration than women. This difference in the blood s oxygen-carrying capacity enables men
to circulate more oxygen during exercise. This advantage increases their aerobic capacities above those of women.

Factors other than lower body fat and higher hemoglobin concentrations may help to explain male female aerobic capacity differences. For example, normal physical activity levels differ between the average male and average female. One could argue that social constraints reduce opportunities for females of all ages to participate in extracurricular athletic activities and recreational pursuits. Among prepubertal children, boys engage in more daily physical activity than girls of the same age. Despite these fitness-inhibiting factors, the aerobic capacities of physically active females generally exceed those of sedentary males. $\mathrm{VO}_{2 \max }$ of female cross-country skiers, for example, exceeds untrained males by $40 \% .{ }^{5}$ Even among normal populations, considerable variability exists within each gender, and the $\mathrm{VO}_{2 \text { max }}$ scores for many women exceed average values for men.

## Are Gender Differences Shrinking for Exercise Performance? Figure 11.12A illustrates the decline in



Figure 11.12 - A. Decline in running pace over increasing race distance for men and women. Performance represents the average of the top 50 times for the 1996 world rankings for the $1500-\mathrm{m}$ ( $1.5-\mathrm{km}$ ), $10-\mathrm{km}$, and marathon ( $42-\mathrm{km}$ ) events. Annual world best (WB) and 100th ranked 1500-m times (B) and marathon times (C) for men and women from 1980 to 1996. White arrows indicate world records. Part D of the figure indicates world best marathon times for men and women from 1980 to 2008. (Modified from Sparling PB, et al. The gender difference in distance running performance has plateaued: an analysis of world rankings from 1980 to 1993. Med Sci Sports Exerc 1998;30:1725.)
running speed with increasing race distances for men and women in events that place a predominant demand on aerobic energy transfer. The average of the top 50 race times for the 1996 world rankings for the $1500-\mathrm{m}, 10-\mathrm{km}$, and marathon events provided the data points to construct the curves.

Despite the decline in running speed with increasing race distance, a nearly identical gender difference emerged for each race. Men ran on average $14.5 \%$ faster than women, with no narrowing of the gender difference as race distance increased. This holds true despite a 37 -fold greater duration for the marathon than the $1500-\mathrm{m}$ run. Clearly, this analysis does not support the contention that gender differences in endurance diminish as distance increases. Analysis of annual world rankings (world-best and 100th-best times) from 1980 to 1996 (Fig. 11.12 B, C, and D, which includes world-best marathon times to 2008) indicates that the gender difference in competitive distance running plateaued and remained stable for both the $1500-\mathrm{m}$ race and the marathon for more than two decades. An analysis of sprint performance in running, swimming, and speed skating during the last 50 years reveals that the difference between males and females has ceased to narrow but has widened since the mid-1990s. This was not explained by declining participation of women in sport, poorer training practice, or reduced access to technological developments. It did, however coincide with dramatic improvements in the scope and sensitivity of drug testing. ${ }^{79}$ Such objective findings run counter to some current speculation that women s exercise performance should improve at a faster rate than men $s$ to a point at which gender differences in performance vanish or reverse. ${ }^{101}$

## Body Size and Composition

Variations in body mass explain nearly $70 \%$ of the differences in $\mathrm{VO}_{2 \max }$ scores among individuals. This limits interpretations of exercise performance or absolute values for oxygen consumption when comparing individuals who differ in body size or composition. The effect of body size on aerobic capacity has led to the common practice of expressing oxygen consumption related to surface area, body mass, FFM, or limb volume. Table 11.5 shows a $43 \%$ difference in $\mathrm{VO}_{2 \text { max }}\left(\mathrm{L} \cdot \min ^{-1}\right)$ for an untrained man and woman differing considerably in body size and composition. When expressed per unit of body mass as $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \min ^{-1}$, the $\mathrm{VO}_{2 \max }$ of the woman remains about $20 \%$ lower than for the man. Expressing aerobic capacity by FFM reduces between-subject difference even more ( $-9 \%$ ). Adjusting for variation in muscle mass activated in exercise provides additional information to explain interindividual variation in $\mathrm{VO}_{2 \max }$. For example, adjusting oxygen consumption values obtained during maximal arm-cranking exercise for variations in estimated arm and shoulder size eliminates gender differences in $\mathrm{VO}_{2 \text { peak. }}{ }^{95}$ Expressing oxygen consumption per unit of appendicular skeletal muscle mass often negates the difference in $\mathrm{VO}_{2 \text { max }}$ between men and women of similar training status. ${ }^{13,67}$ The size of the contracting muscle mass activated in exercise largely accounts for gender differences in aerobic capacity.

TABLE 11.5 - Different Ways to Express Oxygen Consumption

|  | Female |  | Female <br> Vs. Male |
| :--- | :--- | :--- | :--- |
| Variable | Male | \% Difference |  |

## Age

Age does not spare its effect on maximal oxygen consumption. ${ }^{39,55,69}$ Although one can draw only limited inferences from cross-sectional studies of persons of different age groups, available data provide insight into the possible effects of aging on physiologic function. Figure 11.13 summarizes trends in aerobic capacity of children and adults.

Children. Figure 11.13A and B illustrates age trends in the absolute and relative aerobic capacities of boys and girls aged 6 to 16 years.

> Absolute values- $\mathrm{VO}_{2 \max }$ values in $\mathrm{L} \cdot \mathrm{min}^{-1}$ for boys and girls remain similar until about age 12 ; at age $14, \mathrm{VO}_{2 \text { max }}$ for boys averages $25 \%$ higher than that for girls, and by age 16 the difference exceeds $50 \%$. The difference generally relates to the combined effect of a greater muscle mass in boys and their greater daily physical activity levels.
> Relative values-For boys, average aerobic capacity in $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ (Fig. 11.13 B$)$ remains level at about $52 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot$ min $^{-1}$ from ages 6 to 16 ; for girls, the line slopes downward with age, reaching about $40 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ at age 16 , a value $32 \%$ below male counterparts. The greater accumulation of body fat in adolescent females partially accounts for the lower values; females must transport this extra fat that does not enhance the capacity for aerobic metabolism.

Adults. $\mathrm{VO}_{2 \max }$ declines steadily after age 25 at a rate of about $1 \%$ per year, so at age 55 it averages about $27 \%$ below values reported for 20 -year-olds (Fig. 11.13C). $\mathrm{VO}_{2 \max }$ declines at an acclerated rate during aging. ${ }^{24}$ For eight women nearly 80 years of age, $\mathrm{VO}_{2 \max }$ averaged $13.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1}$. $\min ^{-1}$, or about $3.7 \mathrm{METs} .{ }^{25}$ Despite this apparent aging effect, strong evidence indicates that a person s habitual physical activity level exerts far greater influence on aerobic capacity than chronological age per se. ${ }^{59}$ Chapter 31 more fully discusses age-related influences on physiologic function.


Figure 11.13 - Maximal oxygen consumption related to age in boys and girls ( $\mathbf{A}$ and $\mathbf{B}$ ) and men and women (C). (A and B from Krahenbuhl GS, et al. Developmental aspects of maximal aerobic power in children. Exerc Sport Sci Rev. Terjung RL, ed. vol 13, New York: Macmillan, 1985, C modified from Hermansen L. Individual differences. In: Larson LA, ed. Fitness, health, and work capacity. International standards for assessment. New York: Macmillan, 1974. Inset graph in C redrawn from tabled data of strand PO, Rodahl KR. Textbook of work physiology. New York: McGraw-Hill, 1970.)

## Aerobic Capacity Prediction Tests

The direct measurement of $\mathrm{VO}_{2 \text { max }}$ requires an extensive laboratory, specialized equipment, and considerable subject physical effort and motivation. Consequently, laboratory tests remain impractical to assess large groups of untrained subjects. In addition, strenuous exercise could prove risky to adults who do not receive proper medical clearance and appropriate supervision. These considerations increase the importance of submaximal exercise testing to predict $\mathrm{VO}_{2 \max }$ from performance during walking and running or from heart rate during or immediately postexercise.

## A Word of Caution About Predictions

All predictions contain error, referred to as the standard error of estimate (SEE). Errors of estimate are expressed in measurement units of the predicted variable (e.g., $\mathrm{kg}, \mathrm{mL}$, $\mathrm{min}, \mathrm{s})$ or as a percentage. For example, suppose the $\mathrm{VO}_{2 \text { max }}$ $\left(\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \min ^{-1}\right)$ predicted from time on a walking test equals $55 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, with SEE $\pm 10 \mathrm{~mL} \cdot \mathrm{~kg}^{-1}$. $\mathrm{min}^{-1}$. This means that the actual $\mathrm{VO}_{2 \max }$ probably ( $68 \%$ confident) lies within $\pm 10 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$, or between 45 and $65 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ of the predicted value. This represents a relatively large error ( $\pm 18 \%$ of the absolute value).

Some predictions are associated with small errors (SEE $\pm 5 \%$ ) and others with larger errors. Obviously, a larger error translates to a less useful predicted score because the likely true score encompasses such a large range of possible values. Without knowing the magnitude of the SEE, one cannot judge the usefulness of a predicted score. With predictions, one must interpret the predicted score in light of the magnitude of the prediction error. With a relatively small prediction error, prediction of $\mathrm{VO}_{2 \text { max }}$ proves useful in appropriate situations in which direct measurement is not possible.

## Walking Tests

Walking tests can predict $\mathrm{VO}_{2 \max }$ with reasonable accuracy. The following equation predicts $\mathrm{VO}_{2 \max }$ in $\mathrm{L} \cdot \min ^{-1}$ from walking speed, heart rate, body weight, age, and gender in men and women: ${ }^{42}$

$$
\begin{aligned}
\mathrm{VO}_{2 \max }= & 6.9652+(0.0091 \times \mathrm{Wt})-(0.0257 \times \text { Age }) \\
& +(0.5955 \times \text { Gender })-(0.224 \times \mathrm{T} 1) \\
& -(0.0115 \times \text { HR } 1-4)
\end{aligned}
$$

where Wt is body weight in pounds; Age is in years; Gender is 0 for females, 1 for males; T 1 is time for the 1 -mile track walk, expressed as minutes and hundredths of a minute; and HR1 4 is heart rate in beats per minute measured immediately at the end of the last quarter-mile.

The following equation predicts $\mathrm{VO}_{2 \text { max }}$ in $\mathrm{mL} \cdot \mathrm{kg}^{-1}$. $\min ^{-1}$ using the same variables:

$$
\begin{aligned}
\mathrm{VO}_{2 \max }= & 132.853-(0.0769 \times \mathrm{Wt})-(0.3877 \times \text { Age }) \\
& +(0.5955(6.315 \times \text { Gender })-(3.2649 \times \mathrm{T} 1) \\
& -(0.1565 \times \text { HR1 } 4)
\end{aligned}
$$

The multiple correlation is $r=0.92$ for predicting $\mathrm{VO}_{2 \text { max }}$ from 1-mile walking performance for both equations with a SEE of $\pm 0.335 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, or $\pm 4.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$. This means that about $68 \%$ of the people tested have an actual $\mathrm{VO}_{2 \text { max }}$ within $\pm 0.335 \mathrm{~L} \cdot \mathrm{~min}^{-1}\left( \pm 4.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}\right)$ of the predicted value. The group studied ranged in age from 30 to 69 years; thus, the prediction method applies to a large segment of the adult population.

The following data for a 30-year-old female illustrate the prediction method:

$$
\begin{aligned}
\text { Body weight } & =155.5 \mathrm{lb} \\
\mathrm{~T} 1 & =13.56 \mathrm{~min} \\
\text { HR1 } 4 & =145 \mathrm{~b} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

Substituting in the equation to predict $\mathrm{VO}_{2 \max }$ in mL . $\mathrm{kg}^{-1} \cdot \min ^{-1}$ :

$$
\begin{aligned}
\mathrm{VO}_{2 \max }= & 132.853-(0.0769 \times 155.5)-(0.3877 \times 30.0) \\
& +(6.315 \times 0)-(3.2649 \times 13.56) \\
& -(0.1565 \times 145) \\
\mathrm{VO}_{2 \max }= & 132.853-(11.96)-(11.63)+(0) \\
& -(44.27)-(22.69) \\
\mathrm{VO}_{2 \max }= & 42.3 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}
\end{aligned}
$$

## Endurance Runs

As with walking tests, runs of various durations or distances evaluate aerobic fitness. Test use reasonably assumes that a person s ability to maintain a high, steady-rate oxygen consumption largely determines the distance run over at least 5 minutes duration. This ability depends on the maximum capacity to generate energy aerobically (i.e., $\mathrm{VO}_{2 \max }$ ). This rationale provided the framework for a field performance test devised in 1959 to evaluate aerobic fitness of military personnel. ${ }^{2}$ The test required subjects to run as far as possible in 15 minutes. A 1968 study by Cooper shortened run time to 12 minutes. ${ }^{15}$

In his original validation of the 12 -minute test, Cooper reported a strong association between $\mathrm{VO}_{2 \max }$ of Air Force personnel and distances run-walked in 12 minutes. The correlation coefficient was $r=0.90$ between 12-minute run-walk distance and $\mathrm{VO}_{2 \max }\left(\mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}\right)$ in 47 men who varied considerably in age ( 17 to 54 y ), body mass ( 52 to 123 kg ), and $\mathrm{VO}_{2 \max }$ ( 31 to $59 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}$ ). Other researchers reported the same correlation for 9 ninth-grade boys. ${ }^{19}$ Subsequent studies have failed to demonstrate as strong a connection between Cooper 12-minute run scores and aerobic capacity. For example, one study measured 11- to 14 -year-old boys and reported a correlation of $r=0.65 .^{47}$ For a group of 26 female athletes, the correlation between the run-walk scores and $\mathrm{VO}_{2 \max }$ was $r=0.70,{ }^{48}$ and for 36 untrained college women a similar correlation of $r=0.67$ emerged. ${ }^{40}$

Importantly, a simple correlation between run-walk scores and $\mathrm{VO}_{2 \text { max }}$ does not consider the interacting effects of age and body mass. These variables themselves relate to both run-walk times and $\mathrm{VO}_{2 \max }$ scores. When restricting these original data to the same age range as subjects in the
preceding study of 36 untrained women, the computed correlation coefficient decreased dramatically from $r=0.90$ to $r=0.59$.

One must view $\mathrm{VO}_{2 \text { max }}$ predictions based on running performance with caution. The need to establish a consistent level of motivation and effective pacing during running becomes critical with inexperienced subjects. Some individuals achieve an optimal pace throughout the run. Others may run too fast early in the run and be forced to slow down or even stop before completing the test. Other individuals may begin too slowly and continue this way, so that their final performance scores reflect inappropriate pacing or lack of motivation rather than poor physiologic capacity. In addition, $\mathrm{VO}_{2 \text { max }}$ does not singularly determine endurance running performance. Body mass and fatness, running economy, and percentage of aerobic capacity sustained without blood lactate buildup also contribute to successful running. Generally, the SEE of predicting $V_{2_{2 \text { max }}}$ from run-walk performance averages about 8 to $10 \%$ of the predicted value.

Limitations for Use with Children. Maximum 1-mile run or walk times serve only limited use for $\mathrm{VO}_{2 \text { max }}$ prediction in growing children because the age-related exercise performance improvements in youth relate poorly to changes in aerobic capacity. ${ }^{16}$ The largest contributions to test score improvement in children as they grow older result from increased percentage of $\mathrm{VO}_{2 \text { max }}$ sustained during the exercise (i.e., increased blood lactate threshold) and improved running economy. Both factors contribute substantially to faster times independent of any improvement in $\mathrm{VO}_{2 \text { max }}$.

## Predictions Based on Heart Rate

Tests to predict $\mathrm{VO}_{2 \text { max }}$ use exercise or postexercise heart rate during a standardized regimen of submaximal exercise performed on either a bicycle ergometer, treadmill, or step test. These tests apply the essentially linear relationship between heart rate ( HR ) and oxygen consumption $\left(\mathrm{VO}_{2}\right)$ during increasing intensities of light to relatively intense aerobic exercise. The slope of the line to describe the $\mathrm{HR} \mathrm{VO}_{2}$ relationship (i.e., rate of heart rate increase) reflects the adequacy of the cardiovascular response and aerobic fitness capacity. The $\mathrm{VO}_{2 \text { max }}$ is estimated by drawing a best-fit straight line through several submaximal points that relate heart rate and oxygen consumption (or exercise intensity); the $\mathbf{H R} \mathbf{V O}_{\mathbf{2}}$ line is then extended to an assumed maximum heart rate for the subject s age.

Figure 11.14 illustrates the extrapolation procedure for an untrained and an endurance-trained college student. Four submaximal measures during graded exercise provided the data points to construct the $\mathrm{HR} \mathrm{VO}_{2}$ line. Each person s $\mathrm{HR} \mathrm{VO}_{2}$ line tends toward linearity, although the slope of the line often differs considerably. A person of relatively high aerobic fitness performs more intense exercise (achieves higher $\mathrm{VO}_{2}$ ) before reaching a heart rate of 140 or $160 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ than a less-fit person. Because heart rate increases linearly with exercise intensity $\left(\mathrm{VO}_{2}\right)$, the person with the smallest heart rate increase tends to achieve the highest exercise capacity and,


Untrained $\square$ Endurance trained
Figure 11.14 • Extrapolating the linear relationship between submaximal heart rate and oxygen consumption up to an assumed maximum heart rate during graded exercise by an untrained subject and an endurance-trained subject.
hence, the highest $\mathrm{VO}_{2 \text { max }}$. Extrapolation of the $\mathrm{HR} \mathrm{VO}_{2}$ line to a heart rate of $195 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ - the assumed maximum heart rate for subjects of college age-predicted the $\mathrm{VO}_{2 \text { max }}$ of the two subjects depicted in Figure 11.14.

The following four assumptions affect the accuracy of the $\mathrm{VO}_{2 \text { max }}$ prediction from submaximal exercise heart rate:

1. Linearity of heart rate oxygen consumption (exercise intensity) relationship. This assumption generally holds, particularly during light to moderate exercise. In some subjects, the $\mathrm{HR} \mathrm{VO}_{2}$ line curves (asymptotes) at more intense workloads in a direction to indicate larger than expected increase in oxygen consumption per unit increase in heart rate. Oxygen consumption increases more than predicted by linear extrapolation of the $\mathrm{HR} \mathrm{VO} \mathrm{O}_{2}$ line. This underestimates the $\mathrm{VO}_{2 \text { max }}$ of these subjects.
2. Similar maximum heart rates for all subjects. One standard deviation from the average maximum heart rate for individuals of the same age equals $\pm 10 \mathrm{~b}$ • $\mathrm{min}^{-1}$. Extrapolating the $\mathrm{HR} \mathrm{VO}_{2}$ line of a young adult to $195 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, for example, overestimates the $\mathrm{VO}_{2 \text { max }}$ of a person whose actual maximum heart rate is $185 \mathrm{~b} \cdot \mathrm{~min}^{-1}$. The opposite occurs for a subject with an actual maximum heart rate of 210 b -$\mathrm{min}^{-1}$. Maximum heart rate also decreases with age. Failure to consider this age effect (i.e., extrapolating
to a heart rate of $195 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, the average heart rate for 25-year-olds) consistently overestimates $\mathrm{VO}_{2 \text { max }}$ in older subjects. Chapter 31 discusses the effect of age on maximum heart rate.
3. Assumed constant economy and mechanical efficiency during exercise. Variations in exercise economy contribute to $\mathrm{VO}_{2 \max }$ prediction errors with tests that estimate submaximal oxygen consumption from the external workload (rather than measuring $\mathrm{VO}_{2}$ directly). More specifically, an underestimation of $\mathrm{VO}_{2 \text { max }}$ occurs for a subject with poor exercise economy whose submaximal oxygen consumption increases more than assumed on the basis of estimates from exercise intensity. This occurs because of an elevated heart rate from the added oxygen cost of uneconomical exercise. Variation in walking or cycling economy among individuals usually does not exceed $6 \%$; for bench stepping, the variation can equal about $10 \%$, a value unrelated to age, leg length, aerobic fitness, or percentage body fat. ${ }^{87}$ Seemingly small modifications in test procedures profoundly affect exercise economy. Simply allowing individuals to support themselves with the treadmill handrails reduces the oxygen cost of exercise by as much as $30 \% .^{107}$
4. Day-to-day heart rate variation. Even under highly standardized conditions, the day-to-day variation in heart rate averages about $5 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ during submaximal exercise.

Within the framework of these limitations, $V O_{2 \max }$ predicted from submaximal heart rate generally falls within 10 to $20 \%$ of the person s actual value. This accuracy level remains unacceptable for research purposes, yet the prediction tests can effectively screen and classify individuals for aerobic fitness in a gymnasium or health-club setting. The technique also has proved useful to estimate aerobic capacity during pregnancy (see Chapter 9, In a Practical Sense p. 199). ${ }^{76}$

## The Step Test

Prediction equations applied to step-test results can estimate $\mathrm{VO}_{2 \max }$ with reasonable accuracy.

In our laboratories we devised a 3-minute step test to evaluate exercise heart rate responses of thousands of college men and women. ${ }^{53}$ The test used gymnasium bleachers $\left(16^{1 /} / 4\right.$ in. high) to test large numbers of students at the same time. Subjects performed each stepping cycle to a four-step cadence, up-up-down-down. The women performed 22 complete stepups per minute, regulated by a metronome set at 88 beats per minute. Males tended to be fitter for step-up exercise than females, so their cadence was 24 step-ups per minute, or 96 beats per minute on the metronome. The step test began after a brief demonstration and practice period. At the completion of stepping, students remained standing while pulse rate was measured for 15 seconds, 5 to 20 seconds into recovery. Recovery heart rate was converted to beats per minute (15-s $\mathrm{HR} \times 4$ ).

INTEGRATIVE QUESTION

> Explain why $\mathrm{VO}_{2 \max }$ values do not always agree when measured directly in the laboratory and predicted with a 12-minute run.

Based on the linear relationship between heart rate and oxygen consumption during submaximal exercise, one would expect a person with a low step-test heart rate (i.e., farther from maximum) to experience less exercise stress than someone of the same age who performed the identical exercise with a relatively high heart rate. In other words, a lower heart rate during a standard exercise corresponds to a higher $\mathrm{VO}_{2 \max }$. To determine validity of the step test to estimate aerobic capacity, we then measured the $\mathrm{VO}_{2 \max }$ for a group of untrained, young adult men and women who also performed the step test. Figure 11.15 illustrates the relationship between $\mathrm{VO}_{2 \text { max }}$ and the women s step-test scores. The results clearly indicated that step-test heart rate provided useful information about $\mathrm{VO}_{2 \max }$. Subjects with a high recovery heart rate tended to have a lower $\mathrm{VO}_{2 \text { max }}$, whereas a faster recovery (lower heart rate) related to a relatively high $\mathrm{VO}_{2 \max }$. The following equations predict $\mathrm{VO}_{2 \text { max }}\left(\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}\right)$ from step-test pulse rate $\left(\mathrm{ST}_{\text {pulse }}\right)$ for similar groups of young adult men and women:

$$
\begin{aligned}
& \text { Men: } \\
\mathrm{VO}_{2 \max }= & 111.33-\left(0.42 \times \mathrm{ST}_{\text {pulse }}\left[\mathrm{b} \cdot \min ^{-1}\right]\right) \\
& \text { Women: } \\
\mathrm{VO}_{2 \max }= & 65.81-\left(0.1847-\mathrm{ST}_{\text {pulse }}\left[\mathrm{b} \cdot \min ^{-1}\right]\right)
\end{aligned}
$$

For example, an untrained college-aged male with a steptest recovery pulse rate of $152 \mathrm{~b} \cdot \min ^{-1}$ has a predicted $\mathrm{VO}_{2 \text { max }}$ of $47.5 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}(111.33-[0.42 \times 152])$. For predictive accuracy, one can be $95 \%$ confident that the predicted $\mathrm{VO}_{2 \text { max }}$ falls within $16 \%$ of the person s true $\mathrm{VO}_{2 \text { max }}$.


Figure 11.15 - Scattergram and line of best fit that relates step-test heart rate score and maximal oxygen consumption in untrained college women.

## TABLE 11.6 • Input Information on Level of Physical Activity and Perceived Functional Capacity for Predicting from Nonexercise Data

## A. Physical Activity Rating (PA-R)

Select the number that best describes your overall level of physical activity for the previous 6 months:

```
Points Description
    0 inactive: avoid walking or exertion; e.g., always use elevator, drive when possible instead of walking
    l light activity: walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing or perspiration
2 moderate activity: }10\mathrm{ to }60\mathrm{ minutes per week of moderate activity such as golf, horseback riding, calisthenics, table tennis,
    bowling, weightlifting, yard work, cleaning house, walking for exercise
moderate activity: over 1 hour per week of moderate activity described above
vigorous activity: run less than 1 mile per week or spend less than 30 min per week in comparable activity such as running or
    jogging, lap swimming, cycling, rowing, aerobics, skipping rope, running in place, or engaging in vigorous aerobic-type activity
    such as soccer, basketball, tennis, racquetball, or handball
vigorous activity: run }1\mathrm{ mile to less than 5 miles per week or spend 30 min to less than 60 min per week in comparable physical
    activity as described above
vigorous activity: run 5 miles to less than }10\mathrm{ miles per week or spend 1 hour to less than 3 hours per week in comparable
    physical activity as described above
vigorous activity: run }10\mathrm{ miles to less than }15\mathrm{ miles per week or spend 3 hours to less than 6 hours per week in comparable
    physical activity as described above
vigorous activity: run }15\mathrm{ miles to less than }20\mathrm{ miles per week or spend 6 hours to less than 7 hours per week in comparable
    physical activity as described above
9 vigorous activity: run 20 to 25 miles per week or spend 7 to 8 hours per week in comparable physical activity as described above
vigorous activity: run over 25 miles per week or spend over 8 hours per week in comparable physical activity as described above
```


## B. Perceived Functional Ability (PFA) Questions

Suppose you exercise continuously on an indoor track for 1 mile. Which exercise pace is right for you not too easy or not too hard? Circle the appropriate number from 1 to 13.

```
Points Description
    Walking at a slow pace ( 18-min mile or more)
2
3 Walking at a medium pace (16-min mile)
4
5
6
7
8
9
1 0
1 1
1 2
13
```

How fast could you cover a distance of 3 miles and NOT become breathless or overly fatigued? Be realistic. Circle the appropriate number from 1 to 13.

```
Points Description
    I could walk the entire distance at a slow pace (18-min per mile or more)
    I could walk the entire distance at a medium pace (16-min per mile)
    I could walk the entire distance at a fast pace (14-min per mile)
    I could jog the entire distance at a slow pace (12-min per mile)
    I could jog the entire distance at a medium pace (10-min per mile)
    I could jog the entire distance at a fast pace (8-min per mile)
    I could run the entire distance at a fast pace (7-min per mile or less)
```

[^25]
## Predictions from Nonexercise Data

A unique approach to $\mathrm{VO}_{2 \text { max }}$ prediction for quick screening of large groups of individuals requires specific nonexercise data from a questionnaire. ${ }^{27,37}$ The SEE for a predicted score from the method described below equals $\pm 3.44 \mathrm{~mL} \mathrm{O}_{2} \cdot \mathrm{~kg}^{-1}$. $\min ^{-1}$.

Data input to predict $V O_{2 \max }$ from nonexercise data:

1. $\boldsymbol{S e x}$-(female $=0$; male $=1$ ).
2. Body mass index (BMI; kg $\cdot \mathbf{m}^{\mathbf{- 2}}$ )—Self-reported body mass ( kg ) and stature (m) used to compute BMI as follows:

$$
\mathrm{BMI}=\text { Body mass }(\mathrm{kg}) \div \text { Stature }\left(\mathrm{m}^{2}\right)
$$

3. Physical activity rating (PA-R)—A point value between 0 and 10 represents overall physical activity level for the previous 6 months (Table 11.6A).
4. Perceived functional ability (PFA)—Sum of the point values between 0 and 13 for questions about current level of perceived functional ability to maintain a continuous pace on an indoor track for 1 mile and perceived pace to cover a distance of 3 miles without becoming breathless or overly fatigued (Table 11.6B).

## Equation

$\mathrm{VO}_{2 \text { max }}\left(\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}\right)=44.895+(7.042 \times$ Sex $)$
$-(0.823 \times \mathrm{BMI})+(0.738 \times \mathrm{PFA})+(0.688 \times \mathrm{PA}-\mathrm{R})$

## Example

1. Sex, female
2. $\mathrm{BMI}=22.66$ (self-reported body mass $=136 \mathrm{lb}$ [61.7 kg]; self-reported height $=5$ feet 5 inches $[1.65 \mathrm{~m}]) ; \mathrm{BMI}=61.7 \div(1.65 \times 1.65)=22.66$
3. PA-R score $=5($ see Table 11.6A)
4. PFA score $=15$ (sum of 7 scored on first set of questions and 8 on second set; see Table 11.6B.)

## Computation

$$
\begin{aligned}
\mathrm{VO}_{2 \max }= & 44.895+(7.042 \times \text { Sex })-(0.823 \times \mathrm{BMI}) \\
& +(0.738 \times \text { PFA })+(0.688 \times \text { PA-R }) \\
= & 44.895+(7.042 \times 0)-(0.823 \times 22.66) \\
& +(0.738 \times 15)+(0.688 \times 5) \\
= & 44.8950-18.65+11.07+3.77 \\
= & 41.1 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

## Summary

1. The concepts of individual differences and exercise specificity provide an important framework to understand anaerobic and aerobic power capacities.
2. Precise contributions of anaerobic and aerobic energy transfer depend largely on exercise intensity and duration. During strength and power sprint activities, energy transfer primarily involves the
immediate and short-term (anaerobic) energy systems. The long-term (aerobic) energy system becomes progressively more active during exercise lasting longer than 2 minutes.
3. Appropriate physiologic measurements and performance tests evaluate the capacity of each energytransfer system. These tests can evaluate energytransfer capacity at a particular point in time or show changes consequent to a specific exercisetraining program.
4. The stair-sprinting test commonly measures the power capacity of the intramuscular high-energy phosphates ATP and PCr. The 30 -second, all-out Wingate test evaluates peak power and average power output capacity from the glycolytic pathway. Interpretations of test results must consider body size and the exercise specificity principle.
5. The maximal accumulated oxygen deficit (MAOD) correlates positively with other anaerobic performance tests; it demonstrates independence from aerobic energy sources and differentiates between aerobically and anaerobically trained individuals.
6. Training status, acid base regulation, and motivation contribute to individual differences in the capacities of the immediate and short-term anaerobic energy systems.
7. Maximal oxygen consumption $\left(\mathrm{VO}_{2 \text { max }}\right)$ provides important, reproducible information about the power capacity of the long-term energy system, including the functional capacity of the physiologic support systems.
8. Heredity, state and type of training, age, gender, and body composition contribute uniquely to an individual s $\mathrm{VO}_{2 \text { max }}$.
9. Expressing aerobic capacity by some ratio of body size or composition (e.g., $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ or mL $\cdot \mathrm{kg} \mathrm{FFM}{ }^{-1} \cdot \min ^{-1}$ ) reduces the gender difference in $\mathrm{VO}_{2 \max }$.
10. Tests to predict $\mathrm{VO}_{2 \max }$ from submaximal physiologic and performance data often prove useful for fitness classification purposes.
11. Tests to predict $\mathrm{VO}_{2 \text { max }}$ from submaximal physiologic and performance data rely on the validity of four assumptions: (1) linearity of the $\mathrm{HR} \mathrm{VO}_{2}$ relationship, (2) constancy in maximum heart rate, (3) relatively constant exercise economy, and (4) minimal day-to-day variation in exercise heart rate.
12. Field methods provide useful information about cardiovascular-aerobic function in the absence of more valid laboratory methods.
13. Nonexercise data predicts $\mathrm{VO}_{2 \text { max }}$ accurately for screening and classification purposes.

References are available online at http://thepoint.lww.com/mkk7e.

## SECTION



11


# Aerobic Systems of Energy Delivery and Utilization 

## OVERVIEW

Many sports, recreational, and occupational activities require a moderately intense and sustained energy release. The aerobic breakdown of carbohydrates, fats, and proteins provides energy for such exercise by phosphorylating adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Two factors influence how well individuals sustain a high level of steadyrate (aerobic) physical activity with minimal fatigue:

1. Capacity and integration of physiologic systems for oxygen delivery
2. Capacity of specific muscle fibers activated in exercise to generate ATP aerobically

Individual differences in aerobic exercise capacity depend on the combined influence of ventilatory, circulatory, muscular, and endocrine systems during exercise described in this section. Knowledge about the energy requirements and corresponding physiologic adjustments to exercise provides a solid basis to formulate an effective training program and evaluate its results.

# Interview with Dr. Loring B. Rowell 



Education: BS (Springfield College, Springfield, MA); PhD (Physiology, University of Minnesota, MN); postgraduate training (Senior Fellow, Department of Physiology and Biophysics, and of Medicine in Cardiology, University of Washington School of Medicine, St. Louis, MO)

## Current Affiliation: Professor Emeritus, University of Washington

Honors and Awards: See Appendix E, available online at http://thepoint. lww.com/mkk7e.

Research Focus: Human cardiovascular system control and adjustments to exercise

Memorable Publication: Rowell LB. Neural control of muscle blood flow. Importance during dynamic exercise. Clin Exp Pharm Physiol 1997;24:117.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

In recognition of his having achieved excellence in his contributions to cardiovascular physiology, as a scientist, as a teacher and mentor, and as an author and editor.

Dr. Rowells contributions have focused on the regulation of the human cardiovascular system in response to the stresses imposed by exercise, heat, gravity, and hypoxia. Included among a long list of landmark findings:

- Demonstration that decrements in visceral organ blood flow were proportionate to relative exercise intensity
- Evidence that the sympathetically mediated redistribution of blood flow, blood volume, and filling pressures was a critical regulatory response to exercise in the heat
- Proof of the dominant reflex role of systemic baroreceptors in the regulation of blood pressure under stress
- Evidence that muscle chemoreflexes and baroreceptors were reset during exercise and that this was crucial in the matching of cardiovascular responses to metabolic requirements

Tracing Dr. Rowells scientific achievements over the past three decades reveals a fascinating progression of discovery, with one study springing from the questions raised by its predecessor. The questions become more and more difficult, and the methods and experimental designs, more complex and ingenious. Thus, as the years progressed the risk of failure was often high, but this was
overridden by the excitement of producing truly novel and significant advances. Dr. Rowell demonstrated how important basic physiologic understandings could be uncovered in healthy human subjects but did not hesitate to use animal or disease models when necessary to further knowledge. The same thoroughness in scientific inquiry has been perpetuated by the many leading scientists he has mentored.

Dr. Rowells writing has had a major impact on the field. He wrote the first physiological reviews on the topic of exercise physiology over 20 years ago. More recently, he has provided two landmark reference texts concerned with human cardiovascular regulation and was editor-inchief of the first APS-sponsored Handbook of Exercise Physiology. As an author, Dr. Rowell was never merely an information broker; rather, his writings constantly challenged the reader to criticize accepted dogma, tackle the toughest questions, and advance the field.

Dr. Rowell has been especially valuable to his students, his colleagues, his professional societies, and his science because he never trivialized any task or problem. His approach to lifes challenges has always been intense and thorough, whether the problem was of a scientific or humanistic nature. Thus, he tackled the mysteries of baroreceptor resetting with the same zeal and dedication and work ethic that he applied to the editing of a handbook, to traversing the steep terrain of a snow-covered mountain, to the preparation of a single lecture, to debating a controversial point of science, or to solving the predicaments of friends or colleagues whom he felt were dealt with unfairly. In short, Dr. Rowell is indeed good value! He is well deserving of the Colleges highest distinction.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

$>$ Dr. Peter V. Karpovich at Springfield College (MA) provided my first exposure to the science of physiology. His precise and demanding teaching provided the motivation to seek an advanced degree in physiology and to do research in that field.

## What influence did your undergraduate education have on your final career choice?

> Again, the undergraduate teaching of Dr. Karpovich, my experience working in his laboratory, and his urging and support paved the way. His influence led me to the Department of Physiology at the University of Minnesota Medical School and the laboratories of Ancel Keys, Henry L. Taylor, and Francisco Grande and colleagues.

## Who were the most influential people in your career, and why?

> First, Drs. Henry L. Taylor and Francisco Grande guided my graduate education and taught me how to do research. They became lifelong models for an approach to research and scholarship that I admire greatly. Second, my scientific colleagues, students, and fellows have all provided me with constant stimulation and education, and have enriched my career.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> Regarding the most interesting and enjoyable aspects: First are the wonderful colleagues from all over the world who became lifelong friends and enormous positive influences on my life. Second was the research, the excitement of developing methods to answer a scientific question, getting an answer, having it accepted by peers, and seeing it published. The least enjoyable aspects were not having our answers accepted by our peers and any breakdown or failure of our developed methods.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

> Time and history must judge. I think it is the collection of experiments (1964 1974) in which we quantified the reductions in regional organ blood flow, which were
closely related to exercise intensity expressed as percent of $\mathrm{VO}_{2 \text { max }}$ and heart rate. They revealed the quantitative significance of this regional vasoconstriction to blood pressure regulation and to the redistribution of oxygen from resting organs to active muscle. And they showed how this regional vasoconstriction determines the volume of blood available to fill the heart (and thus stroke volume) in exercising humans and how this crucial adjustment is upset by skin vasodilation during heat stress.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

> My advice is based on physiology because that is what I do. I am a cardiovascular physiologist who has used exercise as a powerful precision tool to understand how the cardiovascular system works. Acquisition of a strong background in general physics, mathematics, and chemistry (inorganic, analytical, organic, and especially basic physical chemistry) is essential. In as much as the physiology of exercise is actually the total physiology of a nonresting, nonsupine individual, all areas of physiology are essential because there is no physiological function, regulation, or control that is not vital (i.e., exercise physiology $=$ physiology in toto). Thus, the broader and deeper the training in physiology, the more likely the research will yield basic new information. To quote Sir Joseph Barcroft

(1934), The condition of exercise is not a mere variant of the condition of rest, it is the essence of the machine.

## What interests have you pursued outside your professional career?

- Competitive and recreational Alpine skiing, plus coaching and instruction; Alpinism (glacier and rock climbing); road and mountain bicycling; tennis; landscape painting (oil); and historical literature.


## Where do you see the exercise science field (particularly your area of greatest interest) heading

 in the next 20 years?> This field may play a more vital role in the biological sciences than we had once imagined. If the basic life scientists rush to apply their expertise to provide functional meaning to the genetic code, as is expected, who will be left to teach basic human biology and physiology? Who will explore the functional consequences of aging, for example? Who will discover what controls breathing and circulation during exercise? Who will do the systematic, integrative science that reveals how whole organ systems and organisms actually work? These questions are not likely to be answered by reductionists (e.g., molecular biologists) working upward from molecules to cells to systemsthis is in the wrong direction!

## You have the opportunity to give a last lecture.

 Describe its primary focus.> Its primary focus would be on the question, What reflexes govern cardiovascular function in exercise? This century-old, unanswered question concerns what is being controlled (and how), and what signals or errors are being sensed (and how) and corrected (and how) by the autonomic nervous system. The lecture would present the currently dominant ideas and would argue which ones do not seem feasible (and why) and which ones seem feasible based on current knowledge. It would ask where we turn next. And, finally, it would warn us of the great danger of ignoring historya-danger now encouraged by exclusion of all literature published before 1970 from the computer indexing services.


## CHAPTER 12

## Pulmonary Structure and Function

## CHAPTER OBJECTIVES

- Diagram the ventilatory system-show the glottis, trachea, bronchi, bronchioles, and alveoli
> Discuss the mechanical and muscular aspects of inspiration and expiration during rest and exercise
> Define and quantify static and dynamic lung function measures and their relation to exercise performance
- Define minute ventilation, alveolar ventilation, ventilation-perfusion ratio, and anatomic and physiologic dead space
- Explain the four phases of the Valsalva and discuss the physiologic consequences of this maneuver
> Describe the effects of cold-weather exercise on the respiratory tract


## SURFACE AREA AND GAS EXCHANGE

If oxygen supply to muscle depended only on diffusion through the skin, one could not sustain the basal oxygen requirement of 0.2 to 0.4 L per min, let alone the 4 - to 5 - L per minute oxygen consumption and carbon dioxide elimination required to run a world-class, 5-minute per mile marathon pace. The relatively compact and remarkably efficient ventilatory system meets the requirements for gas exchange. This
system, depicted in Figure 12.1, regulates the gaseous state of the body s external pulmonary environment to effectively aerate body fluids.

## ANATOMY OF VENTILATION

Pulmonary ventilation describes the process of moving and exchanging ambient air with air in the lungs. Air entering the nose and mouth flows into the conductive portions of the

ventilatory system where it adjusts to body temperature and is filtered and almost completely humidified as it travels through the trachea. Air conditioning continues as inspired air passes into two bronchi, the large first generation of airways that serve as primary conduits into each of the lungs. The bronchi further subdivide into numerous bronchioles that conduct inspired air through a winding, narrow route until it eventually mixes with existing air in the alveolar ducts. Microscopic alveoli, hollow terminal cavities that are spherical outcroppings of the respiratory bronchioles, completely envelop these ducts.

## The Lungs

The lungs provide the gas exchange surface that separates blood from the surrounding alveolar gaseous environment. Oxygen transfers from alveolar air into alveolar capillary blood; simultaneously, the blood s carbon dioxide moves into the alveolar chambers where it subsequently flows into ambient air. An average-sized adult s lungs weigh approximately 1 kg , and the volume varies between 4 and 6 L (the volume of air in a basketball). Lung tissue consists of about $10 \%$ solid tissue, with the remainder filled by air and blood. If spread out, lung tissue would cover an area of 50 to $100 \mathrm{~m}^{2}$, an area 20 to 50 times larger than the body s external surface or about half of a tennis court or an entire badminton court (Fig. 12.2).

The highly vascularized, moist surface of the lungs fits within the chest cavity with numerous infoldings. The lung membranes fold over onto themselves to provide a considerable interface to aerate blood. At rest, a single red blood cell remains in a pulmonary capillary for only about 0.5 to 1.0 second as it traverses past two to three individual alveoli. During any 1 second of maximal exercise, no more than 1 pint of blood flows within the fine network of lung tissue blood vessels.

## The Alveoli

The lungs contain more than 600 million alveoli, the final branching of the respiratory tree. These elastic, thin-walled membranous sacs (approximately 0.3 mm in diameter, composed of simple squamous epithelial cells) provide the vital


Figure 12.2 The lungs provide an exceptionally large surface for gas exchange.
surface for gas exchange between lung tissue and blood. Alveolar tissue receives the largest blood supply of any of the body s organs. Millions of short, thin-walled capillaries and alveoli lie side by side; air moves along one side and blood along the other. Gases diffuse across the extremely thin barrier of alveolar and capillary cells $(\sim 0.3 \mu \mathrm{~m})$; the diffusion distance remains relatively constant throughout varying levels of exercise. The integrity of the thin pulmonary blood gas barrier remains constant during sustained exercise. The surface remains as thin as possible (without compromising structural integrity) to facilitate rapid exchange of respiratory gases. In elite endurance athletes, alveolar mechanical stress in near-maximal exercise (large ventilation and accompanying pulmonary blood flow) can impair the blood gas barrier s permeability. For these individuals, an increased permeability is reflected by elevated concentrations of red blood cells, total protein, and leukotriene $\mathrm{B}_{4}$ (a potent chemotactic agent that initiates, coordinates, and amplifies the inflammatory response) in bronchoalveolar lavage fluid with maximal exercise. ${ }^{22,23,46}$

Small pores of Kohn within each alveolus evenly disperse surfactant (see p. 258) over the respiratory membranes to reduce surface tension for easier alveolar inflation. The pores also provide for gas interchange between adjacent alveoli. Mixing in this manner sustains the indirect ventilation of alveoli damaged or blocked from lung disease (see Chapter 32).

Each minute at rest, approximately 250 mL of oxygen leaves the alveoli and enters the blood, and 200 mL of carbon dioxide diffuses in the opposite direction. When endurance athletes exercise intensely, nearly 25 times this quantity of oxygen and carbon dioxide transfers across the alveolar capillary membrane. In healthy individuals, pulmonary ventilation during rest and exercise primarily maintains a constant and favorable oxygen and carbon dioxide concentration in the alveolar chambers. to ensure complete gaseous exchange before the blood leaves the lungs for transport throughout the body.

## MECHANICS OF VENTILATION

Figure 12.3 illustrates the physical principle that underlies breathing dynamics. Note the two lung-shaped balloons suspended in a jar with its glass bottom replaced by a thin rubber membrane. Pulling the membrane down increases jar volume. This reduces air pressure within the jar compared with ambient air outside the jar. This imbalance causes air to rush in to inflate the balloons. Conversely, as the elastic membrane recoils, pressure within the jar temporarily increases and air rushes out. Increasing the depth and rate of descent and ascent of the rubber membrane exchanges a considerable air volume within the balloons in a given time.

Figure 12.4 illustrates the ventilatory system subdivided into two parts: (1) conducting zones (zones 1 16) that includes the trachea and terminal bronchioles and (2) transitional and respiratory zones (zones 17 23) that comprise bronchioles, alveolar ducts, and alveoli. The structures of the conducting zone contain no alveoli, so the term anatomic


Figure 12.3 Mechanics of breathing. During inspiration, the chest cavity increases in size because the ribs raise and the diaphragm descends, causing air to flow into the lungs. Inhalation increases in the anterior posterior (A P) and vertical diameters of the rib cage. Approximately $70 \%$ of lung expansion results from A P enlargement and $30 \%$ from diaphragmatic descent. In addition to diaphragmatic action, the external intercostal muscles become active and the internal intercostal muscles relax during inhalation. During exhalation, the ribs swing down and the diaphragm returns to a relaxed position. This reduces thoracic cavity volume and air rushes out. The movement of the jar s rubber bottom causes air to enter and exit the two balloons, simulating the action of the diaphragm. The movement of the bucket handle simulates rib action. The diaphragm, external intercostals, sternocleidomastoids, scapular elevators, anterior serrati scleni, and spinal erector muscles compose the inspiratory muscles that elevate and enlarge the thorax; muscles of expiration (rectus abdominis, internal intercostals, posterior inferior serrati muscles) depress the thorax and reduce its size.
dead space describes this area (see p. 263). The respiratory zone represents the site of gas exchange. It occupies about 2.5 to 3.0 L and constitutes the largest portion of the total lung volume. Air moving into the lungs literally flows down the trachea to the terminal bronchi, much like water flowing through a hose. As air reaches the smaller air passages in the transitional zone, the tremendous increase in surface area slows airflow into the alveoli.

The two ventilatory conducting zones functions also include air transport, humidification, warming, particle filtration, vocalization, and immunoglobulin secretion. Respiratory zone functions encompass surfactant production (in the alveolar endothelium), molecule activation and inactivation (in the capillary endothelium), blood clotting regulation, and endocrine function.

Figure 12.5 depicts the relationship between airway generation (forward velocity) and total cross-sectional area of the conducting passages of various lung segments. Airway cross section increases considerably (and velocity slows) as air moves through the conducting zone to the terminal bronchioles. At this stage, diffusion provides the primary means for gas movement and distribution. In the alveoli, gas pressures rapidly equilibrate on each side of the alveolar capillary membrane. Ficks law of diffusion (derived in 1845 by German physiologist Adolf Eugen Fick, inventor of contact lenses and the first to devise a technique for measuring cardiac output [see Chapter 17]) governs the diffusion of gas across a fluid membrane. This law states that a gas diffuses through a sheet of tissue at a rate (1) directly proportional to the tissue area, a diffusion constant, and the pressure differential of the gas on each side of the membrane


Figure 12.4 Separation of human lung tissue into a series of discrete conduction zones (zones 1 through 16) and transitional and respiratory zones (zones 17 through 23).
and (2) inversely proportional to tissue thickness. The diffusion constant (D) relates directly to gas solubility (S) and inversely to the square root of the molecular weight (MW) of the gas. On a per-molecule basis, carbon dioxide $(\mathrm{MW}=44)$ diffuses about 20 times faster through thin membranous tissues than oxygen $(\mathrm{MW}=32)$ because of carbon dioxides higher solubility despite the relatively similar MWs of the two gases.

The lungs do not merely remain suspended in the chest cavity as the balloons do in Figure 12.3. Instead, the pressure differential between the air in the lungs and the lung chest wall interface causes them to adhere to the chest wall and literally follow its every movement. Thus, any change in thoracic cavity volume correspondingly alters lung volume.

## Inspiration

The diaphragm, a large, dome-shaped sheet of striated musculofibrous tissue, serves the same purpose as the jars rubber membrane depicted in Figure 12.3. This primary ventilatory muscle, whose mitochondrial volume density, oxidative capacity of muscle fibers, and aerobic capacity exceed by up to fourfold that of most other skeletal muscles, ${ }^{33}$ creates an


Figure 12.5 Airflow in the lungs in relation to the total cross-sectional tissue area. Forward airflow velocity during inspiration decreases considerably because of the large increase in tissue cross-sectional area beginning in the region of the terminal bronchioles. (Modified from West JB. Respiratory physiologythe essentials. 8th ed. Baltimore: Lippincott Williams \& Wilkins, 2008.)
airtight separation between the abdominal and thoracic cavities. The diaphragm contains a series of openings through which the esophagus, blood vessels, and nerves pass. This separating membrane possesses high oxidative potential and the greatest capacity of all the respiratory muscles for shortening and volume displacement. ${ }^{13,34}$

During inspiration, the diaphragm muscle contracts, flattens, and moves downward toward the abdominal cavity by as much as 10 cm . Elongation and enlargement of the chest cavity expands the air in the lungs, causing its intrapulmonic pressure to decrease to slightly below atmospheric pressure. The lungs inflate as the nose and mouth literally suck air inward. The degree of filling depends on the magnitude of inspiratory movements. Maximal activation of the inspiratory muscles of healthy individuals produces pressures that range between 80 and 140 mm Hg . Inspiration ends when thoracic cavity expansion ceases. This causes equality between intrapulmonic pressure and ambient atmospheric pressure.

During exercise, the highly efficient movements of the diaphragm, rib cage (ribs and sternum), and abdominal muscles synchronize to contribute to inspiration and expiration. ${ }^{2,25}$ During inspiration, the scaleni and external intercostal
muscles between the ribs contract, causing the ribs to rotate and lift up and away from the body. This action corresponds to the movement of the handle lifted up and away from the side of the bucket (see Fig. 12.3, upper right). Inspiratory action increases during exercise when the diaphragm descends, the ribs swing upward, and the sternum thrusts outward to increase the lateral and anterior posterior diameter of the thorax. Athletes often bend forward from the waist to facilitate breathing following exercise. This serves two purposes: (1) promotes blood flow back to the heart and (2) minimizes antagonistic effects of gravity on the usual upward direction of inspiratory movements.

## Expiration

Expiration during rest and light exercise represents a passive process of air movement out of the lungs and results from two factors: (1) natural recoil of the stretched lung tissue and (2) relaxation of the inspiratory muscles. The sternum and ribs swing down and the diaphragm rises toward the thoracic cavity. These movements decrease chest cavity volume and compress alveolar gas so air moves from the respiratory tract to the atmosphere. Expiration ends when the compressive force of expiratory muscles ceases and intrapulmonic pressure decreases to atmospheric pressure. During strenuous exercise, internal intercostal and abdominal muscles act powerfully on the ribs and abdominal cavity to reduce thoracic dimensions. ${ }^{14}$ This makes exhalation rapid and more extensive.

No major differences exist in ventilatory mechanics between men and women of different ages. At rest in the supine position, most persons breathe diaphragmatically ( abdominal breathers ), whereas in the upright position rib and sternum actions become more apparent. Rib cage movement dictates the rapid alterations in thoracic volume in strenuous exercise. Distinct biochemical differences among muscles that compose the respiratory pump provide the evidence that the rib musculature acts more rapidly than the diaphragm and abdominal muscles. ${ }^{35}$ The position of the head and back naturally adopted by distance runners-forward lean from the waist, neck flexed, and head extended forward with mandible parallel to the ground-favors pulmonary ventilation during intense exercise.

## Surfactant

Pressures vary continually within the alveolar and pleural spaces throughout the ventilatory cycle. Resistance to normal expansion of the lung cavity and alveoli progressively increases during inspiration from the effect of surface tension, primarily in the alveoli. Surface tension relates to a resisting force created at the surface of a liquid in contact with a gas, structure, or another liquid. The tension or force created causes the liquid to assume a shape that presents the smallest surface area to the surrounding medium. The greater the surface tension surrounding a spherical object such as an alveolus, the greater the force required to overcome the pressure within the sphere and cause it to enlarge or inflate.

Surfactant (a contraction of surface active agent, or literally a wetting agent) consists of a lipoprotein mixture of phospholipids, proteins, and calcium ions produced by alveolar epithelial cells. The main component of surfactant, the phospholipid dipalmitoylphosphatidylcholine, reduces surface tension. It mixes with the fluid that encircles the alveolar chambers. Its action interrupts the surrounding water layer, reducing the alveolar membrane s surface tension to increase overall lung compliance. This effect reduces the energy required for alveolar inflation and deflation. ${ }^{48}$

## LUNG VOLUMES AND CAPACITIES

Figure 12.6 illustrates various lung volume measurements and average values for men and women that affect the ability to increase breathing depth. To obtain these measurements, the subject rebreathes through a water-sealed, volumedisplacement recording spirometer, similar to the one described in Chapter 8 (Fig. 8.3), for measuring oxygen consumption by the closed-circuit method. As with many anatomic and physiologic measures, lung volumes vary with age, gender, and body size and composition, but particularly with stature. Common practice evaluates lung volumes by comparing them to established standards that consider these factors.

## Static Lung Volumes

The spirometer bell falls and rises during inhalation and exhalation to provide a record of ventilatory volume and breathing rate. Tidal volume (TV) describes air volume moved during either the inspiratory or expiratory phase of each breathing cycle (first portion of the record). Under resting conditions, TV usually ranges between 0.4 and 1.0 L of air per breath.

After recording several trials of TV, the subject inspires as deeply as possible following a normal inspiration. The additional 2.5 - to $3.5-\mathrm{L}$ volume above inspired tidal air represents the reserve ability for inhalation, referred to as the inspiratory reserve volume (IRV). Following IRV measurement, the subject reestablishes the normal breathing pattern. After a normal exhalation, the subject continues to exhale and forces as much air as possible from the lungs. This additional volume represents expiratory reserve volume (ERV), which ranges between 1.0 and 1.5 L for an average-sized man. During exercise, encroachment on IRV and ERV, particularly IRV, considerably increases TV.

The total volume of air voluntarily moved in one breath, from full inspiration to maximum expiration, represents the vital capacity (VC), or more precisely forced vital capacity (FVC). FVC includes TV plus IRV and ERV. FVC usually ranges between 4 and 5 L in healthy young men and between 3 and 4 L in healthy young women. Values of 6 to 7 L are not uncommon for tall individuals, and unusually large FVC values have been reported for a professional football player (7.6 L) and an Olympic gold medalist in cross-country skiing (8.1 L). ${ }^{3,47}$ These athletes large lung volumes generally reflect genetic influences and body size characteristics because exercise training does not appreciably change static lung volumes.


| Lung volume/capacity <br> Tidal Volume (TV) | Definition | Average values (mL) <br> Men Women |  |
| :---: | :---: | :---: | :---: |
|  | Volume inspired or expired per breath | 600 | 500 |
| Inspiratory Reserve Volume (IRV) | Maximum inspiration at end of tidal inspiration | 3000 | 1900 |
| Expiratory Reserve Volume (ERV) | Maxium expiration at end of tidal expiration | 1200 | 800 |
| Total Lung Capacity (TLC) | Volume in lungs after maximum inspiration | 6000 | 4200 |
| Residual Lung Volume (RLV) | Volume in lungs after maximum expiration | 1200 | 1000 |
| Forced Vital Capacity (FVC) | Maximum volume expired after maximum inspiration | 4800 | 3200 |
| Inspiratory Capacity (IC) | Maximum volume inspired following tidal expiration | 3600 | 2400 |
| Functional Residual Capacity (FRC) | Volume in lungs after tidal expiration | 2400 | 1800 |

Equation to predict RLV in normal-weight and overweight men and women*


## Residual Lung Volume

The residual lung volume (RLV) represents the air volume remaining in the lungs after exhaling as deeply as possible. This volume averages between 0.8 and 1.2 L for college-aged, healthy women and between 0.9 and 1.4 L for college-aged, healthy men. RLV for apparently healthy professional football
players ranges between 0.96 and $2.46 \mathrm{~L} .{ }^{45}$ RLV increases with age, whereas IRV and ERV decrease proportionally. A decline in the elasticity of lung tissue components with aging probably decreases breathing reserve and concomitantly increases residual lung volume. Alterations in pulmonary function may not entirely reflect an aging phenomenon because regular aerobic
training diminishes the typical age-related decline in static and dynamic lung functions. ${ }^{16}$ The RLV allows an uninterrupted exchange of gas between the blood and alveoli to prevent fluctuations in blood gases during phases of the breathing cycle including deep breathing. RLV plus FVC constitutes total lung capacity (TLC).

Effects of Previous Exercise. The RLV temporarily increases from an acute bout of either short-term or prolonged exercise. In one study, RLV increased during recovery from a maximal treadmill test by $21 \%$ after 5 minutes, $17 \%$ after 15 minutes, and $12 \%$ after 30 minutes. ${ }^{5}$ RLV generally reverts to its original value within 24 hours. Possible factors that increase RLV with exercise include (1) closure of the small peripheral airways and (2) increase in thoracic blood volume. The added blood volume does not alter the lungs mechanical properties, but it does displace air, thus preventing complete exhalation (reduced FVC). ${ }^{8}$ Any temporary increase in RLV would affect subsequent computations of body volume by hydrostatic weighing for body composition studies (see Chapter 28). When RLV measurement is impractical, prediction equations based on the relation between RLV and age, stature, gender, and body mass provide reasonably accurate estimates (see inset table, Fig. 12.6).

## Dynamic Lung Volumes

Adequacy of pulmonary ventilation depends on how well an individual sustains high airflow levels rather than air movement in a single breath. Dynamic ventilation depends on two factors:

1. Maximum stroke volume of the lungs (FVC)
2. Speed of moving a volume of air (breathing rate)

In turn, airflow velocity depends on the resistance of the respiratory passages to the smooth flow of air and the stiffness imposed by the mechanical properties of the chest and lung tissue to a change in shape during breathing, termed lung compliance. Patients with lung disease rarely experience
symptoms of distress until a large part of their ventilatory capacity decreases. Individuals with mild airway obstruction successfully engage in competitive distance running. ${ }^{29}$

## FEV-to-FVC Ratio

Some individuals with severe lung disease achieve nearnormal FVC values if measured with no time limit for this maneuver. For this reason, clinicians prefer a dynamic measurement of lung function such as the forced expiratory volume (FEV), usually measured over 1 second ( $\mathbf{F E V}_{1.0}$ ). $\mathrm{FEV}_{1.0}$ divided by FVC $\left(\mathbf{F E V}_{1.0} \div \mathbf{F V C}\right)$ indicates pulmonary airflow capacity. It reflects pulmonary expiratory power and overall resistance to air movement upstream in the lungs. Healthy individuals normally expel about $85 \%$ of the vital capacity in 1 second. Severe obstructive lung disease (emphysema or bronchial asthma)-with accompanying reduced airway caliber and loss of elastic recoil of lung tissueconsiderably reduces $\mathrm{FEV}_{1.0} / \mathrm{FVC}$, often to values less than $40 \%$ of the vital capacity. ${ }^{28,42}$ The demarcation point for airway obstruction during dynamic spirometry represents an $\mathrm{FEV}_{1.0} / \mathrm{FVC}$ of $70 \%$ or less. Figure 12.7 presents pulmonary function test results for $\mathrm{FEV}_{1.0}$ and FVC in individuals with normal lung function and those with obstructive and restrictive lung diseases. Clinicians also compute other values from portions of the curve generated in the forced spirometry maneuver (e.g., mid- $50 \%$ of the expiratory curve or instantaneous flows at 25,50 , or $75 \% \mathrm{FVC}$ ) to assess airflow dynamics in the small airways of the pulmonary tract. ${ }^{44}$

## Maximum Voluntary Ventilation

The maximum voluntary ventilation (MVV) evaluates ventilatory capacity with rapid and deep breathing for 15 sec onds. The 15 -second volume, extrapolated to the volume if the subject continued for 1 minute, represents MVV and typically ranges between 35 and 40 times the $\mathrm{FEV}_{1.0}{ }^{45}$ MVV also averages $25 \%$ higher than the ventilation during maximal exercise because exercise does not maximally stress how a healthy person breathes. For healthy, college-aged men, MVV ranges


Figure 12.7 Examples of spirometric tracings during standard pulmonary function tests for $\mathrm{FEV}_{1.0}$ and FVC in individuals with normal dynamic lung function and in patients with either obstructive or restrictive lung disease.
between 140 and $180 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, with values for women ranging between 80 and $120 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. MVV in male members of the United States Nordic Ski Team averaged $192 \mathrm{~L} \cdot \mathrm{~min}^{-1}$; the individual high was $239 \mathrm{~L} \cdot \mathrm{~min}^{-1} .{ }^{17}$ Conversely, patients with obstructive lung disease achieve only about $40 \%$ of the MVV considered normal for their age and body size.

Specific exercise training of the ventilatory muscles improves their strength and endurance and increases both inspiratory muscle function and MVV..$^{1,37,42}$ Ventilatory training in patients with chronic pulmonary disease enhances exercise capacity and reduces physiologic strain. ${ }^{9,39}$ Progressive desensitization to the feeling of breathlessness and greater selfcontrol of respiratory symptoms represent important benefits of ventilatory muscle training and regular exercise to patients with chronic obstructive lung disease.

## INTEGRATIVE QUESTION

How does regular resistance and aerobic exercise training affect the typical aging decline in measures of lung function?

## Exercise Implications of Gender Differences in Static and Dynamic Lung Function Measures

Adult women consistently have a reduced lung size and smaller static and dynamic lung function measures, reduced airway diameters and a smaller diffusion surface than men even after accounting for differences in stature. This disparity produces expiratory flow limitations, greater respiratory muscle work, and relatively greater use of ventilatory reserve compared with men during maximal exercise. This is particularly true for highly trained women compared to trained men and less-fit women. ${ }^{31}$ A relatively smaller lung volume plus a high expiratory flow rate requirement in trained women during intense exercise places considerable demand on the maximum flow volume envelope of the airways (i.e., mechanical constraints of TV and pulmonary minute ventilation). This adversely affects how highly fit women maintain alveolar-to-arterial oxygen exchange, which could compromise arterial oxygen saturation to a greater degree than observed for men. ${ }^{19,20}$

## LUNG FUNCTION, AEROBIC FITNESS, AND EXERCISE PERFORMANCE

Unlike the other components of the aerobic system, regular endurance exercise does not stimulate large increases in the functional capacity of the pulmonary system. Dynamic lung function tests indicate the severity of obstructive and restrictive lung diseases, yet generally provide little information about aerobic fitness or exercise performance when values fall within the normal range. For example, no difference emerges when comparing the average FVC of prepubescent and Olympic
wrestlers, middle-distance athletes, and untrained, healthy subjects. ${ }^{36,38}$ Professional football players averaged only $94 \%$ of their predicted FVC; the defensive backs achieved only $83 \%$ of predicted normal values for body size (see In a Practical Sense, p. 262). Somewhat surprisingly, similar values emerged for static and dynamic lung function of accomplished marathon runners and other endurance-trained athletes compared with untrained controls of similar body size. ${ }^{16,30}$

Swimming and diving stimulate development of larger than normal static lung volumes. These sports strengthen the inspiratory muscles that work against additional resistance of the mass of water that compresses the thorax. Enhanced ventilatory muscle strength and power explain the relatively large FVC of skin divers and competitive swimmers. ${ }^{4,6,10,11}$

Little relationship exists among different lung volumes and capacities and various track performances. This includes distance running for a large group of teenage boys and girls, even after adjusting for differences in body size. ${ }^{12}$ For marathon runners versus sedentary subjects of similar body size, no difference existed for lung function values (Table 12.1). ${ }^{24,29}$ For healthy, untrained individuals, no relationship exists between maximal oxygen consumption and FVC or MVV (adjusted for body size). Fatigue from strenuous exercise frequently relates to feeling out of breath, or winded, yet normal capacity for pulmonary ventilation for most individuals does not limit maximal aerobic exercise performance. The larger than normal lung volumes and breathing capacities of some athletes probably reflect genetic endowment. Specific exercise training can increase pulmonary function by strengthening the respiratory muscles.

| TABLE 12.1 | $\begin{array}{l}\text { Anthropometric Data, } \\ \text { Pulmonary } \\ \text { Resting Minute Vention, and } \\ \text { 20 Marathon Runners and in }\end{array}$ |  |
| :--- | :---: | :---: | :---: |
|  | Healthy Controls |  |$\}$

[^26]
## IN A PRACTICAL SENSE

## Predicting Pulmonary Function Variables in Men and Women

Pulmonary function variables do not directly relate to measures of physical fitness in healthy individuals. Instead, their measurement often forms part of a standard medical/health/fitness examination, particularly for individuals at risk for limited pulmonary function (e.g., chronic cigarette smokers, asthmatics). Measurement of pulmonary dimensions and lung functions with a water-filled spirometer (see Fig. 12.6) or electronic spirometer provides the framework for discussions of pulmonary dynamics during rest and exercise. Proper evaluation of measured values for pulmonary function requires comparison to expected values (norms) from the clinical literature.

## EQUATIONS

Pulmonary function scores associate closely with stature (ST) and age (A), enabling these two variables to predict the expected average (normal) lung function value for an individual.

## Data

Man: A, 22 y; ST, 182.9 cm (72 in)
Woman: A, 22 y ; ST, 165.1 cm (65 in)

## EXAMPLES

## Woman

1. Forced vital capacity (FVC)

$$
\begin{aligned}
\mathrm{FVC}(\mathrm{~L}) & =(0.0414 \times \mathrm{ST}[\mathrm{~cm}])-(0.0232 \times \mathrm{A}[\mathrm{y}])-2.20 \\
& =6.835-0.5104-2.20 \\
& =4.12 \mathrm{~L}
\end{aligned}
$$

2. Forced expiratory volume in $1 \mathrm{~s}\left(\mathrm{FEV}_{1.0}\right)$

$$
\begin{aligned}
\mathrm{FEV}_{1.0}(\mathrm{~L}) & =(0.0268 \times \mathrm{ST}[\mathrm{~cm}])-0.0251 \times \mathrm{A}[\mathrm{y}])-0.38 \\
& =4.425-0.5522-0.38 \\
& =3.49 \mathrm{~L}
\end{aligned}
$$

3. Percentage forced vital capacity in 1 s (FEV $1.0 /$ FVC):

$$
\begin{aligned}
\mathrm{FEV}_{1.0} / \mathrm{FVC}(\%) & =(-0.2145 \times \mathrm{ST}[\mathrm{~cm}])-0.1523 \times \mathrm{A}[\mathrm{y}]) 124.5 \\
& =-35.41-3.35 \times 124.5 \\
& =85.7 \%
\end{aligned}
$$

4. Maximum voluntary ventilation (MVV)
$\mathrm{MVV}\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right)=40 \times \mathrm{FEV}_{1.0}$

$$
\begin{aligned}
& =40 \times 3.49(\text { from \#2) } \\
& =139.6 \mathrm{~L} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

## Man

1. Forced vital capacity (FVC)

$$
\begin{aligned}
\mathrm{FVC}(\mathrm{~L}) & =(0.0774 \times \mathrm{ST}[\mathrm{~cm}]-(0.0212 \times \mathrm{A}[\mathrm{y}]-7.75) \\
& =14.156-0.4664-7.75 \\
& =5.49 \mathrm{~L}
\end{aligned}
$$

2. Forced expiratory volume in $1 \mathrm{~s}\left(\mathrm{FEV}_{1.0}\right)$

$$
\begin{aligned}
\mathrm{FEV}_{1.0}(\mathrm{~L}) & =(0.0566 \times \mathrm{ST}[\mathrm{~cm}])-0.0233 \times \mathrm{A}[\mathrm{y}])-0.491 \\
& =10.35-0.5126-4.91
\end{aligned}
$$

$$
=4.93 \mathrm{~L}
$$

3. Percentage forced vital capacity in 1 s ( FEV $_{1.0} /$ FVC)
$\mathrm{FEV}_{1.0} /$ FVC $(\%)=(-0.1314 \times$ ST $\left.[\mathrm{cm}])-0.1490 \times \mathrm{A}[\mathrm{y})\right] \times 110.2$
$=-24.03-3.35 \times 110.2$
= 82.8\%
4. Maximum voluntary ventilation (MVV)
$\operatorname{MVV}\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right)=40 \times \mathrm{FEV}_{1.0}$

$$
\begin{aligned}
& =40 \times 4.93 \mathrm{~L}(\text { from \#2) } \\
& =197.2 \mathrm{~L} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

## Equations to Predict Pulmonary Function Variables by Age and Gender

| Variable | $\begin{aligned} & \text { Men } \\ & <25 Y \end{aligned}$ | $\begin{gathered} \text { Men } \\ >25 \mathrm{Y} \end{gathered}$ | Female $<25 \text { Y }$ | Female $>25 \mathrm{Y}$ |
| :---: | :---: | :---: | :---: | :---: |
| Forced vital capacity (FVC): <br> Maximum volume expired following a maximum inspiration | $\begin{gathered} \text { FVC }(\mathrm{L})=(0.0774 \\ \times \text { ST })-(0.0212 \\ \times \text { A })-7.75 \end{gathered}$ | $\begin{aligned} & \text { FVC }(\mathrm{L})=(0.065 \times \mathrm{ST}) \\ & \quad+(0.029 \times \mathrm{A}) \\ & \quad-5.459 \end{aligned}$ | $\begin{array}{r} \text { FVC }(\mathrm{L})=(0.0414 \times \mathrm{ST}) \\ -(0.0232 \times \mathrm{A})-2.20 \end{array}$ | $\begin{gathered} \text { FVC }(\mathrm{L})=(0.037 \\ \times \mathrm{ST})+(0.092 \\ \times \mathrm{A})-3.469 \end{gathered}$ |
| Forced expiratory volume in $1 s\left(F E V_{1.0}\right)$ : Volume forcibly expired in 1 s following a maximum inspiration | $\begin{gathered} \mathrm{FEV}_{1.0}(\mathrm{~L})=(0.0566 \\ \times \text { ST })-0.0233 \\ \times \mathrm{A})-0.491 \end{gathered}$ | $\begin{aligned} & \mathrm{FEV}_{1.0}(\mathrm{~L})=(0.052 \\ & \quad \times \mathrm{ST})+(0.027 \times \mathrm{A}) \\ & \quad-4.203 \end{aligned}$ | $\begin{aligned} & \mathrm{FEV}_{1.0}(\mathrm{~L})=(0.0268 \times \\ & \mathrm{ST})-(0.0251 \times \mathrm{A}) \\ & \quad-0.38 \end{aligned}$ | $\mathrm{FEV}_{1.0}(\mathrm{~L})=(0.027 \times$ <br> ST) $-(0.021 \times$ <br> A) -0.794 |
| $F E V_{1.0} / F V C$ : Percentage of forced vital capacity expired in 1 s | $\begin{gathered} \mathrm{FEV}_{1.0} / \mathrm{FVC},(\%)= \\ (-0.1314 \times \mathrm{ST}) \\ -(0.1490 \times \mathrm{A}) \\ \quad+110.2 \end{gathered}$ | $\begin{aligned} & \mathrm{FEV}_{1.0} / \text { FVC }(\%)= \\ & 103.64-(0.87 \times \mathrm{ST}) \\ & -(0.14 \times \mathrm{A}) \end{aligned}$ | $\begin{aligned} & \mathrm{FEV}_{1.0} / \mathrm{FVC}(\%)= \\ & \quad(-0.2145 \times \mathrm{ST})- \\ & (0.1523 \times \mathrm{A})+124.5 \end{aligned}$ | $\begin{gathered} \mathrm{FEV}_{1.0} / \mathrm{FVC}(\%) \\ =107.38- \\ (0.111 \times \mathrm{ST}) \\ (0.109 \times \mathrm{A}) \end{gathered}$ |
| Maximum voluntary ventilation (MW): Maximum amount of air forcibly breathed in 1 min | $\begin{gathered} \operatorname{MMV}\left(\mathrm{L} \cdot \min ^{-1}\right)= \\ 40 \times \mathrm{FEV}_{1.0} \end{gathered}$ | $\begin{aligned} & \operatorname{MMV}\left(\mathrm{L} \cdot \min ^{-1}\right)= \\ & (1.15 \times \mathrm{H})-(1.27 \\ & \times \mathrm{A})+14 \end{aligned}$ | $\begin{aligned} & \mathrm{MMV}\left(\mathrm{~L} \cdot \min ^{-1}\right)=40 \\ & \quad \times \mathrm{FEV} \end{aligned}$ | $\begin{gathered} \text { MMV }\left(\mathrm{L} \cdot \mathrm{~min}^{-1}\right)= \\ \left(0.55 \times \text { ST }^{2}-\right. \\ (0.72 \times \mathrm{A})+50 \end{gathered}$ |

[^27]Comroe JH, et al. The lung. Chicago: Year Book Medical Publishers, 1962.
Miller A. Pulmonary function tests in clinical and occupational disease. Philadelphia: Grune \& Stratton, 1986.
Taylor AE, et al. Clinical respiratory physiology. Philadelphia: WB Saunders, 1989.
Wasserman K, et al. Principles of exercise testing and interpretation. Baltimore: Lippincott Williams \& Wilkins, 2004.

## PULMONARY VENTILATION

One can view pulmonary ventilation from two perspectives: (1) volume of air moved into or out of the total respiratory tract each minute and (2) air volume that ventilates only the alveolar chambers each minute.

## Minute Ventilation

The normal breathing rate during quiet breathing at rest in a thermoneutral environment averages 12 breaths per minute and TV averages 0.5 L of air per breath. Consequently, the volume of air breathed each minute, referred to as minute ventilation, equals 6 L .

$$
\text { Minute ventilation } \begin{aligned}
\left(\mathrm{V}_{\mathrm{E}}\right) & =\text { Breathing rate } \times \text { Tidal Volume } \\
& =12 \times 0.5 \mathrm{~L} \\
& =6 \mathrm{~L} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

An increase in either the rate or depth of breathing or both increases minute ventilation. During strenuous exercise, healthy young adults readily increase breathing rate to 35 to 45 breaths per minute. Some elite endurance athletes breathe as rapidly as 60 to 70 times each minute during maximal exercise. TVs of 2.0 L and higher commonly occur during exercise. Such increases in breathing rate and TV increase exercise minute ventilation to 100 L or more (about 17 to 20 times the resting value). In male endurance athletes, ventilation may increase to $160 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ during maximal exercise. Minute ventilation volumes of 200 L , with a high volume of 208 L in a professional football player, have been observed during maximal bicycle exercise. ${ }^{47}$ Despite such large minute ventilations, TVs for trained and untrained individuals rarely exceed $60 \%$ of vital capacity.

## Alveolar Ventilation

A portion of the air in each breath does not enter the alveoli and participate in gaseous exchange with the blood. The term anatomic dead space describes this air that fills the upper airway structures (mouth, nasal passages, nasopharynx, larynx, trachea, and other nondiffusible conducting portions of
foi
Typical Values for Pulmonary Ventilation During Rest and Moderate and Intense Exercise

|  | Breathing <br> Rate <br> $\left(\right.$ Breaths $^{\left.\mathbf{m i n}^{-1}\right)}$ | Tidal <br> Volume <br> $\left(\mathrm{L} \cdot \mathrm{Breath}^{-1}\right)$ | Plumonary <br> Ventilation <br> $\left(\mathrm{L} \cdot \mathbf{m i n}^{-1}\right)$ |
| :--- | :---: | :---: | :---: |
| Condition | 12 | 0.5 | 6 |
| Rest <br> Moderate <br> exercise | 30 | 2.5 | 75 |
| Intense <br> exercise | 50 | 3.0 | 150 |

the respiratory tract). The anatomic dead space generally ranges between 150 and 200 mL (about $30 \%$ of the resting TV) in healthy individuals. The composition of dead-space air remains almost identical to ambient air except for its full saturation with water vapor.

The dead-space volume permits about 350 mL of the 500 mL of inspired TV at rest to enter into and mix with existing alveolar air. This does not mean that only 350 mL of air enters and leaves the alveoli with each breath. Instead, if TV equals 500 mL , then 500 mL of air enters the alveoli, but only 350 mL of this is fresh air. This represents about one seventh of total alveolar air. Such relatively small and seemingly inefficient alveolar ventilation-that portion of inspired air reaching the alveoli and participating in gas exchange-prevents drastic changes in alveolar air composition to ensure consistency in arterial blood gases throughout the breathing cycle.

Table 12.2 indicates that minute ventilation does not always reflect alveolar ventilation. The first example of shallow breathing shows that one can reduce TV to 150 mL , yet still maintain a 6-L minute ventilation by increasing breathing rate to 40 breaths per minute. The same $6-\mathrm{L}$ minute volume results from decreasing breathing rate to 12 breaths per minute and increasing TV to 500 mL . In contrast, doubling TV and halving the breathing rate, as in the example of deep breathing,

TABLE 12.2 Relationships Among Tidal Volume, Breathing Rate, and Both Total and Alveolar Minute Ventilation

| Condition | Tidal Volume (mL) | $\times$ | Breathing Rate (Breaths • $\min ^{-1}$ ) | $=$ | Total Minute Ventilation ( $\mathrm{mL} \cdot \mathrm{min}^{-1}$ ) | - | Dead Space Minute Ventilation ( $\mathrm{mL} \cdot \mathrm{min}^{-1}$ ) | $=$ | Alveolar Minute Ventilation ( $\mathrm{mL} \cdot \mathrm{min}^{-1}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Shallow breathing | 150 |  | 40 |  | 6000 |  | $(150 \mathrm{~mL} \times 40)$ |  | 0 |
| Normal breathing | 500 |  | 12 |  | 6000 |  | $(150 \mathrm{~mL} \times 12)$ |  | 4200 |
| Deep breathing | 1000 |  | 6 |  | 6000 |  | $(150 \mathrm{~mL} \times 6)$ |  | 5100 |

also produces a 6-L minute ventilation. Each of these ventilatory adjustments drastically affects alveolar ventilation. In the example of shallow breathing, dead-space air represents the only air volume moved without any alveolar ventilation. In the other examples, deeper breathing causes a larger portion of each breath to enter into and mix with alveolar air. Alveolar ventilation determines the gaseous concentrations at the alveolar-capillary membrane.

## Dead Space Versus Tidal Volume

The preceding examples of alveolar ventilation represent oversimplifications because they assumed a constant dead space despite changes in TV. Actually, anatomic dead space increases as TV becomes larger; it often doubles during deep breathing from some stretching of the respiratory passages with a fuller inspiration. Importantly, any increase in dead space still represents proportionately less volume than the accompanying increase in TV. Consequently, deeper breathing provides more effective alveolar ventilation than a similar minute ventilation achieved through an increased breathing rate.

## Ventilation Perfusion Ratio

Adequate gas exchange between alveoli and blood requires effective matching of alveolar ventilation to the blood perfusing the pulmonary capillaries. Approximately 4.2 L of air normally ventilates the alveoli each minute at rest, and an average of 5.0 L of blood flows through the pulmonary capillaries. In this case, the ratio of alveolar ventilation to pulmonary blood flow, termed the ventilation perfusion ratio, equals $0.84(4.2 \div 5.0)$. This ratio means that alveolar ventilation of 0.84 L matches each liter of pulmonary blood flow. In light exercise, the ventilation perfusion ratio remains approximately 0.8 . In contrast, intense exercise produces a disproportionate increase in alveolar ventilation. In healthy individuals, the ventilation perfusion ratio may exceed 5.0; in most instances, this response ensures adequate aeration of venous blood.

## Physiologic Dead Space

Sometimes the alveoli may not function adequately in gas exchange because of two factors:

## 1. Underperfusion of blood

2. Inadequate ventilation relative to the alveolar surface

The term physiologic dead space describes the portion of the alveolar volume with a ventilation perfusion ratio that approaches zero. Figure 12.8 shows the negligible physiologic dead space in the healthy lung. In certain pathologic situations, physiologic dead space increases to $50 \%$ of the TV, as with inadequate perfusion from hemorrhage or blockage of the pulmonary circulation by an embolism or inadequate ventilation in emphysema, asthma, and pulmonary fibrosis. An increased physiologic dead space from decreased functional alveolar


Figure 12.8 Distribution of tidal volume (TV) in a healthy subject at rest. TV includes about 350 mL of ambient air that mixes with alveolar air, 150 mL of ambient air that remains in the larger air passages (anatomic dead space), and a small portion of air distributed to either poorly ventilated or poorly perfused alveoli (physiologic dead space).
surface in emphysema produces extreme ventilation even at low exercise intensities. Many patients cannot achieve maximal circulatory capacity because of ventilatory muscle fatigue from excessive breathing. Adequate gas exchange becomes impossible when the dead space of the lung exceeds $60 \%$ of total lung volume.

## Rate Versus Depth

Increasing the rate and depth of breathing increases alveolar ventilation in exercise. In moderate exercise, well-trained athletes maintain alveolar ventilation by increasing TV with only a small increase in breathing rate. ${ }^{15}$ As breathing becomes deeper during exercise, alveolar ventilation increases from $70 \%$ of the total minute ventilation at rest to more than $85 \%$ of the exercise ventilation. Figure 12.9 shows that encroachment on the IRV, with a smaller decrease in the endexpiratory level, increases exercise TV. With more intense exercise, the increase in TV plateaus at approximately $60 \%$ of vital capacity; minute ventilation increases further through nonconscious increases in breathing rate. Each person develops a style of breathing where breathing rate and TV blend to provide effective alveolar ventilation. Conscious manipulation of breathing usually disturbs the exquisitely regulated physiologic adjustments to exercise. Attempts to modify breathing during running or other general physical activities offer no benefit to exercise performance. During rest and all levels of exercise, a healthy person should breathe in the manner that seems most natural.

## INTEGRATIVE QUESTION

How can a person accelerate breathing rate at rest without disrupting normal alveolar ventilation?


Figure 12.9 Tidal volume and subdivisions of pulmonary air during rest and exercise.

## VARIATIONS FROM NORMAL BREATHING PATTERNS

Breathing patterns during exercise generally progress in an effective and highly economical manner, yet some pulmonary responses can adversely affect exercise performance and/or physiologic balance.

## Hyperventilation

Hyperventilation refers to an increase in pulmonary ventilation that exceeds the oxygen consumption and carbon dioxide elimination needs of metabolism. This overbreathing quickly lowers normal alveolar carbon dioxide concentration and causes excess carbon dioxide to leave bodily fluids via the expired air. An accompanying decrease in hydrogen ion concentration $\left[\mathrm{H}^{+}\right]$increases plasma pH . Several seconds of hyperventilation generally produce lightheadedness; prolonged hyperventilation leads to unconsciousness from excessive carbon dioxide unloading.

## Dyspnea

Dyspnea refers to an inordinate shortness of breath or subjective distress in breathing. The sense of breathing incapacity during exercise, particularly in novice exercisers, usually accompanies elevated arterial carbon dioxide and $\left[\mathrm{H}^{+}\right]$. Both conditions excite the inspiratory center to increase breathing rate and depth. Failure to adequately regulate arterial carbon dioxide and $\left[\mathrm{H}^{+}\right]$most likely relates to low aerobic fitness levels and a poorly conditioned ventilatory musculature.

## Valsalva Maneuver

The expiratory muscles, besides their normal role in pulmonary ventilation, provide for the ventilatory maneuvers of coughing and sneezing. They also contribute to stabilizing the abdominal and chest cavities during heavy lifting. In quiet breathing, intrapulmonic pressure decreases only about 3 mm Hg during inspiration and rises a similar amount above atmospheric pressure in exhalation (Fig. 12.10A). Closing the glottis (narrowest part of the larynx through which air passes into the trachea) following a full inspiration while maximally activating the expiratory muscles creates compressive forces that increase intrathoracic pressure more than 150 mm Hg above atmospheric pressure (Fig. 12.10B). Pressures increase to higher levels within the abdominal cavity during a maximal exhalation against a closed glottis. ${ }^{18}$ Forced exhalation against a closed glottis, termed the Valsalva maneuver, occurs commonly in weight lifting and other activities that require a rapid, maximum application of force of short duration. The Valsalva stabilizes the abdominal and thoracic cavities and is thought to enhance muscle action.

## Physiologic Consequences of Performing the Valsalva Maneuver

A prolonged Valsalva maneuver produces an acute drop in blood pressure. Increased intrathoracic pressure during a Valsalva transmits through the thin walls of the veins that pass through the thoracic region. Because venous blood remains under relatively low pressure, thoracic veins collapse, which reduces blood flow to the heart. Reduced venous return sharply lowers the heart s stroke volume, triggering a fall in blood


## C

Figure 12.10 The Valsalva maneuver reduces the return of blood to the heart because increased intrathoracic pressure collapses the inferior vena cava that passes through the chest cavity. A. Normal breathing. B. Straining exercise with accompanying Valsalva maneuver. C. Typical normal response of aortic pulse pressure with a Valsalva maneuver during calibrated muscle strain. The figure illustrates 63 consecutive heartbeats (॰). High-fidelity aortic pressure recordings were obtained at the aortic root level. Pulse pressure represents systolic pressure minus diastolic pressure. (Data from H bert $J-L$, et al. Pulse pressure response to the strain of the Valsalva maneuver in humans with preserved systolic function. J Appl Physiol 1998;85:817.)
pressure below the resting level. ${ }^{7,26}$ Performing a prolonged Valsalva maneuver during static, straining-type exercise dramatically reduces venous return and arterial blood pressure. These effects diminish the brain s blood supply, often producing dizziness, spots before the eyes, or fainting. Once the glottis reopens and intrathoracic pressure normalizes, blood flow reestablishes with an overshoot in arterial blood pressure. ${ }^{41,43}$

Figure 12.10C illustrates four phases of the typical blood pressure response (heartbeat by heartbeat) during the Valsalva maneuver in a healthy subject. Aortic pulse pressure increases slightly as the Valsalva begins (phase I), probably from the mechanical effect of elevated intrathoracic pressure that expels blood from the left ventricle into the aorta. A biphasic response occurs within six heartbeats of Valsalva onset. This consists of a large reduction in aortic pulse pressure (phase IIa) followed by a relatively small gradual rise (phase IIb) and secondary decrease (phase III) during the continued Valsalva strain. When the maneuver ceases (release of strain), blood pressure rises rapidly and overshoots the resting value (phase IV).

A Common Misconception. The Valsalva maneuver does not cause the relatively large increases in blood pressure during heavy resistance exercises. Recall from the preceding figure that a prolonged Valsalva dramatically reduces blood pressure. Confusion arises because a Valsalva maneuver of insufficient duration to lower blood pressure usually accompanies straining muscular efforts common during isometric and dynamic resistance exercise. These exercises (with or without Valsalva) greatly increase resistance to blood flow in active muscle with a resulting rise in systolic blood pressure. ${ }^{21}$ For example, intramuscular fluid pressure increases linearly with all levels of isometric force to the maximum. ${ }^{40}$ Increased peripheral vascular resistance increases the arterial blood pressure and workload of the heart throughout exercise. These responses pose potential danger to individuals with cardiovascular disease; they form the basis for advising cardiac patients to refrain from heavy resistance training. In contrast, performing rhythmic muscular activity, including moderate weight lifting, promotes a steadier blood flow and only modest increase in blood pressure and work of the heart. Chapter 15 more fully discusses the blood pressure response to different exercise modes.

## INTEGRATIVE QUESTION

After completing a maximum-lift standing press, a person exclaims, I feel slightly dizzy and see spots before my eyes. Provide a plausible physiologic explanation.

## THE RESPIRATORY TRACT DURING COLD-WEATHER EXERCISE

Cold ambient air normally does not damage the respiratory passages. Even in extreme cold weather, the incoming air generally warms to 26.5 to 32.2 C by the time it reaches the bronchi. Nonetheless, values as low as 20 C can occur in the

## FOCUS ON RESEARCH

## Physiologic Control of Pulmonary Ventilation


#### Abstract

Dejours $P$. The regulation of breathing during muscular exercise in man. A neuro-humoral theory. In: Cunningham DJC, Lloyd BB, eds. The regulation of human respiration. Oxford, England: Blackwell, 1963.


- Early theories about pulmonary ventilation regulation during exercise centered singularly on arterial $\mathrm{PCO}_{2}$, arterial blood pH , or reflex stimulation originating from muscle receptors. Dejours believed that no factor by itself, but rather a multiplicity of interacting factors, regulated breathing during exercise. He hypothesized that exercise hyperpnea depended on humoral (chemical) and neurogenic stimuli that varied their contributions depending on the phase of exercise and recovery.

The figure presents Dejours observations that the time course of pulmonary minute ventilation (VE) during the transitions from rest to exercise to recovery followed a consistent pattern. Ve increases within the same ventilatory cycle, coinciding with the start of exercise. Some

10 to 20 seconds later, ventilation volumes slowly increase to an eventual steady state. Minute ventilation declines abruptly when exercise stops, remains fairly constant for 20 to 30 seconds, and then decreases progressively to the resting value.

Dejours concluded that ventilatory dynamics in exercise combine rapid (fast component) and slow (slow component) responses that progress in defined stages during exercise and recovery. He proposed that different physiologic factors control the fast and slow components. Two factors contribute to the fast component: (1) cerebral input from afferent impulses from the brain s psychomotor area to the respiratory center in the medulla and (2) extrathoracic mechanoreceptor stimulation from proprioceptors in active body segments. Two mechanisms also modulate the slower component of the ventilatory response. The first, a reflex, originates from muscle chemoreceptors sensitive to progressive physiochemical changes within active muscle as exercise progresses. The


Pulmonary minute ventilation ( $\mathrm{V}_{\mathrm{E}}$ ) during mild exercise and recovery (inset graph). Portion $B$ of inset represents the immediate, rapid increase when exercise begins; $S T$ reflects the more gradual rise to a steady state; $F$ indicates the quick fall when exercise stops; $S$ represents the slower return of ventilation to the preexercise level. The main graph shows the contribution of these ventilatory response components to oxygen consumption. Neurogenic and humoral components both increase with the intensity of the preceding exercise; the fast component at the start of exercise increases with exercise intensity much less than the progressive increase in neurogenic and humoral controls.

## FOCUS ON RESEARCH

second factor represents a humoral mechanism. Dejours belief in humoral control developed from experiments that occluded leg blood flow. Restricting venous return during leg exercise caused VE to decline below resting levels, thus demonstrating ventilatory dependence on blood-borne (humoral) chemicals produced in active tissues.

Dejours stressed the interrelationship between the fast and slow components in exercise ventilation. Reflex and cortical factors initiated the rapid rise in ventilation at exercise onset. Subsequently, humoral factors, and possibly progressive neurogenic output, modulated the slower rise in ventilation during the first minutes of exercise. The
latter steady-state response during exercise probably related to (1) increases in reflex drive through local physical and chemical changes at the peripheral mechanoreceptors and (2) positive interactions between neurogenic and humoral drives. Ventilation decreases precipitously when exercise stops and neurogenic input ceases. Ventilation then becomes regulated exclusively by humoral factors from the recovering musculature.

The studies of Dejours formed the basis for explaining pulmonary ventilation during exercise and recovery. Subsequent research (see Fig. 14.4) provides additional factors to explain exercise hyperpnea and provides a more comprehensive model for ventilatory control.
bronchi when breathing large volumes of cold, dry air. ${ }^{32}$ Airway warming of inspired air greatly increases its capacity to hold moisture, which produces considerable water loss from the respiratory passages. In cold weather, the respiratory tract loses considerable water and heat, most notably during strenuous exercise with large ventilatory volumes. Fluid loss from the airways often contributes to overall dehydration, dry mouth, burning sensation in the throat, and generalized irritation of the respiratory passages. Wearing a scarf or cellulose mask-type balaclava that covers the nose and mouth traps the water in exhaled air and subsequently warms and moistens the next incoming breath of air. This effect reduces the symptoms of respiratory discomfort.

## Postexercise Coughing

Exercise in cold weather can dry the throat and trigger coughing during the recovery period. The response becomes prevalent following exercise in cold weather when the respiratory tract loses considerable water. Postexercise coughing relates directly to the overall respiratory water loss (not respiratory heat loss) associated with the large ventilatory volumes breathed during exercise.

## Summary

1. The lungs provide a large surface between the body s internal fluid environment and the gaseous external environment. During any 1 second of exercise, no more than 1 pint of blood flows in the pulmonary capillaries.
2. Normal regulation of pulmonary ventilation maintains a favorable concentration of alveolar oxygen and carbon dioxide to ensure adequate aeration of blood flowing through the lungs.
3. Pulmonary airflow depends on small pressure differentials between ambient air and air within the lungs. Muscle actions that alter thoracic cavity dimensions produce these pressure differences.
4. Lung volumes vary with age, gender, and body size (particularly stature) and should only be evaluated with established norms based on these factors.
5. The residual lung volume represents air remaining in the lungs following maximal exhalation. This air volume allows uninterrupted exchange of gas during all phases of the breathing cycle.
6. Forced expiratory volume and maximum voluntary ventilation dynamically measure the ability to sustain a high airflow level. These lung function measures serve as excellent screening tests to detect lung disease.
7. Measures of static and dynamic lung function within the normal range poorly predict aerobic fitness and exercise performance.
8. Breathing rate and tidal volume (TV) determine pulmonary minute ventilation. Minute ventilation averages $6 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at rest and can increase to $200 \mathrm{~L} \cdot \min ^{-1}$ during maximal exercise.
9. Alveolar ventilation reflects the portion of minute ventilation that enters the alveoli for gaseous exchange with the blood.
10. The ventilation perfusion ratio reflects the association between alveolar minute ventilation and pulmonary blood flow. At rest, alveolar ventilation of 0.8 L matches each L of pulmonary blood flow. During intense exercise, alveolar ventilation increases disproportionately to increase the ventilation perfusion ratio to 5.0.
11. TV increases during exercise by encroachment into inspiratory and expiratory reserve volumes. During
intense exercise, TV plateaus at approximately $60 \%$ of the vital capacity; minute ventilation increases further through increases in breathing rate.
12. A healthy person should breathe in a manner that seems most natural during rest, exercise, and recovery.
13. Hyperventilation refers to increased pulmonary ventilation that exceeds gas exchange needs of metabolism. This overbreathing quickly lowers normal alveolar carbon dioxide concentration, causing excess carbon dioxide to leave body fluids via expired air.
14. A Valsalva maneuver describes a forced exhalation against a closed glottis. This action causes large
pressure increases within the chest and abdominal cavities that compress the thoracic veins, thereby reducing venous return to the heart. This ultimately reduces arterial blood pressure.
15. The straining muscular effort that typically accompanies the Valsalva temporarily elevates blood pressure and adds to the heart s workload. Individuals with heart and vascular disease should refrain from heavy weight lifting and isometric muscle actions.
16. Breathing cold ambient air normally does not damage the respiratory passages.

## CHAPTER 13



## Gas Exchange and Transport

## CHAPTER OBJECTIVES

- List the partial pressures of respired gases during rest and maximal exercise in the alveoli, arterial blood, active muscles, and mixed-venous blood
- Explain the impact of Henrys law on pulmonary gas exchange
- Quantify oxygen transport (1) in arterial plasma and (2) combined with hemoglobin under sea-level, ambient conditions
> Discuss the physiologic advantages of oxyhemoglobins S -shaped dissociation curve
> Describe factors that produce the Bohr effect and outline its major benefit in physical activity
- Explain the role of myoglobin during highintensity, physical activity
- List and quantify three ways for carbon dioxide transport in blood

The body s supply of oxygen in ambient air depends on two factors: (1) concentration and (2) pressure. Ambient air remains relatively constant in composition that contains $20.93 \%$ oxygen, $79.04 \%$ nitrogen (including small quantities of other inert gases that behave physiologically like nitrogen), $0.03 \%$ carbon dioxide, and usually small quantities of water vapor. The gas molecules move at relatively high speeds and exert a pressure against any surface they contact. At sea level, the pressure of air molecules raises a column of mercury in a barometer to a height of 760 mm (29.9 in), or 1 torr. The torr-named for the Italian physicist and mathematician Evangelista Torricelli (1608 1647) who invented the barometer in 1644 -is not an SI unit but an expression of gas pressure. One torr equals the pressure necessary to raise a $1-\mathrm{mm}$ column of mercury 1 mm high at 0 C against the standard acceleration of gravity at 45 north latitude ( $980.6 \mathrm{~cm} \cdot \mathrm{~s}^{2}$ ). One standard atmosphere equals 760 torr. The barometric reading varies with changing weather conditions and becomes lower with increasing altitude (see Chapter 24).

## Part 1 GASEOUS EXCHANGE IN THE LUNGS AND TISSUES

## CONCENTRATIONS AND PARTIAL PRESSURES OF RESPIRED GASES

The molecules of each specific gas in a mixture of gases exert their own partial pressure. The mixture s total pressure equals the sum of the partial pressures of the individual gases in the mixture. This association, known as Dalton s law, was named after British chemist and physicist John Dalton (1766 1844), who also developed the atomic theory of matter. Partial pressure computes as follows:

Partial pressure $=$ Percentage concentration of specific gas $\times$ Total pressure of gas mixture

## Ambient Air

Table 13.1 lists the volumes, percentages, and partial pressures of the gases in dry ambient air at sea level. The partial

## TABLE 13.1 Partial Pressure and Volume of Gases in Dry Ambient Air at Sea Level

| Gas | Percentage | Partial <br> Pressure $^{a}$ <br> $(\mathbf{m m ~ H g})$ | Gas Volume <br> $\left(\mathbf{m L} \cdot \mathrm{L}^{-1}\right)$ |
| :--- | :---: | :---: | :---: |
| Oxygen | 20.93 | 159 | 209.3 |
| Carbon <br> dioxide | 0.03 | 0.2 | 0.4 |
| Nitrogen | $79.04^{b}$ | 600 | 790.3 |

[^28]pressure of oxygen equals $20.93 \%$ of the total 760 mm Hg pressure exerted by air or $159 \mathrm{~mm} \mathrm{Hg}(20.93 \div 100 \times 760 \mathrm{~mm}$ Hg ). Carbon dioxide exerts a pressure of only 0.23 mm Hg $(0.03 \div 100 \times 760 \mathrm{~mm} \mathrm{Hg})$, whereas the molecules of nitrogen exert a pressure that raises the mercury in a manometer about $600 \mathrm{~mm}(79.04 \div 100 \times 760 \mathrm{~mm} \mathrm{Hg})$. A $P$ placed in front of the gas symbol denotes partial pressure. The partial pressures at sea level for the principal components of ambient air average as follows: oxygen $\left(\mathrm{PO}_{2}\right)=159 \mathrm{~mm} \mathrm{Hg}$, carbon dioxide $\left(\mathrm{PCO}_{2}\right)=$ 0.2 mm Hg , and nitrogen $\left(\mathrm{PN}_{2}\right)=600 \mathrm{~mm} \mathrm{Hg}$.

## fyi <br> Common Symbols for Gas Pressure in Respiratory Physiology

$\mathbf{P}_{\mathbf{A}} \mathbf{O}_{\mathbf{2}}$ : Partial pressure of oxygen in alveolar chambers
$\mathbf{P a O}_{2}$ : Partial pressure of oxygen in arterial blood $\mathbf{S a O}_{\mathbf{2}} \%$ : Percent saturation of arterial blood with oxygen
$\mathbf{P v O}_{2}$ : Partial pressure of oxygen in venous blood $\mathbf{P}_{\mathrm{A}} \mathbf{C O}_{2}$ : Partial pressure of carbon dioxide in alveolar chambers
$\mathbf{P a C O}_{2}$ : Partial pressure of carbon dioxide in arterial blood
$\mathbf{P v C O}_{2}$ : Partial pressure of carbon dioxide in venous blood
$\mathbf{S v O}_{\mathbf{2}} \%$ : Percent saturation of venous blood with oxygen
$\mathbf{a - v} \mathrm{O}_{\mathbf{2}}$ diff: Arteriovenous oxygen difference; difference between oxygen carried in arterial blood and carried in venous blood a-vO $\mathbf{O}_{\mathbf{2}}$ diff: Arterial mixed-venous oxygen difference; difference between oxygen carried in arterial blood and carried in mixed-venous blood $\mathbf{v}$ : mixed-venous blood

## Tracheal Air

Air completely saturates with water vapor as it enters the nasal cavities and mouth and passes down the respiratory tract. The vapor dilutes the inspired air mixture somewhat. At a body temperature of 37 C , for example, the pressure of water molecules in humidified air equals 47 mm Hg ; this leaves 713 mm $\mathrm{Hg}(760-47 \mathrm{~mm} \mathrm{Hg})$ as the total pressure exerted by the inspired dry air molecules. Consequently, the effective $\mathrm{PO}_{2}$ in tracheal air decreases by about 10 mm Hg from its ambient value of 159 mm Hg to 149 mm Hg [ $0.2093 \times(760-47 \mathrm{~mm}$ $\mathrm{Hg})$ ]. Carbon dioxide s negligible contribution to inspired air means that humidification exerts little effect on inspired $\mathrm{PCO}_{2}$.

## Alveolar Air

Alveolar air composition differs considerably from the incoming breath of moist ambient air because carbon dioxide continually enters the alveoli from the blood; in contrast,

## TABLE 13.2 Partial Pressure and Volume of Dry Alveolar Gases at Sea Level ( $37^{\circ} \mathrm{C}$ )

| Gas | Percentage | Partial <br> Pressure $^{a}$ <br> $(\mathbf{m m ~ H g})$ | Gas <br> Volume <br> $\left(\mathbf{m L} \cdot \mathbf{L}^{-1}\right)$ |
| :--- | :---: | :---: | :---: |
| Oxygen | 14.5 | 103 | 145 |
| Carbon <br> dioxide | 5.5 | 39 | 55 |
| Nitrogen |  |  |  |
| Water vapor | 80.0 | 571 | 800 |

${ }^{a}$ At $760-47 \mathrm{~mm}$ Hg alveolar gas pressure.
${ }^{b}$ Nitrogen occupies a slightly greater percentage of alveolar air than ambient air because energy metabolism generally produces less carbon dioxide than oxygen consumed (i.e., the respiratory quotient $[\mathrm{RQ}=$ $\left.\begin{array}{lll} & \mathrm{VCO}_{2} & \mathrm{VO}_{2}\end{array}\right]$ equals less than 1.00). Because of this exchange imbalance, the nitrogen percentage increases.
oxygen flows from the lungs into the blood for transport throughout the body. Table 13.2 shows that alveolar air contains on average $14.5 \%$ oxygen, $5.5 \%$ carbon dioxide, and $80.0 \%$ nitrogen. After subtracting the vapor pressure from moist alveolar gas, the average alveolar $\mathrm{PO}_{2}$ becomes 103 mm Hg $[0.145 \times(760-47 \mathrm{~mm} \mathrm{Hg})]$ and $39 \mathrm{~mm} \mathrm{Hg}[0.055 \times(760$ $-47 \mathrm{~mm} \mathrm{Hg})]$ for $\mathrm{Pco}_{2}$. These values represent average pressures exerted by oxygen and carbon dioxide molecules against the alveolar side of the alveolar capillary membrane. They do not remain physiologic constants; rather, they vary somewhat with the ventilatory cycle phase and the adequacy of ventilation in various lung regions. Recall that a relatively large volume of air remains in the lungs after each normal exhalation. This functional residual capacity (FRC) serves as a damper, so each incoming breath exerts only a small effect on alveolar air composition. This explains why the partial pressures of alveolar gases remain relatively stable.

## MOVEMENT OF GAS IN AIR AND FLUIDS

In accordance with Henry s law (named for English chemist and physician William Henry [1774 1836]), the mass of a gas that dissolves in a fluid at a given temperature varies in direct proportion to the pressure of the gas over the liquid (provided no chemical reaction takes place between the gas and liquid). Two factors govern the rate of gas diffusion into a fluid:

1. The pressure differential between the gas above the fluid and the gas dissolved in the fluid
2. The solubility of the gas in the fluid

## Pressure Differential

Oxygen molecules continually bombard the surface of the water in the three chambers illustrated in Figure 13.1. The pure water in chamber $A$ contains no oxygen ( $\mathrm{P}=0 \mathrm{~mm} \mathrm{Hg}$ ), and a large number of oxygen molecules enter the water and dissolve in it. Dissolved gas molecules also move randomly, allowing for the exit of some oxygen molecules. In chamber $B$, oxygen still shows a net movement into the fluid from the gaseous state. Eventually, the number of molecules entering and leaving the fluid equalizes, as occurs in chamber $C$. In this case, the gas pressures equilibrate without net oxygen diffusion into or out of the water. Conversely, if the pressure of dissolved oxygen molecules exceeds the pressure of the free gas in air, oxygen leaves the fluid until it attains a new pressure equilibrium. In humans, the pressure difference between alveolar and pulmonary blood gases creates the driving force for gas diffusion across the pulmonary membrane.

## Solubility (The Dissolving Power of a Gas)

For two different gases at identical pressure differentials, the solubility of each gas determines the number of molecules that move into or out of a fluid. Gas solubility is expressed as milliliters of a gas per 100 mL (dL) of a fluid. Oxygen, carbon


FIGURE 13.1 Solution containing oxygen in water. A. When oxygen first comes in contact with pure water. B. Dissolved oxygen halfway to equilibrium with gaseous oxygen. C. Equilibrium between oxygen in air and in water.
dioxide, and nitrogen have different solubility coefficients in whole blood. Carbon dioxide dissolves most readily with a solubility coefficient of 57.03 mL of carbon dioxide per dL of fluid at 760 mm Hg and 37 C . Oxygen, with a solubility coefficient of 2.26 mL , remains relatively insoluble. Nitrogen is least soluble with a coefficient of 1.30 mL .

The amount of gas dissolved in a fluid computes as follows:

Quantity of gas $=$ Solubility coefficient $\times($ Gas partial pressure $\div$ Total barometric pressure)

For example, the amount of oxygen dissolved in 1 dL of arterial whole blood $\left(\mathrm{PO}_{2}=100 \mathrm{~mm} \mathrm{Hg}\right)$ at sea level $(760 \mathrm{~mm} \mathrm{Hg})$ computes as:

$$
\begin{aligned}
\text { Quantity of gas } & =2.26 \times(100 \div 760) \\
& =0.3 \mathrm{~mL} \cdot \mathrm{dL}^{1}
\end{aligned}
$$

## Gas Exchange in the Lungs

At rest, the $100-\mathrm{mm} \mathrm{Hg}$ pressure of oxygen molecules in the alveoli exceeds by about 60 mm Hg the $40-\mathrm{mm} \mathrm{Hg}$ oxygen pressure in blood that enters the pulmonary capillaries. Consequently, oxygen travels from a higher to lower pressure as it dissolves and diffuses through the alveolar membranes into the blood. In contrast, carbon dioxide exists under a slightly greater pressure in returning venous blood than in the alveoli; this causes net diffusion of carbon dioxide from the blood into the lungs. Despite the relatively small pressure gradient of 6 mm Hg for carbon dioxide diffusion (compared with the $60-\mathrm{mm} \mathrm{Hg}$ diffusion gradient for oxygen), carbon dioxide transfer occurs rapidly because of its high solubility in plasma. Nitrogen, neither used nor produced in metabolic reactions, remains essentially unchanged in alveolar capillary gas.

| Approximate Solubility Coefficients of Gases in Physiologic Fluids |  |  |  |  |
| :--- | :---: | :---: | :---: | :---: |
| Gas | Water | Plasma | Blood | Quantity Dissolved (per dL Blood) |
| Oxygen | 2.39 | 2.14 | 2.26 | 0.3 mL |
| Carbon dioxide | 56.7 | 51.5 | 57.03 | 3.0 mL |
| Nitrogen | 1.23 | 1.18 | 1.30 | 0.8 mL |

For each unit of pressure that favors diffusion, approximately 25 times more carbon dioxide than oxygen moves into (or out of) a fluid. Viewed another way, equal quantities of oxygen and carbon dioxide enter or leave a fluid under considerably different pressure gradients for each gas-precisely what occurs in the body.

At rest, dissolved oxygen contributes about $4 \%$ of the total oxygen consumed by the body each minute; in maximal exercise, it provides less than $2 \%$ of the total requirement. Even increasing arterial $\mathrm{PO}_{2}$ by breathing $100 \%$ oxygen (ambient $\mathrm{PO}_{2}=760 \mathrm{~mm} \mathrm{Hg}$ ), dissolved oxygen ( 1.5 to $2.0 \mathrm{~mL} \cdot \mathrm{dL}$ of blood) still supplies only $40 \%$ of the total oxygen for rest and about $10 \%$ during maximal exercise. The physiologic significance of dissolved oxygen and carbon dioxide comes not from its role as a transport vehicle, but in determining the partial pressures of these gases. Partial pressure plays a central role in loading and unloading oxygen and carbon dioxide in the lungs and tissues.

## GAS EXCHANGE IN THE LUNGS AND TISSUES

Exchange of gases between the lungs and blood and gas movement at the tissue level progress passively by diffusion, depending on their pressure gradients. Figure 13.2 illustrates pressure gradients that favor gas transfer in different regions of the body at rest.

Gas exchange occurs so rapidly in the healthy lung that alveolar gas blood gas equilibrium takes place in about 0.25 seconds, or within one-third of the blood s transit time through the lungs. Even in high-intensity exercise, a red blood cell s velocity through a pulmonary capillary generally does not exceed by more than $50 \%$ its velocity at rest. With increasing exercise intensity, the pulmonary capillaries increase the blood volume within them by about three times the resting value. ${ }^{2}$ Accommodating a larger blood volume helps to maintain a relatively slow pulmonary blood flow velocity during physical activity. With complete aeration, the blood leaving the lungs contains oxygen at an average pressure of 100 mm Hg and carbon dioxide at 40 mm Hg . For most healthy people, these values vary little during vigorous exercise.

The $\mathrm{PO}_{2}$ of arterial blood usually remains slightly lower than alveolar $\mathrm{PO}_{2}$ because some blood in the alveolar capillaries passes through poorly ventilated alveoli; also, the blood leaving the lungs mixes with venous blood from the bronchial and cardiac circulations. The term venous admixture defines this small amount of poorly oxygenated blood. Venous admixture reduces the arterial $\mathrm{Po}_{2}$ slightly below the value in pulmonary end-capillary blood, and only exerts a small effect in healthy individuals.

## Impaired Alveolar Gas Transfer

Two factors impair gas transfer capacity at the alveolar capillary membrane: (1) buildup of a pollutant layer that


Figure 13.2 Pressure gradients for gas transfer within the body at rest. A. The $\mathrm{Po}_{2}$ and $\mathrm{PCO}_{2}$ of ambient, tracheal, and alveolar air and these gas pressures in venous and arterial blood and muscle tissue. Gas movement at the alveolar capillary and tissue capillary membranes always progresses from an area of higher partial pressure to lower partial pressure. B. Time required for gas exchange. At rest, blood remains in the pulmonary and tissue capillaries for about 0.75 seconds. Pulmonary disease (dashed line) impairs the rate of gas transfer across the alveolar capillary membrane, thus prolonging the time for equilibration of gases. Bloods transit time through the pulmonary capillaries during maximal exercise decreases to about 0.4 seconds, but this still remains adequate for complete aeration in the healthy lung. C. Gas exchange (diffusion) between a pulmonary capillary and its adjacent alveolus.
thickens the alveolar membrane and/or (2) reduction in alveolar surface area. Each factor extends the time before alveolar capillary gas equilibrates. For individuals with impaired lung function, the added demand for rapid gas exchange in exercise compromises aeration, negatively affecting exercise performance.

## INTEGRATIVE QUESTION

Why do minute amounts of $\mathrm{CO}_{2}$ and CO impurities in a breathing mixture exert such profound physiologic effects?

## Gas Transfer in Tissues

In tissues, where energy metabolism consumes oxygen and produces an almost equal amount of carbon dioxide, gas pressures differ considerably from those recorded in arterial blood. At rest, the $\mathrm{PO}_{2}$ in the fluid immediately outside a muscle cell averages 40 mm Hg , and intracellular $\mathrm{PCO}_{2}$ averages 46 mm Hg . In vigorous exercise, oxygen pressure within muscle tissue falls toward 0 mm Hg , while the pressure of carbon dioxide approaches 90 mm Hg . Pressure differences between gases in plasma and tissues establish diffusion gradients. Oxygen leaves the blood and diffuses toward cells, while carbon dioxide flows from cells into the blood. Blood then passes into the venous circuit (venules and veins) for return to the heart and delivery to the lungs. Diffusion occurs rapidly as blood enters the dense pulmonary capillary network. The body does not attempt to rid itself completely of carbon dioxide. To the contrary, each liter of blood leaving the lungs with a $\mathrm{PCO}_{2}$ of 40 mm Hg contains about 50 mL of carbon dioxide. As discussed in Chapter 14, this small background level of carbon dioxide provides the chemical basis for ventilatory control through its stimulating effect on the neurons of the pons and medullary centers of the brainstem. The term respiratory center describes this collection of neural tissue that controls ventilation.

Alveolar ventilation couples tightly to metabolic demands to keep alveolar gas composition remarkably constant. Stability in alveolar gas concentrations persists even during strenuous exercise that increases oxygen consumption and carbon dioxide output 25 times the values at rest.

## Summary

1. Gas molecules in the lungs and tissues diffuse down their concentration gradients from an area of higher concentration (higher pressure) to lower concentration (lower pressure).
2. The partial pressure of a specific gas in a mixture of gases varies directly with the concentration of the gas and the mixture s total pressure.
3. Henry s law states that pressure gradient and solubility determine how much gas dissolves in a fluid. Oxygen, carbon dioxide, and nitrogen exhibit different solubilities in whole blood. Carbon dioxide
dissolves most readily while oxygen and nitrogen show relatively low solubility.
4. Carbon dioxide solubility in plasma exceeds oxygen solubility by 25 times, allowing carbon dioxide to move into and from body fluids down a relatively small diffusion (pressure) gradient.
5. Maintaining a remarkably constant alveolar gas composition during rest and exercise reflects fine adjustments in pulmonary ventilation. Alveolar ventilation maintains $\mathrm{PO}_{2}$ at about 100 mm Hg and $\mathrm{PCO}_{2}$ at 40 mm Hg .
6. Oxygen diffuses into the blood and carbon dioxide diffuses into the lungs because venous blood contains oxygen at lower pressure and carbon dioxide at higher pressure than alveolar gas.
7. Alveolar blood gas exchange achieves equilibrium in the healthy lung at about the midpoint of the blood s transit through the pulmonary capillaries. Even in intense exercise, blood flow velocity through the lungs generally does not compromise full loading of oxygen and unloading of carbon dioxide.
8. Diffusion gradients favor oxygen movement from the capillaries to the tissues and carbon dioxide from the tissues to the blood. Oxygen and carbon dioxide diffuse rapidly as their pressure gradients widen during exercise.

## Part 2 OXYGEN TRANSPORT

## TRANSPORT OF OXYGEN IN THE BLOOD

The blood carries oxygen in two ways:

1. In physical solution dissolved in the fluid portion of blood
2. In loose combination with hemoglobin, the ironprotein molecule within the red blood cell

## Oxygen in Physical Solution

Oxygen s relative insolubility in water keeps its concentration low within bodily fluids. At an alveolar $\mathrm{PO}_{2}$ of 100 mm Hg , only about 0.3 mL of gaseous oxygen dissolves in each deciliter of blood ( 0.003 mL for each additional $1-\mathrm{mm} \mathrm{Hg}$ increase in $\mathrm{PO}_{2}$ ). This equals 3 mL of oxygen per liter of blood. The blood volume of a $70-\mathrm{kg}$ person averages about 5 L ; thus, 15 mL of oxygen dissolves in the fluid portion of the blood ( 3 mL per $\mathrm{L} \times 5$ ). This small amount of oxygen would sustain life for about 4 seconds. Viewed from a different perspective, if oxygen in physical solution provided the sole oxygen source to the body, about 80 L of blood would need to circulate each minute to supply the resting oxygen requirementsa blood flow about twice the maximum ever recorded!

As with carbon dioxide, the small quantity of oxygen transported in physical solution serves several important


Figure 13.3 The hemoglobin molecule (left) consists of the protein globin, composed of four subunit polypeptide chains. Each polypeptide (right) contains a single heme group with its single iron atom that acts as a magnet for oxygen.
functions. The random movement of dissolved oxygen molecules establishes the $\mathrm{PO}_{2}$ of the plasma and tissue fluids. The pressure of oxygen in solution helps to regulate breathing, particularly at higher altitudes when ambient $\mathrm{PO}_{2}$ decreases considerably; it also determines oxygen loading of hemoglobin in the lungs and subsequent release in tissues.

## Oxygen Combined with Hemoglobin

Metallic compounds exist in the blood of many animal species to augment its oxygen-carrying capacity. Figure 13.3 illustrates the iron-containing globular protein pigment hemoglobin carried within the more than 25 trillion red blood cells of humans. This concentration carries 65 to 70 times more oxygen than normally dissolves in plasma. Thus, the approximately 280 million hemoglobin molecules temporarily capture and transport about 197 mL of oxygen in each liter of blood. Each of the four iron atoms in the hemoglobin molecule can loosely bind one oxygen molecule in the following reversible reaction:

$$
\mathrm{Hb}_{4}+4 \mathrm{O}_{2} \leftrightarrow \mathrm{Hb}_{4} \mathrm{O}_{8}
$$

The reaction requires no enzymes; it proceeds without a change in the valence of $\mathrm{Fe}^{2+}$ as in the more permanent oxidation process. The partial pressure of oxygen dissolved in physical solution dictates the oxygenation of hemoglobin to oxyhemoglobin.

## Oxygen-Carrying Capacity of Hemoglobin

In men, each dL of blood contains about 15 g of hemoglobin. The value decreases 5 to $10 \%$ for women and averages nearly 14 g per dL of blood. This gender difference partly explains the lower aerobic capacity of women relative to men, even when considering differences in body mass and body fat. The reason for higher hemoglobin concentrations in men relates to the stimulating effects on red blood cell production of the male hormone testosterone.

Each gram of hemoglobin combines loosely with 1.34 mL of oxygen. Thus, if one knows the hemoglobin
content of the blood, its oxygen-carrying capacity computes as follows:
Blood s oxygen

| capacity <br> $\left(\mathrm{mL} \cdot \mathrm{dL}\right.$ blood $\left.{ }^{-1}\right)$ | $=$Hemoglobin <br> $\left(\mathrm{g} \cdot \mathrm{dL}\right.$ blood $\left.^{-1}\right)$ | $\times$Oxygen capacity <br> of hemoglobin |
| :---: | :---: | :---: |
| $20 \mathrm{~mL} \mathrm{O}_{2}$ | $=$ | 15 |$\times$| $1.34 \mathrm{~mL} \cdot \mathrm{~g}^{-1}$ |
| :--- |

With full oxygen saturation (i.e., when all hemoglobin converts to $\mathrm{HbO}_{2}$ ) and with normal hemoglobin levels, hemoglobin carries nearly 20 mL of oxygen in each dL of whole blood.

Anemia Affects Oxygen Transport. The blood s oxygen transport capacity changes only slightly with normal variations in hemoglobin content. In contrast, a significant decrease in the iron content of red blood cells reduces the blood s oxygen-carrying capacity. Such iron deficiency anemia diminishes a person s capacity to sustain even mildintensity aerobic exercise. ${ }^{1,5}$

Table 13.3 presents data from 29 iron-deficient anemic men and women with low hemoglobin levels. They formed two groups; one received intramuscular iron injections over an 80-day period, while the placebo group received similar intramuscular injections of a colored saline solution. A third group with normal hemoglobin levels served as controls. The researchers tested all groups during exercise prior to the experiment and after 80 days of either iron therapy or placebo treatment. The results clearly show that the anemic group given iron supplements improved in exercise response compared with nonsupplemented counterparts. Peak heart rate during 5 minutes of stepping exercise decreased from 155 to $113 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ for men and from 152 to $123 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ for women. This translates into an average of $15 \%$ more oxygen delivered per heartbeat.

## $\mathrm{PO}_{2}$ and Hemoglobin Saturation

The term cooperative binding describes the union of oxygen with hemoglobin. The binding of an oxygen molecule to the iron atom in one of the four globin chains in Figure 13.3

## TABLE 13.3 Hemoglobin (Hb) Levels and

 Exercise Heart Rates of Normal and Anemic Subjects Prior to and Following Supplemental Iron Treatment| Subjects | Hb (g per <br> dL Blood) | Peak Exercise <br> Heart Rate |
| :--- | :---: | :---: |
| Normal |  |  |
| Men | 14.3 | 119 |
| $\quad$ Women | 13.9 | 142 |
| Iron-deficient men <br> Pretreatment <br> Posttreatment | 7.1 | 155 |
| Iron-deficient women <br> Pretreatment <br> Posttreatment | 14.0 | 113 |
| Iron-deficient men <br> $\quad$ Preplacebo <br> Postplacebo | 12.4 | 152 |
| Iron-deficient women | 7.7 | 123 |
| $\quad$ Preplacebo | 7.4 | 146 |
| Postplacebo | 8.1 | 137 |

From Gardner GW, et al. Cardiorespiratory, hematological, and physical performance responses of anemic subjects to iron treatment. Am J Clin Nutr 1975;28:982.
Values represent group averages.
progressively facilitates the binding of subsequent molecules. The cooperative binding phenomenon explains hemoglobin s sigmoid, or S-shaped, oxygen saturation curve.

The oxyhemoglobin dissociation curve (Fig. 13.4) illustrates the saturation of hemoglobin with oxygen at various $\mathrm{PO}_{2}$ values including alveolar capillary gas at sea level $\left(\mathrm{PO}_{2}, 100 \mathrm{~mm} \mathrm{Hg}\right)$. The right ordinate gives the quantity of oxygen carried in each deciliter of normal blood at a particular plasma $\mathrm{PO}_{2}$ value. The term volume percent (vol\%) describes blood s oxygen content. In this regard, volume percent refers to the milliliters of oxygen extracted (in a vacuum) from a deciliter sample of either whole blood (with plasma) or packed red blood cells (without plasma).

Physical chemists establish dissociation curves (oxygen content and percentage saturation) by exposing about 200 mL of blood in a sealed glass vessel (tonometer) to various pressures of oxygen at a given pH in a water bath of known temperature. Percentage saturation computes as follows:
Percentage saturation $=\frac{\mathrm{O}_{2} \text { combined with hemoglobin }}{\mathrm{O}_{2} \text { capacity of hemoglobin }} \times 100$
If an individual s hemoglobin oxygen-carrying capacity in whole blood equals $20 \mathrm{vol} \%$ and only $12 \mathrm{vol} \%$ oxygen actually combines with hemoglobin, then:
Percentage saturation $=12 \mathrm{vol} \% \div 20 \mathrm{vol} \% \times 100=60 \%$
One hundred percent saturation indicates that the oxygen combined with hemoglobin equals the oxygen-carrying capacity of hemoglobin.

Figure 13.4B depicts the oxygen transport cascade for oxygen partial pressure as oxygen moves from ambient air at sea level to the mitochondria of maximally active muscle tissue.

## $\mathrm{Po}_{2}$ in the Lungs

In the discussion about hemoglobin, the assumption has been that hemoglobin fully saturates with oxygen when exposed to alveolar gas. This does not occur because at the sea-level alveolar $\mathrm{PO}_{2}$ of 100 mm Hg , hemoglobin achieves only $98 \%$ oxygen saturation. The right ordinate of Figure 13.4 A shows that at a $\mathrm{PO}_{2}$ of 100 mm Hg , the hemoglobin in each deciliter of blood leaving the lungs carries about 19.7 mL of oxygen. Clearly, any additional increase in alveolar $\mathrm{PO}_{2}$ contributes little to how much more oxygen can combine with hemoglobin. In addition to the oxygen bound to hemoglobin, the plasma of each deciliter of arterial blood contains 0.3 mL of oxygen in solution. In healthy individuals who breathe ambient air at sea level, each deciliter of blood leaving the lungs carries approximately 20.0 mL of oxygen- 19.7 mL bound to hemoglobin and 0.3 mL dissolved in plasma. Figure 13.5 shows the percentage composition of centrifuged whole blood for red blood cells (termed hematocrit) and plasma, including representative values for the quantity of oxygen carried in each component.

On television, one frequently sees competitive athletes on the sidelines breathing a gas mixture of concentrated oxygen following strenuous exercise. This makes no sense from an oxygen-transport perspective. The oxyhemoglobin dissociation curve shows little or no potential for increased hemoglobin loading from additional pressure of supplemental oxygen inhaled at sea level or at relatively low altitude. We discuss the topic of breathing hyperoxic gas mixtures and exercise performance in more detail in Chapter 23.

Figure 13.4 also shows that hemoglobin saturation with oxygen changes little until the pressure of oxygen declines to about 60 mm Hg . This flat upper portion of the oxyhemoglobin dissociation curve provides a margin of safety to ensure adequate saturation of arterial blood with oxygen despite considerable fluctuations in ambient $\mathrm{PO}_{2}$. Even if alveolar $\mathrm{PO}_{2}$ decreases to 75 mm Hg , as occurs in lung disease or at higher altitudes, the saturation of hemoglobin decreases by only about $6 \%$. At an alveolar $\mathrm{Po}_{2}$ of 60 mm Hg , hemoglobin still remains nearly $90 \%$ saturated with oxygen! Below this pressure, the quantity of oxygen combined with hemoglobin declines more rapidly.

INTEGRATIVE QUESTION
Advise a coach who wants football players to breathe from an oxygen tank during time-outs or rest breaks to speed recovery.

## $\mathrm{PO}_{2}$ in the Tissues

At rest, the $\mathrm{Po}_{2}$ in the cell fluids averages 40 mm Hg . This makes dissolved oxygen from the plasma diffuse across the


## B Oxygen Transport Cascade

Figure 13.4 A. Oxyhemoglobin dissociation curve. Lines indicate the percentage saturation of hemoglobin (solid line) and myoglobin (dashed line) in relation to oxygen pressure. The right ordinate shows the quantity of oxygen carried in each deciliter of blood under normal conditions. The inset curves within the figure illustrate the effects of temperature and acidity in altering hemoglobins affinity for oxygen (Bohr effect). Inset box presents oxyhemoglobin saturation and arterial bloods oxygen-carrying capacity for different $\mathrm{PO}_{2}$ values with hemoglobin concentration of $14 \mathrm{~g} \cdot \mathrm{dL}$ blood $^{-1}$ at a pH of 7.40. The white horizontal line at the top of the graph indicates percentage saturation of hemoglobin at the average sea-level alveolar $\mathrm{PO}_{2}$ of 100 mm Hg .
B. Partial pressures as oxygen moves from ambient air at sea level to the mitochondria of maximally active muscle tissue (oxygen transport cascade).

## Centrifuged Whole Blood



## A Pre training


(B) Post training

Figure 13.5 A. Major components of centrifuged whole blood, including the quantity of oxygen carried in each deciliter of blood ( Hb , hemoglobin) in an untrained individual. B. Changes in constituents of whole blood following 4 days of aerobic exercise training. Note that the increase in plasma volume (hemodilution) early in training decreases red blood cell concentration toward borderline anemia (see Chapters 2 and 21). Oxygen transport capacity does not decrease with training because the total erythrocyte mass of the blood remains constant or increases slightly.
capillary membrane through the tissue fluids into the cells. This reduces plasma $\mathrm{PO}_{2}$ below the $\mathrm{PO}_{2}$ in the red blood cell, causing hemoglobin to lower its oxygen saturation level. The released oxygen $\left(\mathrm{HbO}_{2} \rightarrow \mathrm{Hb}+\mathrm{O}_{2}\right)$ moves out of the blood cells through the capillary membrane into the tissues.

At the tissue capillary $\mathrm{PO}_{2}$ at rest of 40 mm Hg , hemoglobin holds about $70 \%$ of its original oxygen (see Fig. 13.4). Thus, when blood leaves the tissues and returns to the heart, it carries about 15 mL of oxygen in each deciliter of blood, giving up 5 mL of oxygen to the tissues.

## Arteriovenous Oxygen Difference

The arterio-mixed-venous oxygen difference (a-vO2 difference) describes the difference between the oxygen content of arterial blood and mixed-venous blood. The a- $\mathrm{vO}_{2}$ difference at rest normally averages 4 to 5 mL of oxygen per deciliter of blood. The large quantity of oxygen still attached to hemoglobin provides an automatic reserve so cells can immediately obtain oxygen should metabolic demands suddenly increase. Tissue $\mathrm{PO}_{2}$ decreases as the cell s use of oxygen increases in exercise. This causes hemoglobin to immediately release a larger amount of oxygen. During intense exercise when extracellular $\mathrm{PO}_{2}$ decreases to nearly 15 mm Hg , only about 5 mL of oxygen remains bound to hemoglobin. This makes the a-vO $\mathrm{O}_{2}$ difference increase to 15 mL of oxygen per 100 mL of blood. When active muscle $\mathrm{Po}_{2}$ falls to

2 or 3 mm Hg during exhaustive exercise, the blood perfusing these tissues gives up virtually all its oxygen. ${ }^{13}$ Oxygen release from hemoglobin can occur without any increase in local tissue blood flow. The amount of oxygen released to the muscles increases almost three times above that normally supplied at rest-just by a more complete unloading of hemoglobin as it flows through the active muscles (see Focus on Research, p. 280). An active muscles uncompromising capacity to use available oxygen in its large blood flow supports the position that oxygen supply (blood flow), not muscle oxygen use, limits aerobic exercise capacity. ${ }^{11}$

## The Bohr Effect

The sigmoid, solid yellow line in Figure 13.4A represents the oxyhemoglobin dissociation curve under resting physiologic conditions at an arterial pH of 7.4 and tissue temperature of 37 C . The inset curves depict other important characteristics of hemoglobin s affinity for oxygen. Any increase in plasma acidity (including carbon dioxide concentration) and temperature causes the dissociation curve to shift downward and to the right. This phenomenon, called the Bohr effect for its 1891 discoverer, Danish physiologist Christian Bohr (1855 1911; father of Nobel physicist Niels Bohr), indicates that hydrogen ions and carbon dioxide alter hemoglobin s molecular structure to decrease its oxygenbinding affinity. The reduced effectiveness of hemoglobin to hold oxygen occurs particularly in the $\mathrm{PO}_{2}$ range between 20 and 50 mm Hg . The Bohr effect remains evident during intense exercise as more oxygen releases to tissues from associated increases in (1) metabolic heat, (2) carbon dioxide, and (3) acidity from blood lactate accumulation. At normal alveolar $\mathrm{PO}_{2}$ the Bohr effect exerts almost no effect on pulmonary capillary blood (even during maximal exercise), so hemoglobin loads (or binds) fully with oxygen as blood flows through the lungs.

## Red Blood Cell 2,3-DPG

A red blood cell derives its energy solely from the anaerobic reactions of glycolysis because they contain no mitochondria; this establishes the normal plasma lactate levels at rest. Red blood cells produce the compound 2,3-diphosphoglycerate (2,3-DPG; also referred to as 2,3-biphosphoglycerate [2,3-BPG]) during glycolysis. 2,3-DPG binds loosely with subunits of the hemoglobin molecule, reducing its affinity for oxygen. This causes greater oxygen release to the tissues for a given decrease in $\mathrm{PO}_{2} .{ }^{3}$

Increased levels of red blood cell 2,3-DPG occur in individuals with cardiopulmonary disorders and those who live at high altitudes. This compensatory adjustment facilitates oxygen release to the cells. During strenuous exercise, 2,3-DPG also aids in oxygen transfer to muscles. ${ }^{6}$ Conflicting results emerge in comparison of 2,3-DPG levels of trained and untrained subjects. ${ }^{4,7,10}$ One study reported higher resting levels of $2,3-\mathrm{DPG}$ in two groups of athletes than in untrained subjects. ${ }^{14}$ The level of this metabolic intermediate increased by
$15 \%$ for middle-distance runners following short-duration maximal exercise. In contrast, prolonged steady-rate exercise in endurance athletes produced a small decrease in 2,3-DPG. These data support the proposition that increases in 2,3-DPG concentration with intense exercise (and perhaps training) reflect an adaptive response that augments oxygen delivery to more metabolically active tissues. More than likely, the effect of different types of exercise on erythrocyte 2,3-DPG levels reflects the specific metabolic demands of exercise. Females have higher levels of red blood cell 2,3-DPG than males of similar fitness status and physical activity level. This gender
difference might compensate for the lower hemoglobin levels in females. ${ }^{9}$

## Myoglobin, the Muscles Oxygen Storage

Myoglobin, an iron-containing globular protein in skeletal and cardiac muscle fibers, provides intramuscular oxygen storage. X-ray crystallography in 1960 revealed myoglobin s structural details. The molecule contains a peptide backbone embedded with the heme group and its metallic $\mathrm{Fe}^{2+}$. Reddish muscle fibers have a high concentration of this respiratory

## FOCUS ON RESEARCH

## Muscle: A Remarkably Adaptable Tissue

Holloszy JO. Biochemical adaptations in muscle: effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. J Biol Chem 1967;242:2278.
$>$ For years, conventional wisdom maintained that central cardiovascular adaptations exclusively increased capacity to deliver oxygen to active muscle and thus increased endurance performance with aerobic training. Proponents of this view argued that training-induced improvements in $\mathrm{VO}_{2 \text { max }}$ resulted from increased maximal cardiac output due to an increase in the heart s maximal stroke volume. Central to this concept was the belief that working muscle became hypoxic during high-intensity exercise and became less hypoxic after training, due to increased oxygen consumption ability.

The study by Holloszy was the first to show that endurance training increased skeletal muscle mitochondrial content in rats. The author hypothesized that local (peripheral) changes in muscle (primarily in mitochondria) contribute to improved endurance performance with training. This study and subsequent research with colleagues ushered in a burgeoning new area in exercise biochemistry research.

In this study, rats ran on a treadmill 5 days per week for 12 weeks. Running speed and duration gradually increased so that after 12 weeks, the animals ran for 120 minutes daily on an $8 \%$ incline at $31 \mathrm{~m} \cdot \mathrm{~min}^{-1}$, including 12,30 -second intervals at $42 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ interspersed at 10 -minute intervals. The protocol was the most strenuous reported in the exercise literature of that time. The animals were placed into one of four groups of 12: (1) exercise trained; (2) exercise control pair weighted, who performed only mild daily exercise ( $10 \mathrm{~min}, 5$ days per week) with food intake adjusted to maintain the same body weight as group 1 ; (3) sedentary control pair weighted,
with food intake adjusted to maintain the same body weight as group 1 ; and (4) sedentary, freely eating.

The dependent variables were measured from the gastrocnemius and soleus muscles to show evidence for exercise training adaptations in muscle mitochondria and mitochondrial enzymes. These measures included levels of succinate dehydrogenase, NADH dehydrogenase, NADH-cytochrome c reductase, level of respiratory control, mitochondrial protein, and succinate and cytochrome oxidase activity per gram of muscle.

The table shows that the capacity of the mitochondrial fraction from gastrocnemius muscle to oxidize pyruvate doubled in the trained rats. Succinate dehydrogenase, NADH dehydrogenase, NADH-cytochrome c reductase, and cytochrome oxidase activities per gram of muscle also increased approximately twofold. The near doubling of cytochrome c activity provided evidence that increases in respiratory chain enzyme activities resulted from increased mitochondrial enzyme activity. The total protein content of the mitochondrial fraction of trained muscle increased about $60 \%$. The high level of mitochondrial respiratory control and tightly coupled oxidative phosphorylation revealed that the increase in electron transport capacity with training accompanied rises in the capacity to generate ATP via oxidative phosphorylation.

Subsequent investigations with animals and humans soon confirmed Holloszy s findings of increased respiratory capacity and mitochondrial enzyme levels in aerobically trained muscle. This pioneering work served as a catalyst for further research concerning the profound effect of exercise training on muscle biochemistry. The research also helped to explain why regular aerobic overload increases ability to exercise at a higher percentage of $\mathrm{VO}_{2 \text { max }}$ and provided an important cellular component to verify the specificity of training principle for aerobic exercise.

## FOCUS ON RESEARCH <br> Continued

## Effects of Endurance Exercise Training on Rat Muscle Mitochondria

| Variable | Sedentary Trained | Control |
| :---: | :---: | :---: |
| Body mass, g | $353 \pm 17$ | $491 \pm 21.9$ |
| Gastrocnemius muscle weight, g | $2.1 \pm 0.06$ | $2.62 \pm 0.12$ |
| Treadmill run to exhaustion (min) at $31 \mathrm{~m} \cdot \mathrm{~min}^{-1}$ | $186 \pm 18$ | $29.0 \pm 3$ |
| $\mathrm{VO}_{2}, \mathrm{~mL} \cdot \mathrm{~h}^{-1} \cdot \mathrm{~g}^{-1}$ | $1022 \pm 118$ | $506 \pm 53$ |
| Respiratory control index | $16.1 \pm 2.2$ | $14.7 \pm 2.6$ |
| Cytochrome oxidase, mL $\mathrm{O}_{2} \cdot \mathrm{~min}^{-1} \cdot \mathrm{~g}$ muscle ${ }^{-1}$ |  |  |
| Gastrocnemius | $551 \pm 31$ | $305 \pm 15$ |
| Soleus | $691 \pm 52$ | $427 \pm 16$ |
| Succinate oxidase, mL $\mathrm{O}_{2} \cdot \mathrm{~min}^{-1} \cdot \mathrm{~g}$ muscle $^{-1}$ |  |  |
| Gastrocnemius | $117 \pm 8$ | $73 \pm 5$ |
| Soleus | $160 \pm 8$ | $95 \pm 10$ |
| Succinate dehydrogenase activity, mmol $\cdot \mathrm{g}$ muscle ${ }^{-1}$ | $15.1 \pm 1.4$ | $8.3 \pm 0.7$ |
| Cytochrome c concentration, $\mathrm{mmol} \cdot \mathrm{g}$ muscle ${ }^{-1}$ | $6.46 \pm 0.58$ | $3.47 \pm 0.18$ |
| DPNH dehydrogenase, mmol $\cdot \mathrm{g}$ muscle ${ }^{-1}$ | $11.8 \pm 1.5$ | $5.6 \pm 0.6$ |
| Mitochondrial protein, $\mathrm{mmol} \cdot \min ^{-1} \cdot \mathrm{mg}^{2}$ protein ${ }^{-1}$ | $4.67 \pm 0.30$ | $2.97 \pm 0.20$ |
| DPNH cytochrome c reductase, $\mathrm{mmol} \cdot \mathrm{g}$ muscle ${ }^{-1}$ | $0.60 \pm 0.09$ | $0.25 \pm 0.06$ |

pigment, whereas myoglobin-deficient fibers appear pale or white. ${ }^{8}$ Myoglobin resembles hemoglobin because it also combines reversibly with oxygen but each molecule contains one iron atom while hemoglobin contains four. Myoglobin adds additional oxygen to the muscle in the following chemical reaction:

$$
\mathrm{Mb}+\mathrm{O}_{2} \rightarrow \mathrm{MbO}_{2}
$$

## Oxygen Released at Low Pressures

Myoglobin facilitates oxygen transfer to the mitochondria when exercise begins and during intense exercise when cellular $\mathrm{PO}_{2}$ declines rapidly. The dissociation curve for myoglobin (Fig. 13.4; dashed yellow line) does not form an S-shaped line as does hemoglobin, but instead plots as a rectangular hyperbola. Compared with the oxygen saturation curve for hemoglobin, the curve for myoglobin shows that it much more readily binds and retains oxygen at low oxygen pressures. During rest and moderate exercise, myoglobin maintains high oxygen saturation. For example, at a $\mathrm{PO}_{2}$ of 40 mm Hg , myoglobin retains $95 \%$ of its oxygen. The greatest quantity of oxygen releases from $\mathrm{MbO}_{2}$ when tissue $\mathrm{PO}_{2}$ declines below $5 \mathrm{~mm} \mathrm{Hg} .{ }^{12}$ Unlike hemoglobin, acidity, carbon
dioxide, and temperature do not affect myoglobin s oxygenbinding affinity so it does not exhibit a Bohr effect. Chapter 21 discusses the effects of aerobic exercise training on the muscles myoglobin content.

## Summary

1. Hemoglobin, the iron-protein pigment in the red blood cell, increases the amount of oxygen carried in whole blood about 65 times that carried in physical solution in the plasma.
2. The small amount of oxygen dissolved in plasma exerts molecular movement and establishes the partial pressure of oxygen $\left(\mathrm{PO}_{2}\right)$ in the blood. Plasma $\mathrm{PO}_{2}$ determines the loading of hemoglobin at the lungs (oxygenation) and its unloading at the tissues (deoxygenation).
3. The blood s oxygen-transport capacity varies only slightly with normal variations in hemoglobin content. Iron deficiency anemia lowers hemoglobin concentration, thus decreasing the blood s oxygencarrying capacity. Lowered hemoglobin concentration impairs aerobic exercise performance.
4. The shape of the oxyhemoglobin dissociation curve indicates that hemoglobin saturation changes little until $\mathrm{PO}_{2}$ declines below 60 mm Hg . The quantity of oxygen bound to hemoglobin falls sharply as oxygen moves from capillary blood to the tissues when metabolic demands increase.
5. Arterial blood releases only about $25 \%$ of its total oxygen content to the tissues at rest; the remaining $75 \%$ returns unused to the heart in venous blood.
6. The difference in oxygen content of arterial and venous blood under resting conditions indicates an automatic reserve of oxygen for rapid use should metabolism suddenly increase.
7. The Bohr effect reflects alterations in the molecular structure of hemoglobin from increased acidity, temperature, carbon dioxide concentration, and red blood cell 2,3-DPG that reduce its effectiveness to hold oxygen. Exercise accentuates these factors to further facilitate oxygen s release to the tissues.
8. The iron-protein pigment myoglobin in skeletal and cardiac muscle provides an extra oxygen store to release oxygen at low $\mathrm{PO}_{2}$. During intense exercise, myoglobin facilitates oxygen transfer to the mitochondria when intracellular $\mathrm{PO}_{2}$ in active skeletal muscle decreases dramatically.

## Part 3 CARBON DIOXIDE TRANSPORT

## CARBON DIOXIDE TRANSPORT IN THE BLOOD

Once carbon dioxide forms in the cell, diffusion and subsequent transport in the venous blood provides the only means for its escape through the lungs. The blood carries carbon dioxide in three ways:

1. In physical solution in plasma (small amount)
2. Combined with hemoglobin within the red blood cell
3. As plasma bicarbonate

Figure 13.6 illustrates the three ways for transporting carbon dioxide from the tissues to the lungs.

## Carbon Dioxide in Physical Solution

Approximately 5\% of the carbon dioxide formed during energy metabolism moves into physical solution in the plasma as free carbon dioxide. The random movement of this small quantity of dissolved carbon dioxide molecules establishes the $\mathrm{PCO}_{2}$ of the blood.


Figure 13.6 Transport of carbon dioxide in the plasma and red blood cells as dissolved $\mathrm{CO}_{2}$, bicarbonate, and carbamino compounds. By far, the greatest amount of carbon dioxide combines with water to form carbonic acid.

## Carbon Dioxide Transport As Bicarbonate

Carbon dioxide in solution slowly combines with water to form carbonic acid in the following reversible reaction:

$$
\mathrm{CO}_{2}+\mathrm{H}_{2} \mathrm{O} \longleftrightarrow \mathrm{H}_{2} \mathrm{CO}_{3}
$$

Little carbon dioxide transport as carbonic acid would occur without carbonic anhydrase, a zinc-containing enzyme within the red blood cell. One mole of this catalyst tremendously accelerates the union of a mole of carbon dioxide and water to a rate of about 800,000 times a second (about 5000 times faster than without enzymatic action). The reaction attains equilibrium as the blood cell moves through the tissue s capillary.

Once carbonic acid forms in the tissues, most of it ionizes into hydrogen ions $\left(\mathrm{H}^{+}\right)$and bicarbonate ions $\left(\mathrm{HCO}_{3}{ }^{-}\right)$ as follows:

## In tissues

$$
\mathrm{CO}_{2}+\mathrm{H}_{2} \mathrm{O} \xrightarrow{\text { carbonic anhydrase }} \mathrm{H}_{2} \mathrm{CO}_{3} \rightarrow \mathrm{H}^{+}+\mathrm{HCO}_{3}^{-}
$$

Buffering of the $\mathrm{H}^{+}$by the protein portion of hemoglobin maintains blood pH within relatively narrow limits (see Acid Base Regulation, Chapter 14). The $\mathrm{HCO}_{3}^{-}$remains soluble so it diffuses from the red blood cell into plasma. There it exchanges for a chloride ion $\left(\mathrm{Cl}^{-}\right)$that moves into the blood cell to maintain ionic equilibrium. This phenomenon, termed the chloride shift, increases the $\mathrm{Cl}^{-}$content of

## IN A PRACTICAL SENSE

## Factors that Contribute to the Smoking Habit

Cigarette smoking represents the single greatest cause of death worldwide. Each year, more than 450,000 people in the United States die from smoking-related diseasesheart disease, cancer, stroke, aortic aneurysm, chronic bronchitis, emphysema, and peptic ulcers. Chronic cigarette smokers live an average of 18 years less than nonsmokers, and each cigarette smoked shortens life by 7 minutes! In addition to its adverse effects on health, cigarette smoking (both short and long term) has the potential to negatively affect exercise performance, which is discussed in greater detail in Chapter 14. Because of the potential for adverse effects on exercise and sports performance, we have included this In a Practical Sense in this chapter due to the fact that it provides insight into factors related to the smoking habit.

## WHY PEOPLE START SMOKING

People usually start smoking without realizing its detrimental effects. Cigarette smoking generally begins during the teen years or earlier. Health problems from smoking accrue quickly in young smokers. Three reasons generally explain why youths begin smoking: (1) peer pressure, (2) desire to appear grown up, and (3) rebellion against authority.

## CIGARETTES CAUSE ADDICTION

Tobacco smoke contains more than 1200 toxic chemicals; tar alone contains nearly 30 known carcinogens. Within seconds of inhalation, nicotine affects the central nervous system to act simultaneously as a tranquilizer and stimulant. Nicotines stimulating effect produces a strong physiologic and psychologic dependency. Estimates place the physiologic addiction to nicotine at about 6 to 8 times the addictive power of alcohol. Psychologic dependency develops over a longer time and associates with calming and pleasurable activities such as drinking coffee or alcohol, participating in social gatherings, relaxing after a meal, talking on the telephone, driving, reading, and watching television.

## THE WHY-DO-YOU-SMOKE TEST

The Why-Do-You-Smoke Test (see table) identifies reasons for smoking, which provides the important first step in behavioral approaches to smoking cessation.

The test lists 18 statements about why people smoke. A score between 1 and 5 indicates the strength of agreement with the statement, with 5 representing the strongest agreement. The responses to each of the statements provide input about one of six factors most frequently related to a persons smoking behavior. The information obtained provides (1) insight as to why a person smokes and (2) possible behavioral substitutes to aid in cessation.

Stimulation (cigarettes are stimulating): You feel that they help wake you up, organize your energies, and keep you going. Choose a safe substitutea brisk walk or moderate exercise.
Handling (keep my hands busy): Toy with a pen or pencil or doodle, play with a coin, piece of jewelry, or some other harmless object while quitting.
Accentuation of pleasure/pleasurable relaxation (makes me feel good): Substitute social and physical activities or other relaxing activities to accentuate pleasure.
Reduction of negative feelings/crutch (gets me through the tough times): Learning to handle stress helps with quitting.
Craving or dependence (cant get through the day without them): Cold turkey is the most effective way to quit; biofeedback has shown some success. Habit (dont even know when Im smoking): You need to break the habitual smoking pattern; being more aware of conditions and situations when smoking occurs aids in quitting.

Scores for each factor can vary between 3 and 15. A score of 11 or above indicates that for this factor smoking represents an important source of satisfaction. Scoring low ( $<7$ ) on a factor indicates a greater likelihood of successful smoking cessation.

## IN A PRACTICALSENSE

## Why-Do-You-Smoke Test

Question
A. I smoke in order to keep myself from slowing
down.
B. Handling a cigarette is part of the enjoyment of
smoking it.
C. Smoking is pleasant and relaxing.
D. I light up when I feel angry about something.
E. When I have run out of cigarettes, I find it almost
unbearable until I can get them.
F. I smoke automatically without even being aware of it.
G. I smoke to stimulate myself, to perk myself up.
H. Part of the enjoyment of cigarettes comes from
the steps I take to light up.
I. I find cigarettes pleasurable.
J. When I feel uncomfortable or upset about something,
I light up.
K. I am very much aware of the act when I am not
smoking.
L. I light up without realizing I still have one burning
in the ashtray.
M. I smoke to give myself a lift.
N. When I smoke, part of the enjoyment is watching
the smoke as I exhale it.
O. I want a cigarette most when I am comfortable
and relaxed.
P. When I feel blue or want to take my mind off
cares and worries, I smoke.
Q. I get a real gnawing hunger for a cigarette when I
haven $t$ smoked for a while.
R. I ve found a cigarette in my mouth and didn $t$
remember putting it there.

| Always | Frequently | Occasionally | Seldom | Never |
| :---: | :---: | :---: | :---: | :---: |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |
| 5 | 4 | 3 | 2 | 1 |

## Scoring

Enter the number you circled on the test questions in the spaces provided below, putting the number you circled to question A on line A, to question B on line B, etc. Add the three scores on each line to get a total for each factor. For example, the sum of your scores over lines A, G, and M gives the score on Stimulation ; lines B, H, and N give the score on Handling, etc. Scores can vary between 3 and 15. Any score above 11 is high; any score 7 and below is low and indicates greater likelihood for successful smoking cessation.


From A self-test for smokers. U.S. Department of Health and Human Services, 1983.
erythrocytes in venous blood more than in arterial red blood cells, particularly during exercise.

Sixty to $80 \%$ of the total carbon dioxide exists as plasma bicarbonate. Bicarbonate forms in accordance with the law of mass action; carbonic acid formation accelerates as tissue $\mathrm{PCO}_{2}$ increases. Plasma $\mathrm{PCO}_{2}$ lowers as carbon dioxide leaves the blood via the lungs. This disturbs the equilibrium between car-
bonic acid and bicarbonate ion formation. The $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}^{-}$ recombine to form carbonic acid. In turn, carbon dioxide and water re-form and carbon dioxide exits through the lungs as follows:

## In lungs

$$
\mathrm{H}^{+}+\mathrm{HCO}_{3}^{-} \rightarrow \mathrm{H}_{2} \mathrm{CO}_{3} \xrightarrow{\text { carbonic anhydrase }} \mathrm{CO}_{2}+\mathrm{H}_{2} \mathrm{O}
$$

The $\mathrm{CI}^{-}$moves from the red blood cell back into the plasma because plasma $\mathrm{HCO}_{3}^{-}$decreases in the pulmonary capillaries.

## Carbon Dioxide Transport as Carbamino Compounds

At the tissue level, carbamino compounds form when carbon dioxide reacts directly with the amino acid molecules of blood proteins. The globin portion of hemoglobin, which carries about $20 \%$ of the body s carbon dioxide, forms a carbamino compound as follows:
$\underset{\text { (Hemoglobin) }}{\mathrm{CO}_{2}+\underset{\text { (Carbaminohemoglobin) }}{\mathrm{HbNH}}}$

A decrease in the plasma $\mathrm{PCO}_{2}$ in the lungs reverses carbamino formation. This causes carbon dioxide to move into solution and enter the alveoli. Concurrently, oxygenation of hemoglobin reduces its ability to bind carbon dioxide. The interaction between oxygen loading and carbon dioxide release, termed the Haldane effect after Scottish physiologist J. S. Haldane (1860 1936; inventor of the gas mask during World War 1 and developer of the first decompression tables for
diving [see Chapter 26]), facilitates carbon dioxide removal in the lung.

## Summary

1. About $5 \%$ of carbon dioxide travels in the plasma as free carbon dioxide in physical solution. Dissolved carbon dioxide establishes the $\mathrm{PCO}_{2}$ of the blood, which modulates important physiologic functions.
2. The major quantity of carbon dioxide ( $80 \%$ ) transports in chemical combination with water to form bicarbonate as follows:

$$
\mathrm{CO}_{2}+\mathrm{H}_{2} \mathrm{O} \longrightarrow \mathrm{H}_{2} \mathrm{CO}_{3} \longrightarrow \mathrm{H}^{+}+\mathrm{HCO}_{3}^{-}
$$

In the lungs, the reaction reverses and carbon dioxide exits the blood into the alveoli.
3. About $20 \%$ of the body s carbon dioxide combines with blood proteins, including hemoglobin, to form carbamino compounds.

## CHAPTER 14



## Dynamics of Pulmonary Ventilation

## CHAPTER OBJECTIVES

> Describe how the hypothalamic neural command center controls pulmonary ventilation

- Explain how major chemical and nonchemical factors regulate pulmonary ventilation during rest and exercise
> Describe how hyperventilation extends breathholding time but also poses a danger in sport diving
- Outline the dynamic phases of minute ventilation at the onset, early phase, and late stage of moderate exercise and recovery
> Graph the relationships among pulmonary ventilation, blood lactate, and oxygen consumption during incremental exercise, indicating the point of onset of blood lactate accumulation (OBLA)
- Explain the reasons for the increase in ventilatory equivalent during the transition from steady-rate to non steady-rate exercise
> Give the rationale for substituting the blood lactate threshold or OBLA for $\mathrm{VO}_{2 \text { max }}$ to predict endurance performance
> Quantify the energy cost of breathing during rest and strenuous exercise in health and pulmonary disease
- Describe the acute effects of cigarette smoking on heart rate and energy cost of breathing during exercise
- Outline endurance training adaptations in pulmonary ventilation during submaximal and maximal exercise
> Discuss pros and cons to the argument that pulmonary ventilation represents the weak link in oxygen supply during maximal exercise
> Summarize how chemical and physiologic buffer systems regulate acid base quality of body fluids during rest and exercise


## Part 1 REGULATION OF PULMONARY VENTILATION

## VENTILATORY CONTROL

Complex mechanisms exquisitely adjust breathing rate and depth to the bodys metabolic needs. Intricate neural circuits relay information from higher brain centers, lungs, and other sensors throughout the body to coordinate ventilatory control. ${ }^{7,68}$ The gaseous and chemical states of the blood that bathes the medulla and aortic and carotid artery chemoreceptors also mediate alveolar ventilation. In healthy individuals, these control mechanisms maintain relatively constant alveolar (and arterial) gas pressures throughout a broad range of exercise intensities. Figure 14.1 presents a schematic view of the input for ventilatory control.

## Neural Factors

The inherent activity of inspiratory neurons with cell bodies located in the medial portion of the medulla governs the normal respiratory cycle. These neurons activate the diaphragm and intercostal muscles to cause the lungs to inflate. The inspiratory neurons cease firing because of self-limitations and inhibitory influence of expiratory neurons also located in the medulla. Inhibitory and excitatory signals from throughout the body influence the normal rhythm of medullary neurons. For example, lung inflation stimulates stretch receptors mainly in the bronchioles. These receptors act through afferent fibers to inhibit inspiration and stimulate expiration. Exhalation occurs as the inspiratory muscles relax, allowing for the passive recoil of the stretched lung tissue and raised ribs. This passive phase relies on synchronous activation of expiratory neurons and associated muscles that facilitate expiration. As expiration proceeds, the inspiratory center becomes progressively less inhibited and once again becomes active.


Figure 14.1 Schematic representation of factors that affect medullary control of pulmonary ventilation.

The inherent activity of the respiratory center alone cannot account for the smooth pattern of ventilatory adjustment to metabolic demands. The duration and intensity of the inspiratory cycle responds to the neural center in the hypothalamus that integrates input from descending neurons in the higher locomotor areas of the cerebral hemispheres, the pons, and other brain regions. During exercise, ventilatory adjustments occur from mechanical and/or chemical changes within active muscles and its vasculature from ascending neural signals initiated to provide peripheral feedback control from the cerebellum to the respiratory center.

The lungs contain sensory receptors that communicate with the respiratory center through vagal nerve afferents. Various irritants activate these receptors to initiate a cough reflex. Irritation of the tracheal or bronchial mucosa by dust, air pollutants, cigarette smoke, noxious fumes, inhaled debris, or accumulated mucus promotes coughing, while the same irritants in the nasal cavity trigger sneezing. Both reflexes help to clear keep the airways because bronchial irritation often constricts them.

## Humoral Factors

At rest, the chemical state of the blood exerts the greatest control of pulmonary ventilation. Variations in arterial $\mathrm{PO}_{2}$, $\mathrm{PCO}_{2}, \mathrm{pH}$, and temperature activate sensitive neural units in
the medulla and arterial system to adjust ventilation and maintain arterial blood chemistry within narrow limits.

## Plasma $\mathrm{Po}_{2}$ and Peripheral Chemoreceptors

Inhaling a gas mixture with $80 \%$ oxygen greatly increases alveolar $\mathrm{PO}_{2}$ and reduces minute ventilation by $20 \%$. Conversely, ventilation increases if inspired oxygen concentration decreases below ambient levels, particularly if alveolar $\mathrm{PO}_{2}$ falls below 60 mm Hg . Hemoglobin saturation at this $\mathrm{PO}_{2}$ begins to decrease considerably (see Fig. 13.4).

Sensitivity to reduced oxygen pressure does not reside in the respiratory center. Rather, peripheral chemoreceptors serve as the primary site to detect arterial hypoxia and reflexly initiate a ventilatory response. ${ }^{55}$ Figure 14.2 shows these tiny specialized neurons located in the arch of the aorta and branching of the carotid arteries in the neck. The strategic positioning of the carotid bodies monitors the state of arterial blood just before it perfuses the brain. Decreased arterial $\mathrm{PO}_{2}$, as occurs in pulmonary disease or ascent to high altitude, increases alveolar ventilation because of aortic and carotid chemoreceptor stimulation. These receptors alone protect the organism against reduced oxygen pressure in inspired air.

Peripheral chemoreceptor afferents also stimulate ventilation in exercise, even though reductions in arterial $\mathrm{PO}_{2}$ do not normally occur. ${ }^{51,53}$ The stimulating effects of exercise on


Figure 14.2 The aortic arch and bifurcation of the carotid arteries contain cell bodies sensitive to reduced $\mathrm{PO}_{2}$ and increased $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$and potassium concentrations in arterial blood. The peripheral chemoreceptors defend the body against arterial hypoxia in pulmonary disease and ascent to high altitude. The chemoreceptors also help to regulate exercise hyperpnea through the stimulating effects of increased arterial carbon dioxide and $\mathrm{H}^{+}$concentrations.
carotid afferent chemoreceptor discharge mainly comes from increases in temperature, acidity, and carbon dioxide and potassium concentrations. ${ }^{23,74}$

## Plasma $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$Concentration

At rest, carbon dioxide pressure in arterial plasma provides the most important respiratory stimulus. Small increases in $\mathrm{PCO}_{2}$ in inspired air trigger large increases in minute ventilation. For example, the resting ventilation nearly doubles by increasing inspired $\mathrm{PCO}_{2}$ to just 1.7 mm Hg ( $0.22 \% \mathrm{CO}_{2}$ in inspired air).

Molecular carbon dioxide per se does not mediate the ventilatory response to arterial $\mathrm{PCO}_{2}$. Instead, plasma acidity, which varies directly with the blood s carbon dioxide content, exerts significant command over minute ventilation. A fall in blood pH signals acidosis and usually reflects carbon dioxide retention and subsequent carbonic acid formation. Blood pH also can decrease from lactate accumulation in strenuous exercise or fatty acid (ketone) accumulation in diabetes. Regardless of cause, as arterial pH declines and hydrogen ions accumulate, inspiratory activity increases to eliminate carbon dioxide and reduce arterial levels of carbonic acid (see Chapter 13).

## Hyperventilation and Breath Holding

If a person breath holds after a normal exhalation, it takes approximately 40 seconds before the urge to breathe increases enough to initiate inspiration. The stimulus to breathe comes primarily from increased arterial $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$concentration, not decreased $\mathrm{PO}_{2}$ in the breath-holding condition. The break point for breath holding corresponds to an increase in arterial $\mathrm{PCO}_{2}$ to approximately 50 mm Hg .

If one consciously increases ventilation above the normal level (hyperventilation) before breath holding, alveolar air composition becomes more like ambient air. Alveolar $\mathrm{PCO}_{2}$ decreases from its normal value of 40 mm Hg to a low of 15 mm Hg . This creates a considerable diffusion gradient for carbon dioxide runoff into the alveoli from venous blood that enters the pulmonary capillaries. Consequently, a larger than normal quantity of carbon dioxide leaves the blood and arterial $\mathrm{PCO}_{2}$ decreases. Hyperventilation extends breath-holding duration until arterial $\mathrm{PCO}_{2}$ and/or $\mathrm{H}^{+}$concentration rises to levels that again stimulate the urge to breathe.

Swimmers and divers use hyperventilation and subsequent breath holding to improve performance. In sprint swimming, for example, many sprinters hyperventilate on the starting blocks to prolong the breath-hold during the swim and avoid taking a breath. In sport diving, hyperventilation offers a similar effect-to extend breath holding time. Tragedy while diving can occur with extended breath holding from hyperventilation. As the length and depth of a dive increase, the blood s oxygen content decreases to a critically low level before arterial $\mathrm{PCO}_{2}$ rises enough to stimulate breathing and signal ascent. The diver, unfortunately, often loses consciousness before surfacing. Chapter 26 discusses hyperventilation and other factors important to sport diving.

## REGULATION OF VENTILATION DURING EXERCISE

## Chemical Control

Neither chemical stimulation nor any other single mechanism entirely accounts for the increase in ventilation (hyperpnea) during physical activity. For example, the classic feedback control of resting ventilation via oxygen- and carbon dioxide mediated mechanisms does not adequately explain exercise hyperpnea. Inducing maximum changes in plasma acidity and inspired $\mathrm{PO}_{2}$ and $\mathrm{PCO}_{2}$ does not increase minute ventilation to values during vigorous exercise.

Figure 14.3 illustrates the relationships among oxygen consumption during graded exercise and venous and alveolar $\mathrm{P}_{\mathrm{CO} 2}$ and alveolar $\mathrm{PO}_{2}$. As exercise intensity increases, alveolar (arterial) $\mathrm{PO}_{2}$ does not decrease to an extent that increases ventilation through chemoreceptor stimulation. In fact, the large ventilatory volumes during intense exercise cause alveolar $\mathrm{PO}_{2}$ to rise above the average resting value of 100 mm Hg . Any increase in alveolar $\mathrm{PO}_{2}$ in exercise hastens oxygenation of blood in the alveolar capillaries. Pulmonary ventilation during light and moderate exercise closely couples with metabolism proportional to oxygen consumption and carbon dioxide production. Under these conditions, alveolar (and arterial) $\mathrm{PCO}_{2}$ generally averages 40 mm Hg . During strenuous exercise with its relatively large anaerobic component (lactate accumulation), increased carbon dioxide and subsequent $\mathrm{H}^{+}$concentrations provide an additional ventilatory stimulus. The resulting hyperventilation reduces alveolar and arterial $\mathrm{PCO}_{2}$, sometimes as low as 25 mm Hg . Any reduction in arterial $\mathrm{PCO}_{2}$ decreases the ventilatory drive from carbon dioxide during exercise.

## Nonchemical Control

The rapidity of the ventilatory response at the onset and cessation of exercise suggests that input other than changes in arterial $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$concentration mediates these phases of exercise hyperpnea.

## Neurogenic Factors

Neurogenic factors for ventilatory control include cortical and peripheral influences.

Cortical influence: Neural outflow from regions of the motor cortex and cortical activation in anticipation of exercise stimulate respiratory neurons in the medulla to initiate the abrupt increase in exercise ventilation. Peripheral influence: Sensory input from joints, tendons, and muscles influences the ventilatory adjustments throughout exercise. Experiments involving passive limb movements, electrical muscle stimulation, and voluntary exercise with the muscle s blood flow occluded support the contribution of local mechanoreceptors and chemoreceptors to a reflex exercise hyperpnea.


Figure 14.3 Relationship between oxygen consumption during graded exercise and (1) values for $\mathrm{PCO}_{2}$ in mixed-venous blood entering the lungs and (2) alveolar $\mathrm{PO}_{2}$ and $\mathrm{PCO}_{2}$. Alveolar $\mathrm{PO}_{2}$ and $\mathrm{PCO}_{2}$ remain near resting levels throughout a broad range of exercise intensities, despite relatively large increases in mixed-venous $\mathrm{PCO}_{2}$. (Data from the Laboratory of Applied Physiology, Queens College, Flushing, NY.)

## Influence of Temperature

Except for extreme hyperthermia, an increase in body temperature exerts little effect on ventilatory regulation during exercise. In most conditions, the rise in ventilation at exercise onset and its decline during recovery occur too quickly to reflect control from core temperature changes.

## Integrated Regulation

## During Exercise

The combined and perhaps simultaneous effects of several chemical and neural stimuli initiate and modulate exercise alveolar ventilation. Figure 14.4 shows the dynamic phases of minute ventilation during moderate exercise and recovery. In phase I at the start of exercise, neurogenic stimuli from the cerebral cortex (central command), combined with feedback from the active limbs, stimulate the medulla to increase ventilation abruptly. Cortical and locomotor peripheral input continues throughout the exercise period. After a short plateau (approximately 20 s ), minute ventilation then rises exponentially (in phase II) to achieve a steady level related to the metabolic gas exchange demands. Central command input, including factors intrinsic to neurons of the respiratory control system, regulates this phase of exercise ventilation. Continued activity of respiratory neurons in the medulla causes short-term potentiation that augments their responsiveness to the same continuing stimulation. This brings minute ventilation to a new, higher level. In all likelihood, input from peripheral chemoreceptors in the carotid


Figure 14.4 Three phases of exercise hyperpnea. Phase I: rapid increase from rest and brief plateau from central command drive and input from active muscles. Phase II: Slower exponential rise begins approximately 20 seconds after exercise onset. Central command continues, along with feedback from active muscles plus the added effect of shortterm potentiation of respiratory neurons. Phase III: Major regulatory mechanisms reach stable values; added input from peripheral chemoreceptors fine-tunes the ventilatory response. The lower green curve depicts only the contribution of central neuronal short-term potentiation and rising arterial $\mathrm{H}^{+}$concentration to the total respiratory response. (Modified from Eldridge FL. Central integration of mechanisms in exercise hyperpnea. Med Sci Sports Exerc 1994;26:319.)
bodies also contributes to regulation during phase II. ${ }^{74}$ The final phase of control (phase III) involves fine-tuning of the steady-state ventilation through peripheral sensory feedback mechanisms. Central and reflex stimuli from main byproducts of increased muscle metabolism-carbon dioxide and $\mathrm{H}^{+}$concentration-modulate alveolar gas pressures in this phase. These factors stimulate chemoreceptor group IV unmyelinated neurons that communicate with regions of the central nervous system to regulate cardiorespiratory function. ${ }^{52}$ An additional stimulus to increase ventilation in strenuous exercise occurs from the lactate anion itself, apart from lactic acidosis. ${ }^{27}$ Reflexes related to pulmonary blood flow and mechanical movement of the lung and respiratory muscles also provide regulatory input during exercise.

## In Recovery

The abrupt decline in ventilation when exercise ceases reflects removal of the central command drive and the sensory input from previously active muscles. More than likely, the slower recovery phase results from (1) gradual diminution of the short-term potentiation of the respiratory center and (2) reestablishment of the body s normal metabolic, thermal, and chemical milieu.

## Summary

1. Inherent activity of neurons in the medulla regulates the normal respiratory cycle.
2. Input from higher brain centers, the lungs, and other sensors throughout the body interacts with medullary neural output to regulate ventilation.
3. Chemical factors that act directly on the respiratory center or modify its activity through peripheral chemoreceptors control alveolar ventilation at rest. Arterial $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$concentration are the most important regulatory factors.
4. Hyperventilation lowers arterial $\mathrm{PCO}_{2}$ and $\mathrm{H}^{+}$ concentration. This prolongs breath-holding time until levels of carbon dioxide and acidity increase to stimulate breathing.
5. Three nonchemical regulatory factors augment ventilatory adjustments to exercise: (1) cortical activation in anticipation of exercise and outflow from the motor cortex when exercise begins, (2) peripheral sensory input from chemoreceptors and mechanoreceptors in joints and muscles, and (3) increased body temperature.
6. The ventilatory response to exercise occurs in three phases. Phase I cortical stimulus plus feedback from active limbs causes the abrupt increase in ventilation as exercise begins. Phas II ventilation then rises exponentially to reach a steady level related to exercise demands. Phase III involves fine-tuning of steady-state ventilation through peripheral sensory feedback mechanisms.

## Part 2 PULMONARY VENTILATION DURING EXERCISE

## VENTILATION AND ENERGY DEMANDS IN EXERCISE

Physical activity affects oxygen consumption and carbon dioxide production more than any other physiologic stress. With exercise, oxygen diffuses from the alveoli into the venous blood as it returns to the lungs, while about the same quantity of carbon dioxide moves from the blood into the alveoli. Concurrently, increased alveolar ventilation maintains the proper gas concentrations to facilitate rapid gas exchange.

## Ventilation in Steady-Rate Exercise

Figure 14.5 relates oxygen consumption and minute ventilation during increasing levels of exercise up to maximal oxygen consumption $\left(\mathrm{VO}_{2 \max }\right)$. During light-to-moderate exercise, ventilation increases linearly with oxygen consumption and carbon dioxide production, averaging between 20 and 25 L of air for each liter of oxygen consumed. Ventilation, in this case, increases mainly through increases in tidal volume; at higher exercise intensities, breathing frequency takes on a more important role. Such ventilatory adjustments provide complete aeration of blood because alveolar $\mathrm{PO}_{2}$ and $\mathrm{PCO}_{2}$ remain near resting levels. Transit time for blood in the pulmonary capillaries remains long enough for complete equilibration of the lung blood gases (see Fig. 13.2).

The term ventilatory equivalent (symbolized $\mathrm{V}_{\mathrm{E}} / \mathrm{VO}_{2}$ ) describes the ratio of minute ventilation to oxygen consumption. Healthy young adults usually maintain this ratio at 25 (i.e., 25 L of air breathed per liter of $\mathrm{O}_{2}$ consumed) during submaximal exercise up to approximately $55 \%$ of the $\mathrm{VO}_{2 \text { max }}$. Higher ventilatory equivalents occur in children, with values averaging 32 L of air breathed per liter of $\mathrm{O}_{2}$ consumed. Exercise mode also affects the ventilatory equivalent. Prone swimming, for example, generates lower $\mathrm{V}_{\mathrm{E}} / \mathrm{VO}_{2}$ ratios than running at all levels of energy expenditure. The restrictive nature of swimming on breathing lowers the ventilatory equivalent; this could constrain adequate gas exchange at maximal swimming velocities and partly explain the lower $\mathrm{VO}_{2 \text { max }}$ during swimming than during running.

## Ventilation in Non Steady-Rate Exercise

At higher levels of progressively more intense submaximal exercise, minute ventilation moves sharply upward and increases disproportionately in relation to oxygen consumption. The ventilatory equivalent can attain values of 35 or 40 L of air breathed per liter of oxygen consumed.

## Ventilatory Threshold

The term ventilatory threshold $\left(\mathbf{V}_{\mathbf{T}}\right)$ describes the point at which pulmonary ventilation increases disproportionately


Figure 14.5 Pulmonary ventilation, blood lactate concentration, and oxygen consumption during graded exercise to maximum. The lower dashed white line extrapolates the linear relationship between $\mathrm{VE}_{\mathrm{E}}$ and $\mathrm{VO}_{2}$ during submaximal exercise. The lactate threshold (not necessarily the threshold for anaerobic metabolism) represents the highest exercise intensity (oxygen consumption) not associated with elevated blood lactate concentration. It occurs at the point at which the relationship between $\mathrm{V}_{\mathrm{E}}$ and $\mathrm{VO}_{2}$ deviates from linearity, indicated as the point of ventilatory threshold. OBLA represents the point of lactate increase just above a $4.0-\mathrm{mM}$ baseline. Respiratory compensation represents a further disproportionate increase in ventilation (indicated by deviation from upper dashed white line) to counter the decrease in plasma pH in intense exercise.
with oxygen consumption (i.e., there is a marked and precipitous increase in the $\mathrm{V}_{\mathrm{E}} / \mathrm{VO}_{2}$ ratio) during graded exercise (see Fig. 14.5, dashed white line) and In a Practical Sense, p. 293). At this point, pulmonary ventilation no longer links tightly to oxygen demand at the cellular level. In fact, the excess ventilation comes directly from carbon dioxide s release from the buffering of lactic acid that begins to accumulate from increased glycolysis. Sodium bicarbonate in the blood buffers almost all of the lactic acid generated in anaerobic metabolism to sodium lactate in the following reaction:


The excess carbon dioxide released in the buffering reaction stimulates pulmonary ventilation that disproportionately increases $\mathrm{V}_{\mathrm{E}} / \mathrm{VO}_{2}$. Additional carbon dioxide exhaled from acid buffering causes the respiratory exchange ratio (R; $\mathrm{VCO}_{2} / \mathrm{VO}_{2}$ ) to exceed 1.00. Traditionally, researchers believed that the disproportionate increase in $\mathrm{V}_{\mathrm{E}}$ and increase in R above 1.00 indicated that the oxygen demands of the active muscles
exceeded mitochondrial oxygen supply with an increase in anaerobic energy transfer. They maintained that $\mathrm{V}_{\mathrm{T}}$ indicated the threshold for anaerobiosis and termed it the anaerobic threshold or simply $\mathrm{A}_{\mathrm{T}}$, to indicate increased reliance on anaerobic processes (see Focus on Research, p. 295).

Attempts to validate a linkage between ventilatory changes and glycolytic events at the cellular level have proved elusive.

## Onset of Blood Lactate Accumulation (OBLA)

During steady-rate exercise, aerobic metabolism matches the energy requirements of the active muscles. Little or no blood lactate accumulates because any lactate production equals lactate disappearance. The term lactate threshold describes the highest oxygen consumption or exercise intensity achieved with less than a 1.0 mM increase in blood lactate concentration above the preexercise level. ${ }^{71} \mathrm{By}$ convention, blood lactate concentration is usually expressed in millimoles (mM) per liter of whole blood or as mg per $\mathrm{dL}^{-1}$ of whole blood, also termed volume percent (vol\%); 1.0 mM equals $9.0 \mathrm{vol} \%$.

## IN A PRACTICAL SENSE

## Measuring Lactate Threshold

Conceptually, the lactate threshold (LT) represents an exercise level (power output, $\mathrm{VO}_{2}$, or energy expenditure) where tissue hypoxia triggers an imbalance between lactate formation and its clearance, with a resulting increase in blood lactate concentration. All of the following terms refer essentially to the same LT phenomenon: expiratory compensation threshold, anaerobic threshold, onset of blood lactate accumulation, optimal ventilatory efficiency, aerobic anaerobic threshold, onset of plasma lactate accumulation, individual anaerobic threshold, and point of metabolic acidosis.

The measurement of LT serves three important functions:

1. Provides a sensitive indicator of aerobic training status
2. Predicts endurance performance, often with greater accuracy than $\mathrm{VO}_{2 \text { max }}$
3. Establishes an effective training intensity geared to the active muscles aerobic metabolic dynamics

## DIFFERENT INDICATORS OF LT

1. Fixed blood lactate concentration
2. Ventilatory threshold
3. Blood lactate exercise $\mathrm{VO}_{2}$ response

## 1. FIXED BLOOD LACTATE CONCENTRATION

During low-intensity, steady-rate exercise, blood lactate concentration does not increase beyond normal biologic variation observed at rest. As exercise intensity increases, blood lactate levels exceed normal variation. Exercise intensity ( $\mathrm{or}_{\mathrm{VO}}^{2}$ ) associated with a fixed blood lactate concentration that exceeds normal resting variation denotes the LT. This often coincides with a 2.5 -millimole ( mM ) value. A $4.0-\mathrm{mM}$ lactate value indicates the onset of blood lactate accumulation (OBLA). The top figure illustrates LT and OBLA computations from fixed blood lactate concentrations during incremental, 4-minute exercise stages on a bicycle ergometer. Interpolation from a visual plot of power output $\left(\mathrm{VO}_{2}\right)$ versus blood lactate determines the exercise level associated with the fixed blood lactate concentrations.

The decision regarding stage duration, number of stages, and interval between stages becomes important. Stages 4 minutes or longer provide better predictability than shorter ones. For the data illustrated, LT occurred at an exercise power output of 205 W; 225 W predicted the fixed blood lactate concentration for OBLA.

## 2. VENTILATORY THRESHOLD

Pulmonary minute ventilation $\left(\mathrm{V}_{\mathrm{E}}\right)$ during exercise increases disproportionately in its relationship to oxygen consumption at about the same time blood lactate begins to accumulate. The ventilatory threshold (VT) predicts LT from the $\mathrm{V}_{\mathrm{E}}$ response during graded exercise. The mechanistic link of lactate buffering by plasma bicarbonate to produce additional $\mathrm{CO}_{2}$ (and respiratory stimulus unrelated to $\mathrm{VO}_{2}$ ) justifies the use of VT on a physiologic basis.

The test involves exercise with increments of short duration (a ramp test of 1- or 2-min increments) with continuous measurement of $\mathrm{V}_{\mathrm{E}}$ (breath by breath or every 10,20 , or 30 s ) to the point of fatigue (usually within 8 to 12 min ). The point of nonlinear increase in $\mathrm{V}_{\mathrm{E}}$ versus $\mathrm{VO}_{2}$ represents VT , expressed as a specific $\mathrm{VO}_{2}$ value rather than as running speed or power output common with the fixed blood lactate concentration method. The middle figure shows the relationship between $\mathrm{V}_{\mathrm{E}}$ and $\mathrm{VO}_{2}$ during incremental exercise; VT occurs at an exercise $\mathrm{VO}_{2}$ of $3.04 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. It is common to express the $\mathrm{VO}_{2}$ at LT as a percentage of $\mathrm{VO}_{2 \text { max }}$ ( $71 \%$ in this example).


Top. Fixed blood lactate concentration method to determine lactate threshold (LT) and onset of blood lactate accumulation (OBLA). This example shows LT at a fixed blood lactate of 2.5 mM and OBLA at a fixed blood lactate of 4.0 mM . Middle. Determination of LT from the relationship between pulmonary minute ventilation and oxygen consumption during incremental exercise. Bottom. Determination of LT from relationship between blood lactate concentration and oxygen consumption during incremental exercise.

## IN A PRACTICAL SENSE

## 3. BLOOD LACTATE EXERCISE $\mathrm{VO}_{2}$ RESPONSE

This protocol plots blood lactate concentration versus either $\mathrm{VO}_{2}$ or exercise intensity in a manner similar to determination of fixed blood lactate concentration. The person exercises for 3- or 4minute increments on a bicycle ergometer or treadmill. With treadmill exercise, blood is sampled for lactate determination during a

Continued
brief pause at the end of each stage, or without pause when using stationary cycling exercise. The bottom figure plots blood lactate versus oxygen consumption throughout the test. A best-fitting straight line depicts the linear portion of the curve; a second line describes the upward-trending curve after it breaks from linearity. The intersection of the two lines represents LT.

OBLA signifies when blood lactate concentration systematically increases to $4.0 \mathrm{mM} .{ }^{15,60,71}$ Some researchers often use the terms lactate threshold and OBLA interchangeably, although each represents an operationally different precise point for exercise intensity and blood lactate level.

## INTEGRATIVE QUESTION

In what ways are the terms lactate threshold and onset of blood lactate accumulation biochemically more precise than anaerobic threshold?

The exact cause of OBLA remains controversial. Some researchers assume it represents a distinct point for the onset of muscle anaerobiosis even though blood lactate values do not always reflect lactate concentration in specific muscles. Lactate can accumulate not only from muscle anaerobiosis, but also from decreased total lactate clearance or increased lactate production in specific muscle fibers.

A threshold of lactate appearance could result from four factors:

1. Imbalance between the rate of glycolysis and mitochondrial respiration
2. Decreased redox potential (increased NADH relative to $\mathrm{NAD}^{+}$)
3. Lower blood oxygen content
4. Lower blood flow to skeletal muscle

Caution should temper interpretations of the specific metabolic significance (and cause) of OBLA. However, it probably does signify initiation of an exponential accumulation of lactate in active muscle caused by exercise. ${ }^{36}$

Blood lactate accumulation is reflected by plasma changes in pH , bicarbonate and $\mathrm{H}^{+}$concentrations, and carbon dioxide production via buffering, so these variables provide an indirect assessment of OBLA. ${ }^{3,37,38,69}$ Changes in these measures do indeed relate to OBLA, but they probably cannot serve independently to establish the onset of anaerobic metabolism in muscle. However, they do provide practical information about exercise performance. In a Practical Sense, p. 293, illustrates several common methods to indicate tissue an imbalance between lactate formation and its clearance during exercise.

Specificity of OBLA. Exercise task specificity characterizes OBLA, as it does many measures of physiologic function and exercise performance. Differences in OBLA relative to the level of oxygen consumption occur in comparing bicycle, treadmill, and arm-crank exercise. ${ }^{75}$ Variations in muscle mass activated in each form of exercise help to explain these differences. At a particular exercise intensity or submaximal oxygen consumption, a higher metabolic rate per unit of active muscle mass exists for arm-crank and bicycle exercise than treadmill walking or running. OBLA therefore occurs at a lower exercise level (oxygen consumption) during bicycling and arm-crank exercise. Different exercise modes cannot interchangeably define the point of OBLA during graded exercise testing. Each must be determined in its own exercise mode.

Some Independence Between OBLA and $\mathrm{VO}_{2 \text { max }}$. In Chapter 7 we indicated that blood lactate in trained individuals accumulates at higher submaximal oxygen consumptions and at higher percentages of $\mathrm{VO}_{2 \max }$ than in untrained individuals. For children and adults, endurance training often improves the exercise intensity at OBLA without concomitant increases in $\mathrm{VO}_{2 \max }{ }^{5,18,39,43}$ This suggests that different factors influence OBLA and $\mathrm{VO}_{2 \max }$. Muscle fiber type, capillary density, mitochondrial size and number, and enzyme concentrations play major roles in establishing the percentage of aerobic capacity sustainable without lactate accumulation. ${ }^{13,34,70}$ In contrast, the functional capacity of the cardiovascular system for oxygen transport and the total muscle mass activated in exercise determine the $\mathrm{VO}_{2 \max }$.

OBLA and Endurance Performance. Figure 14.6 illustrates the major variables that contribute to oxygen transport and use. They ultimately determine the maximum intensity a person can maintain in prolonged exercise. Two important factors influence endurance performance in a specific exercise mode:

1. Maximum capacity to consume oxygen $\left(\mathrm{VO}_{2 \max }\right)$
2. Maximum level for steady-rate exercise (OBLA)

Most exercise physiologists apply $\mathrm{VO}_{2 \max }$ as a yardstick to gauge capacity for endurance exercise. This measure generally relates to exercise performance, but it does not fully explain success because one does not perform endurance exercise at $\mathrm{VO}_{2 \text { max }}$. The exercise intensity at the point of OBLA consistently and powerfully predicts endurance exercise performance of men

## FOCUS ON RESEARCH

## Detecting the Onset of Anaerobic Metabolism

Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 1964;14:844.

$>$ The onset of anaerobiosis during exercise powerfully predicts a person s capability for sustained aerobic exercise. The pioneering work of Wasserman and colleagues relied on simple respiratory gas exchange data to detect the threshold of anaerobic metabolism that they called the anaerobic threshold. These researchers argued that one could detect the threshold of anaerobic metabolism during exercise in one of three ways: (1) increased blood lactate concentration, (2) decreased arterial blood bicarbonate and pH , and (3) increased respiratory gas exchange ratio (R). A method that assesses R avoids blood-sampling procedures while using equipment common to exercise physiology, human performance, and medically related facilities.

Subjects performed a graded exercise test by either pedaling a cycle ergometer or walking on a treadmill for 4-minute exercise intervals. Measurements included heart rate, minute ventilation, oxygen consumption, and endtidal $\mathrm{CO}_{2}$ and $\mathrm{N}_{2}$ concentrations. End-tidal oxygen and carbon dioxide concentrations provided data for computing R. The upper figure shows a sigmoid curve from plotting R from the last 30 seconds of each exercise level against $\mathrm{VO}_{2}$. They called the inflection point at the onset of the steepest part of this curve the threshold of anaerobic metabolism. They posited that at this $\mathrm{VO}_{2}$ level anaerobic metabolism became significant. The anaerobic threshold also corresponded to the exercise intensity at which arterial blood bicarbonate concentrations decreased and blood lactate increased.

The lower figure displays the anaerobic threshold data for 37 patients with heart disease. Subjects with the poorest fitness attained anaerobic threshold at a lower $\mathrm{VO}_{2}$ (i.e., lower exercise intensity). From a clinical perspective, the respiratory exchange ratio during exercise provides a useful measure of cardiovascular function to indicate how much exercise a patient performs before cardiovascular dynamics fail to meet the tissues oxygen requirements. Current research indicates that factors other than the onset of exercise anaerobiosis affect pulmonary and gas exchange
dynamics. The initial research of Wasserman and coworkers, however, provided an important impetus to study interactions among pulmonary, cardiovascular, and metabolic dynamics during graded exercise.


Top. Respiratory exchange ratio (R) and plasma bicarbonate $\left(\mathrm{HCO}_{3}{ }^{-}\right)$during rest and continuous graded exercise in one subject. Bottom. Threshold for anaerobic metabolism in 37 heart disease patients.
and women. ${ }^{8,16,49,63}$ For race-walkers, race-walking velocity at the point of OBLA predicted $20-\mathrm{km}$ times to within $0.6 \%$ of the actual time. ${ }^{26}$ Similar results occurred in elite cyclists. Cycling power output at lactate threshold showed a strong relationship ( $r=0.93$ ) to average absolute power output maintained during
a 1-hour ride in the laboratory. ${ }^{17}$ The laboratory measurement accurately predicted performance in a $40-\mathrm{km}$ road race. Improved endurance performance with training more closely relates to training-induced improvement in the exercise level for OBLA than $\mathrm{VO}_{2 \max }$ changes. ${ }^{76}$


Figure 14.6 Major variables related to maximal oxygen consumption, onset of blood lactate accumulation, and maximal running velocity during endurance exercise. Q , cardiac output; [Hb], hemoglobin concentration; $\%_{\mathrm{SaO}_{2}}$, percentage saturation with oxygen; max $\mathrm{a}-\mathrm{vO}_{2}$ diff, maximum arteriovenous oxygen difference; LT, lactate threshold. (Modified from Bassett DR Jr, Howley ET. Maximal oxygen uptake: classical versus contemporary viewpoints. Med Sci Sports Exerc 1997;29:591.)

## INTEGRATIVE QUESTION

Explain the rationale to measure pulmonary ventilation and gas exchange dynamics during graded exercise to indicate the onset of lactate buildup at the cellular level.

Racial Differences. The overwhelming dominance of African athletes in competitive endurance running between 3000 and $10,000 \mathrm{~m}$ has stimulated research into the possibility of racial differences in resistance to fatigue, blood lactate
accumulation, temperature regulation, and intramuscular oxidative enzyme capacity. ${ }^{66}$ African and South African endurance runners consistently show greater resistance to fatigue at the same percentage of peak treadmill running velocity than Caucasian counterparts despite similar values for $\mathrm{VO}_{2 \text { max }}$ and peak treadmill velocity. ${ }^{12,71,72}$ The African athletes sustained a relatively higher percentage of maximal exercise capacity (i.e., superior fatigue resistance) from considerably higher oxidative enzyme profiles (citrate synthase and 3-hydroxyacyl-CoA dehydrogenase) and lower plasma lactate concentrations during sustained submaximal exercise. ${ }^{59}$ Greater running economy probably contributes to superior endurance performance of elite African runners. ${ }^{73}$ African runners also perform better in the heat than Caucasians due partly to their smaller size. This size benefit (larger surface-to-mass ratio) augments capacity to run faster in the heat while storing heat at the same rate as the slower, heavier Caucasian runners. ${ }^{44}$

## INTEGRATIVE QUESTION

Explain the biochemical rationale for measuring oxygen consumption and carbon dioxide production to infer the onset of metabolic anaerobiosis (lactate accumulation) during exercise.

## ENERGY COST OF BREATHING

Figure 14.7 specifies the oxygen cost of breathing during whole-body graded exercise up to maximum. The left panel indicates the effects of increasing minute ventilation on the oxygen cost of breathing expressed as a percentage of the total exercise oxygen consumption. The right panel illustrates the influence of increasing minute ventilation on the oxygen cost per liter of air breathed per minute. The oxygen requirement of breathing remains relatively small at rest and during light-to-moderate exercise. ${ }^{11}$ For exercise ventilations up to about $100 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, oxygen cost averaged between 1.5 and 2.0 mL per liter of air breathed each minute (right panel). This represented from 3 to $5 \%$ of the total oxygen consumption in moderate exercise and 8 to $11 \%$ for minute ventilations at $\mathrm{VO}_{2 \text { max }}$ values typical for most individuals (left panel). Among highly trained endurance athletes with maximum minute ventilations of $150 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ and higher, the cost of exercise hyperpnea can exceed $15 \%$ of the total oxygen consumption. At this level, the inspiratory muscles operate at 40 to $60 \%$ of maximum capacity to generate force. ${ }^{1}$ The rate of blood flow to these muscles may equal that of limb locomotor muscles. ${ }^{21}$

A significant portion of total blood flow sustains the metabolic demands of respiratory muscles during maximal exercise. Up to $15 \%$ of the exercise cardiac output sustains these muscles. ${ }^{28,30}$ Evidence from healthy, fit individuals indicates a competition for blood flow and oxygen between respiratory and locomotor muscles during intense exercise.


Figure 14.7 Oxygen cost of breathing during whole-body graded exercise up to maximum. Left panel. Effects of increasing minute ventilation $\left(\mathrm{V}_{\mathrm{E}}\right)$ on the total oxygen cost of breathing expressed as a percentage of total exercise oxygen consumption. Right panel. Effects of increasing minute ventilation on the oxygen cost per liter air breathed per minute. (From Dempsey JA, et al. Respiratory muscle perfusion and energetics during exercise. Med Sci Sports Exerc 1996;28:1123.)

For example, altering respiratory muscle work during maximal exercise to increase the energy cost of breathing vasoconstricts the locomotor muscles. Redirection of cardiac output to the respiratory musculature compromised perfusion of the active, nonrespiratory muscles. This reduced the total percentage of $\mathrm{VO}_{2 \max }$ used by the active locomotor muscles. Conversely, easing the work of breathing during maximal exercise with an assist ventilator elicited a corresponding increase in oxygen consumption (greater $\% \mathrm{VO}_{2 \max }$ ) of the active leg muscles.

## Respiratory Disease

During even moderate exercise, the healthy person rarely senses the effort to breathe. In respiratory disease, however, the work of breathing becomes an exhaustive exercise in itself. In chronic obstructive pulmonary disease (COPD), the added expiratory resistance can triple the normal cost of breathing at rest; during light exercise, ventilatory cost may reach 10 mL of oxygen for each liter of air breathed. In severe pulmonary disease, the cost of breathing easily attains $40 \%$ of the total exercise oxygen consumption. Competition between the oxygen blood flow needs of locomotor and respiratory muscles encroaches on the oxygen available to the active, nonrespiratory muscle mass. ${ }^{29}$ In COPD, the increased cost of breathing severely limits the exercise capacity of individuals with this debilitating medical condition. Unfortunately, exercise training produces only small improvements in pulmonary function parameters or disease status. Regular exercise can, however, improve exercise capacity, reduce dyspnea, decrease ventilatory equivalents for oxygen, improve respiratory and peripheral muscle function, and enhance psychologic state. ${ }^{10,19,47,61}$ Chapter 32 more fully discusses the role of regular physical activity in rehabilitating COPD patients.

## Cigarette Smoking

Research relating smoking habits to exercise performance remains meager, yet most endurance athletes avoid cigarettes for fear of hindering performance from a loss of wind. Chronic cigarette smokers tend toward more sedentary lifestyles and have lower fitness levels than nonsmoking counterparts. ${ }^{6,58,62}$ For some unknown reason, cigarette smoking increases one s dependence on carbohydrate for energy during rest and sustained exercise. ${ }^{14}$ Smokers also have lower dynamic lung function that, if severe, manifests in COPD. In adolescent smokers, chronic cigarette smoking obstructs the airways and slows normal lung function development, with greater deficits in girls than boys. ${ }^{24}$ Children who smoked had higher rates of asthma and wheezing and reduced dynamic lung function capacity in a dose response relationship to their smoking habits. Female smokers who trained vigorously for 12 weeks improved aerobic capacity and endurance performance compared with smokers who remained sedentary. ${ }^{2}$ The females who exercised and quit smoking made greater fitness improvements than counterparts who trained similarly but continued to smoke. In a Practical Sense, Chapter 13, provides an objective means to uncover factors that contribute to a person s smoking behavior.

## Acute Effects

Airway resistance at rest increases up to threefold in both chronic smokers and nonsmokers following 15 puffs on a cigarette during a 5-minute period. ${ }^{48}$ The added resistance to breathing lasts an average of 35 minutes; it probably exerts only a minor effect during light exercise when breathing cost remains small. The residual smoking effect could prove detrimental during vigorous exercise because of the additional oxygen cost to move larger air volumes. Increased peripheral
airway resistance with smoking comes mainly from two sources: (1) vagal reflex-possibly triggered from sensory stimulation by minute particles in cigarette smoke and (2) stimulation of parasympathetic ganglia by nicotine.

Researchers determined the oxygen cost of breathing in six habitual smokers immediately after smoking two cigarettes and 1 day after tobacco abstinence. The subjects ran on a treadmill at a speed and grade requiring $80 \%$ of $\mathrm{VO}_{2 \max }$. Two methods increased ventilation during the smoking and nonsmoking runs: (1) Subjects voluntarily hyperventilated during the run (voluntary HV) and (2) researchers induced hyperventilation by increasing alveolar $\mathrm{PCO}_{2}$ by having subjects breathe through a large-diameter tube that increased anatomic dead space by 1400 mL (dead space HV). The oxygen cost of the extra breathing equaled the difference between the normal oxygen consumption and that in the hyperventilation experiments.

Table 14.1 indicates that the oxygen cost of breathing decreased between 13 and $79 \%$ with smoking abstinence. The energy requirement of breathing during exercise averaged $14 \%$ of the total exercise oxygen consumption after smoking, but only $9 \%$ in the nonsmoking trials for the heaviest smokers. Also, heart rate averaged 5 to $7 \%$ lower during exercise following 1 day of cigarette abstinence; all subjects reported feeling better when they exercised in the nonsmoking condition. These findings indicate a substantial reversibility of the increased cost of breathing with smoking in chronic smokers with only 1 day of abstinence. From a practical standpoint, an athlete who cannot eliminate smoking completely should at least abstain the day before a competition. Additional research complements these findings; a 7-day smoking abstinence period by young men reduced submaximal exercise heart rate and enhanced time to exhaustion during graded treadmill testing. ${ }^{32}$
icantly less endurance during graded exercise to maximum than nonsmokers. ${ }^{6,32,40,62}$ Despite their poorer performance in maximal testing (i.e., shorter time to fatigue), the smokers spent more time to reach a heart rate of $130 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ during a graded exercise test. This indicates a relatively higher fitness level (i.e., more exercise accomplished before reaching the submaximal heart rate value). An altered sensitivity in autonomic neural control from cigarette smoking may inhibit the heart rate response of smokers to submaximal exercise. ${ }^{41}$ This emphasizes the need to consider smoking status when evaluating fitness data from submaximal heart rate response to a standard step test or a heart rate prediction test. Failure to account for cigarette smoking would inflate fitness estimates because the blunted (lower) heart rate response of smokers erroneously implies higher aerobic fitness.

## DOES VENTILATION LIMIT AEROBIC POWER AND ENDURANCE?

Aerobic training produces considerably less adaptation in pulmonary structure and function than in cardiovascular and neuromuscular adaptations. Current interest concerns how the lack of pulmonary system plasticity affects aerobic exercise performance, mainly at the high exercise levels routinely performed by elite endurance athletes. ${ }^{20,22}$

## INTEGRATIVE QUESTION

Advise a person who performs specific breathing exercises rather than endurance training to increase wind and eliminate breathlessness when running continuously for 20 to 30 minutes.

## Cigarette Smoking Blunts Exercise Heart Rate Response

A paradox exists between the maximal exercise capacity of cigarette smokers and their submaximal heart rate response to exercise. Otherwise healthy chronic smokers exhibit signif-

With inadequate breathing during graded exercise, the relationship between pulmonary ventilation and oxygen consumption would curve in a direction opposite to that indicated in Figure 14.5 (i.e., decreased ventilatory equivalent). This common response in COPD patients indicates a failure of

TABLE 14.1 Oxygen Cost of Hyperventilation (HV) in Smoking and Nonsmoking Exercise at Approximately $\mathbf{8 0 \%}$ of $\mathrm{VO}_{2 \text { max }}$

| Subject | Smoking |  |  |  | Nonsmoking |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Voluntary HV |  | Dead Space HV |  | Voluntary HV |  | Dead Space HV |  |
|  | $\left(\begin{array}{c} \dot{V}_{E} \\ (\mathrm{~min} \end{array}\right.$ | $\begin{gathered} \mathrm{O}_{2} \operatorname{Cost} \\ \left(\mathrm{~mL} \cdot \mathrm{~L}^{-1}\right) \end{gathered}$ | $\left(\mathrm{L} \cdot \dot{\mathrm{~V}}_{\mathrm{E}} \mathrm{~min}^{-1}\right)$ | $\begin{gathered} \mathrm{O}_{2} \operatorname{Cost} \\ \left(\mathrm{~mL} \cdot \mathrm{~L}^{-1}\right) \end{gathered}$ | $\left(\mathrm{L} \cdot{\dot{\dot{V}_{E}}}_{\min ^{-1}}\right)$ | $\begin{aligned} & \mathrm{O}_{2} \operatorname{Cost} \\ & \left(\mathrm{~mL} \cdot \mathrm{~L}^{-1}\right) \end{aligned}$ | $\left(\mathrm{L} \cdot{\dot{\dot{V}_{E}}}_{\mathrm{min}^{-1}}\right)$ | $\begin{gathered} \mathrm{O}_{2} \operatorname{Cost} \\ \left(\mathrm{~mL} \cdot \mathrm{~L}^{-1}\right) \end{gathered}$ |
| 1 | 26.4 | 15.1 | 18.9 | 12.7 | 22.7 | 11.4 | 23.0 | 6.5 |
| 2 | 39.0 | 10.3 | 28.1 | 5.9 | 42.6 | 11.3 | 41.3 | 4.8 |
| 3 | 22.8 | 7.9 | 27.2 | 7.0 | 23.8 | 7.2 | 22.8 | 5.7 |
| 4 | 36.3 | 5.0 | 28.7 | 5.6 | 44.7 | 3.8 | 18.6 | $-1.6^{a}$ |
| 5 | 52.7 | 13.5 | 26.7 | 12.4 | 75.2 | 6.1 | 22.8 | 5.7 |
| 6 | 22.4 | 8.5 | 27.3 | 1.1 | 23.2 | 3.4 | 30.1 | 3.0 |
| Average | 32.6 | 10.1 | 26.2 | 7.4 | 38.7 | 7.2 | 26.5 | 4.0 |

[^29]ventilation to keep pace with oxygen consumption ${ }^{4}$; in this case, one truly would run out of breath. During strenuous exercise, healthy individuals overbreathe at higher levels of oxygen consumption. The hyperventilation response generally decreases alveolar $\mathrm{PCO}_{2}$ (see Fig. 14.3) and slightly increases alveolar $\mathrm{PO}_{2}$. Exercise conditions that trigger hyperventilationinduced reductions in arterial carbon dioxide restrict cerebral blood flow, which may compromise oxygen delivery to active brain areas and contribute to central fatigue. ${ }^{50}$ Even during maximal exercise, a considerable breathing reserve exists because minute ventilation at $\mathrm{VO}_{2 \max }$ equals only 60 to $85 \%$ of a healthy person s maximum voluntary ventilation (MVV). Most individuals have a 20 to $40 \%$ MVV reserve during highintensity exercise. Pulmonary function does not form a weak link in the oxygen transport system of healthy individuals with average to moderately large aerobic capacities.

## An Important Exception

For endurance athletes, the pulmonary system lags behind their exceptional cardiovascular and aerobic muscular adaptations to training. ${ }^{67}$ The potential for inequality in alveolar ventilation relative to pulmonary capillary blood flow (i.e., impaired ventilation perfusion ratio) during high-intensity exercise may compromise arterial saturation and oxygen transport capacitya condition termed exercise-induced arterial hypoxemia (EIH). ${ }^{31,35,42,45,46,54,56} \mathrm{EIH}$ among trained individuals remains variable. It sometimes occurs at exercise levels as low as $40 \% \mathrm{VO}_{2 \max }$ at sea level and mild to moderate altitudes. ${ }^{9,25,57}$ When highly trained endurance athletes exercised near $\mathrm{VO}_{2 \max }$ ( $>65 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$; Figure 14.8), pressure differentials between alveolar and arterial oxygen widened to more than 30 mm Hg . This caused arterial oxygen saturation to fall below $90 \%$ with a corresponding arterial $\mathrm{PO}_{2}$ below 75 mm Hg . Some elite endurance athletes cannot achieve complete aeration of the blood in the pulmonary capillaries in high-intensity exercise; in this situation, arterial desaturation becomes more apparent as exercise duration progresses. It does not appear that alterations in pulmonary structure at the alveolar capillary interface produce EIH, although recruitment of intrapulmonary shunt vessels during exercise may contribute to the exercise-induced impairment in pulmonary gas exchange. ${ }^{64,65}$

Possible functionally based causes for arterial desaturation include:

1. Inequality in ventilation-perfusion ratio within the lungs or specific lung regions
2. Shunting of blood between venous and arterial circulations, thus bypassing areas for diffusion
3. Failure to achieve end-capillary equilibrium between alveolar oxygen pressure and pressure of oxygen in blood perfusing the pulmonary capillaries

INTEGRATIVE QUESTION
Explain why pulmonary ventilation for most healthy persons does not limit aerobic exercise performance.


Figure 14.8 Average values for blood gas pressures ( $\mathrm{PaO}_{2}$ and $\mathrm{PaCO}_{2}$ ), acid base status ( pH ), and difference between alveolar $\left(\mathrm{PAO}_{2}\right)$ and arterial $\left(\mathrm{PaO}_{2}\right)$ oxygen pressure in eight male athletes during graded exercise up to $\mathrm{VO}_{2 \text { max }}$. Note the widening of the $(\mathrm{A}-\mathrm{a}) \mathrm{O}_{2}$ gradient and the fall in $\mathrm{PaO}_{2}$ during maximal exercise. (From Johnson BD, et al. Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol 1992;73:874.)

## Summary

1. In light-to-moderate exercise, pulmonary ventilation increases linearly with oxygen consumption so the ventilatory equivalent $\left(\mathrm{VE} / \mathrm{VO}_{2}\right)$ averages 20 to 25 L of air breathed per liter of oxygen consumed.
2. In non steady-rate exercise, ventilation increases disproportionately with increases in oxygen consumption, and the ventilatory equivalent can exceed 35 L .
3. A disproportionately sharp rise in minute ventilation during incremental exercise provides a bloodless way to estimate the onset of blood lactate accumulation (OBLA).
4. OBLA provides a submaximal exercise measure of aerobic fitness that relates to the beginning of anaerobiosis in the active muscles. OBLA occurs without significant metabolic acidosis or severe cardiovascular strain.
5. The oxygen cost of breathing for healthy individuals remains relatively small throughout a broad range of submaximal exercise. The work of breathing becomes excessive for individuals with respiratory disease, often producing inadequate alveolar ventilation.
6. Cigarette smoking causes airway resistance to rise considerably and increase the cost of breathing to adversely affect endurance performance.
7. Exercise training generally reduces the ventilatory equivalent in submaximal exercise, which conserves oxygen during a particular exercise task.
8. For individuals of average aerobic fitness, maximal exercise does not tax pulmonary ventilation to a point that limits optimal alveolar gas exchange and arterial saturation.
9. Pulmonary function improvements for the endurance athlete can lag behind their exceptional adaptations in cardiovascular and muscle function, thereby compromising aeration of blood during maximal effort.

## Part 3 ACID BASE REGULATION

## BUFFERING

Acids dissociate in solution and release $\mathrm{H}^{+}$, whereas bases accept $\mathrm{H}^{+}$to form hydroxide ions $\left(\mathrm{OH}^{-}\right)$. The term buffering designates reactions that minimize changes in $\mathrm{H}^{+}$concentration; buffers refer to chemical and physiologic mechanisms that prevent this change.

The symbol $\mathbf{p H}$ designates a quantitative measure of acidity or alkalinity (basicity) of a liquid solution. Specifically,
pH refers to the concentration of protons or $\mathrm{H}^{+}$. Acid solutions have more $\mathrm{H}^{+}$than $\mathrm{OH}^{-}$at a pH below 7.0, and vice versa for basic solutions whose pH exceeds 7.0. Chemically pure (distilled) water, considered neutral, has equal $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$and thus a pH of 7.0. The pH scale shown in Figure 14.9, devised in 1909 by Danish chemist $S$ ren $S$ rensen (1868 1939; known for his work in amino acid synthesis and enzyme reactions at Carlsberg laboratory in Copenhagen, Denmark), ranges from 1.0 to 14.0. An inverse relation exists between pH and $\mathrm{H}^{+}$concentration. The logarithmic nature of the pH scale means a 1 -unit change in pH produces a 10 -fold change in $\mathrm{H}^{+}$concentration. For example, lemon juice and gastric juice ( $\mathrm{pH}=2.0$ ) have 1000 times the $\mathrm{H}^{+}$concentration of black coffee ( $\mathrm{pH}=5.0$ ), whereas hydrochloric acid $(\mathrm{pH}=1.0)$ has approximately 1 million times the $\mathrm{H}^{+}$concentration of blood at a pH of 7.4.

The pH of bodily fluids ranges from a low of 1.0 for the digestive acid hydrochloric acid to a slightly basic pH between 7.35 and 7.45 for arterial and venous blood and most other bodily fluids. A decrease in $\mathrm{H}^{+}$concentration (increased pH or alkalosis) produces an increase in pH above the normal average of 7.4. Conversely, acidosis refers to increased $\mathrm{H}^{+}$concentration (decreased pH ). The acid base characteristics of bodily fluids fluctuate within narrow limits because metabolism remains highly sensitive to $\mathrm{H}^{+}$concentrations in the reacting


Figure 14.9 The pH scale provides a quantitative measure of the acidity or alkalinity (basicity) of a liquid solution. Blood pH normally stabilizes at the slightly alkaline pH of 7.4 . Values for blood pH rarely fall below pH of 6.9 , even during the most strenuous exercise, although values at the active muscle are lower. The digital pH meter accurately determines the pH of any substance. The example shows a pH of 6.32 for the urine sample.

## CHAPTER 14 Dynamics of Pulmonary Ventilation

medium. Three mechanisms regulate the pH of the internal environment:

1. Chemical buffers
2. Pulmonary ventilation
3. Renal function

## Chemical Buffers

The chemical buffering system consists of a weak acid and salt of that acid. Bicarbonate buffer, for example, consists of the weak acid carbonic acid and its salt, sodium bicarbonate. Carbonic acid forms when bicarbonate binds $\mathrm{H}^{+}$. When $\mathrm{H}^{+}$concentration remains elevated, the reaction produces the weak acid because excess $\mathrm{H}^{+}$ions bind in accord with the general reaction:

$$
\mathrm{H}^{+}+\text {Buffer } \rightarrow \text { H-Buffer }
$$

In contrast, when $\mathrm{H}^{+}$concentration decreases-as during hyperventilation, when plasma carbonic acid declines because carbon dioxide leaves the blood and exits through the lungs-the buffering reaction moves in the opposite direction and releases $\mathrm{H}^{+}$:

$$
\mathrm{H}^{+}+\text {Buffer } \leftarrow \text { H-Buffer }
$$

Most of the carbon dioxide generated in energy metabolism reacts with water to form the relatively weak carbonic acid that dissociates into $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}{ }^{-}$. Likewise, the stronger lactic acid reacts with sodium bicarbonate to form sodium lactate and carbonic acid; in turn, carbonic acid dissociates and increases the $\mathrm{H}^{+}$concentration of the extracellular fluids. Other organic acids such as fatty acids dissociate and liberate $\mathrm{H}^{+}$, as do sulfuric and phosphoric acids generated during protein catabolism. Bicarbonate, phosphate, and protein chemical buffers provide the rapid first line of defense to maintain consistency in the acid base character of the internal environment.

## Bicarbonate Buffer

The bicarbonate buffer system consists of carbonic acid and sodium bicarbonate in solution. During buffering, hydrochloric acid (a strong acid) converts to the much weaker carbonic acid by combining with sodium bicarbonate in the following reaction:

$$
\mathrm{HCl}+\mathrm{NaHCO}_{3} \rightarrow \mathrm{NaCl}+\mathrm{H}_{2} \mathrm{CO}_{3} \leftrightarrow \mathrm{H}^{+}+\mathrm{HCO}_{3}^{-}
$$

The buffering of hydrochloric acid produces only a slight reduction in pH . Sodium bicarbonate in plasma exerts a strong buffering action on lactic acid to form sodium lactate and carbonic acid. Any additional increase in $\mathrm{H}^{+}$concentration from carbonic acid dissociation causes the dissociation reaction to move in the opposite direction to release carbon dioxide into solution as follows:

## Result of acidosis

$$
\mathrm{H}_{2} \mathrm{O}+\mathrm{CO}_{2} \leftarrow \mathrm{H}_{2} \mathrm{CO}_{3} \leftarrow \mathrm{H}^{+}+\mathrm{HCO}_{3}^{-}
$$

An increase in plasma carbon dioxide or $\mathrm{H}^{+}$concentration immediately stimulates ventilation to eliminate excess carbon dioxide.

Conversely, a decrease in plasma $\mathrm{H}^{+}$concentration inhibits the ventilatory drive and retains carbon dioxide that then combines with water to increase acidity (carbonic acid) and normalize pH .

$$
\begin{aligned}
& \text { Result of alkalosis } \\
& \qquad \mathrm{H}_{2} \mathrm{O}+\mathrm{CO}_{2} \rightarrow \mathrm{H}_{2} \mathrm{CO}_{3} \rightarrow \mathrm{H}^{+}+\mathrm{HCO}_{3}^{-}
\end{aligned}
$$

## Phosphate Buffer

The phosphate buffering system consists of phosphoric acid and sodium phosphate. These chemicals act similarly to the bicarbonate buffers. Phosphate buffer exerts an important effect on acid base balance in the kidney tubules and intracellular fluids where phosphate concentration remains high.

## Protein Buffer

Venous blood buffers the $\mathrm{H}^{+}$released from the dissociation of relatively weak carbonic acid (produced from $\mathrm{H}_{2} \mathrm{O}+$ $\mathrm{CO}_{2}$ ). By far, hemoglobin provides the most important $\mathrm{H}^{+}$ acceptor for this buffering function. Hemoglobin is almost six times more potent in regulating acidity than the other plasma proteins. Hemoglobin s release of oxygen to the cells makes hemoglobin a weaker acid, thereby increasing its affinity to bind $\mathrm{H}^{+}$. The $\mathrm{H}^{+}$generated when carbonic acid forms in the erythrocyte combines readily with deoxygenated hemoglobin $\left(\mathrm{Hb}^{-}\right)$in the reaction:

$$
\mathrm{H}^{+}+\mathrm{Hb}^{-}(\text {Protein }) \rightarrow \mathrm{HHb}
$$

Intracellular tissue proteins also regulate plasma pH . Some amino acids possess free acidic radicals. When dissociated, they form $\mathrm{OH}^{-}$, which readily reacts with $\mathrm{H}^{+}$to form water.

## Relative Power of Chemical Buffers

TABLE 14.2 lists the relative power of the blood s chemical buffers with those in blood and interstitial fluids combined. As a frame of reference, the buffering power of the bicarbonate system receives the value 1.00 .

## PHYSIOLOGIC BUFFERS

The pulmonary and renal systems present the second line of defense in acid base regulation. Their buffering function occurs only when a change in pH has already occurred.

## TABLE 14.2 Relative Buffering Power of the Chemical Buffers

| Chemical Buffer | Blood | Blood Plus <br> Interstitial Fluids |
| :--- | :---: | :---: |
| Bicarbonate | 1.0 | 1.0 |
| Phosphate | 0.3 | 0.3 |
| Proteins (excluding Hb) | 1.4 | 0.8 |
| Hemoglobin | 5.3 | 1.5 |

## Ventilatory Buffer

When the quantity of free $\mathrm{H}^{+}$in extracellular fluid and plasma increases, it directly stimulates the respiratory center to immediately increase alveolar ventilation. This rapid adjustment reduces alveolar $\mathrm{PCO}_{2}$ and causes carbon dioxide to be blown off from the blood. Reduced plasma carbon dioxide levels accelerate the recombination of $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}{ }^{-}$, lowering free $\mathrm{H}^{+}$concentration in plasma. For example, doubling alveolar ventilation by hyperventilation at rest increases blood alkalinity and pH by 0.23 units from 7.40 to 7.63. Conversely, reducing normal alveolar ventilation (hypoventilation) by one-half increases blood acidity by approximately 0.23 pH units. The


## $\square$ Blood lactate $\square$ Blood pH

Figure 14.10 Top. Relationship between blood pH and blood lactate concentration during rest and increasing intensities of short-duration exercise up to maximum. Bottom. Blood pH and blood lactate concentration related to exercise intensity expressed as a percentage of the maximum. Decreases in blood pH accompany increases in blood lactate concentration. (From Osnes JB, Hermansen L. Acid base balance after maximal exercise of short duration. J Appl Physiol 1972;32:59.)
potential magnitude of ventilatory buffering equals twice the combined effect of all the body s chemical buffers.

## Renal Buffer

Chemical buffers only temporarily affect excess acid buildup. Excretion of $\mathrm{H}^{+}$by the kidneys, although relatively slow, provides an important longer-term defense that maintains the body $s$ buffer reserve (alkaline reserve). To this end, the kidneys stand as the final sentinels. The renal tubules regulate acidity through complex chemical reactions that secrete ammonia and $\mathrm{H}^{+}$into the urine and then reabsorb alkali, chloride, and bicarbonate.

## EFFECTS OF INTENSE EXERCISE

Increased $\mathrm{H}^{+}$concentration from carbon dioxide production and lactate formation during strenuous exercise makes pH regulation progressively more difficult. Acid base regulation becomes exceedingly difficult during repeated, brief bouts of all-out exercise that elevate blood lactate values to 30 mM ( 270 mg of lactate per dL of blood) or higher. ${ }^{33}$ Figure 14.10 illustrates the inverse linear relationship between blood lactate concentration and blood pH . Blood lactate concentration in these experiments varied between 0.8 mM at rest $(\mathrm{pH} 7.43)$ and 32.1 mM during exhaustive exercise ( pH 6.80 ). In active muscle, pH reaches even lower values than in blood, declining to 6.4 or lower at exhaustion.

The above data indicate that humans temporarily tolerate pronounced disturbances in acid base balance during maximal exercise, at least to an overall blood pH as low as 6.80 one of the lowest blood lactate values ever reported. A plasma pH below 7.00 does not occur without consequences; this level of acidosis produces nausea, headache, and dizziness, in addition to discomfort and pain that ranges from mild to severe within active muscles.

## Summary

1. The chemical and physiologic buffer systems normally regulate the acid base quality of bodily fluids within narrow limits.
2. The bicarbonate, phosphate, and protein chemical buffers provide the rapid first line of defense in acid base regulation. Buffers consist of a weak acid and the salt of that acid. Their action during acidosis converts a strong acid to a weaker acid and a neutral salt.
3. The lungs and kidneys also contribute to pH regulation. Changes in alveolar ventilation rapidly alter free $\mathrm{H}^{+}$concentration in extracellular fluids. The renal tubules act as the body s final defense by secreting $\mathrm{H}^{+}$into the urine and reabsorbing bicarbonate.
4. Anaerobic exercise increases the demand for buffering, and makes pH regulation progressively more difficult.

References are available online at http://thepoint.lww.com/mkk7e.


## CHAPTER 15

## The Cardiovascular System

## CHAPTER OBJECTIVES

List four important functions of the cardiovascular system
> Describe the interactions among cardiac output, total peripheral resistance, and arterial blood pressure

- Explain the role of the venous system as an active blood reservoir
- Explain how to measure blood pressure with the auscultatory method, and quantify typical systolic and diastolic blood pressures at rest and moderate aerobic exercise
- Discuss how blood pressure responds during resistance exercise and upper-body exercise
- Explain why a hypotensive response might occur in recovery from exercise
- Diagram the major vessels of the coronary circulation
> Describe the pattern of myocardial blood flow, oxygen consumption, and substrate use during rest and various intensities of physical activity
- Explain the rate pressure product and rationale for its use in clinical exercise physiology

As physiologists in antiquity proposed, the cardiovascular system integrates the body as a unit. For the exercise physiologist, one of its most important functions provides the active muscles with a continuous stream of nutrients and oxygen to sustain high levels of energy transfer and removal of metabolic byproducts from the active sites of energy release.

Chapters 15,16 , and 17 explore the dynamics of circulation, particularly its role in oxygen delivery during exercise. The maximum level for aerobic energy transfer during exercise depends on oxygen transport and delivery, and how muscles generate adenosine triphosphate (ATP) aerobically.

## CARDIOVASCULAR SYSTEM COMPONENTS

The cardiovascular system consists of the continuous linkage of a pump, a high-pressure distribution circuit, exchange vessels, and a low-pressure collection and return circuit. If stretched in a line, the 100,000 miles of blood vessels of an average-sized adult would encircle the earth about four times. Figure 15.1 presents a schematic view of the cardiovascular system including the major arteries. The table inset shows the distribution of blood in absolute and percentage terms. Note the small arteries, veins, and capillaries of the systemic circulation contain approximately $75 \%$ of the total blood volume, whereas the heart contains only $7 \%$.

## The Heart

The heart provides the impetus for blood flow. Situated in the mid-center of the chest cavity, about two thirds of its mass lies to the left of the bodys midline. The four-chambered muscular organ weighs 11 oz for an average-sized adult male and 9 oz for an average-sized female and pumps about 2.4 oz , or 70 mL for each beat. At rest, the hearts output of blood averages 1900 gallons daily, or 52 million gallons over a 75 -year lifetime. For a person of average fitness status, the maximum output of blood from the heart in 1 minute exceeds the fluid output from a household faucet turned wide open.

Figure 15.2 summarizes general functional and structural characteristics and mode of activation of the bodys three types of muscleskeletal, cardiac, and smooth. The heart muscle, or myocardium, represents a form of striated muscle similar to skeletal muscle. In contrast to skeletal muscle, the multinucleated, individual cells or fibers interconnect in latticework fashion. The stimulation or depolarization of one cell consequently spreads the action potential through the myocardium to all cells to make the heart function as a unit.

Figure 15.3 shows the structural details of the heart as a pump. Functionally, one can view the heart as two separate pumps. The hollow chambers on the right side of the heart (right heart) perform two crucial functions:

1. Receive blood returning from throughout the body
2. Pump blood to the lungs for aeration through the pulmonary circulation

The left side of the heart (left heart) performs two crucial functions:

1. Receive oxygenated blood from the lungs
2. Pump blood into the thick-walled, muscular aorta for distribution throughout the body in the systemic circulation

A thick, solid muscular wall, or interventricular septum, separates the hearts left and right sides. The atrioventricular valves within the heart provide one-way blood flow from the right atrium to the right ventricle via the tricuspid valve, and from the left atrium to the left ventricle through the mitral or bicuspid valve. The semilunar valves, located in the arterial wall just outside the heart, prevent blood from flowing back into the heart between contractions. The relatively thinwalled, saclike atrial chambers serve as primer, or booster, pumps to receive and store blood during ventricular contraction. Approximately $70 \%$ of the blood returning to the atria flows directly into the ventricles before the atria contract. The simultaneous contraction of both atria then forces the remaining blood into their respective ventricles directly below. Almost immediately after atrial contraction, the ventricles contract and propel blood into the arterial system. (To learn more, visit this excellent Internet site that deals with important aspects of heart function: http://www.pbs.org/wgbh/nova/ eheart/human.html.

As ventricular pressure builds, the atrioventricular valves snap closed. All heart valves remain closed for 0.02 to 0.06 seconds. This brief interval of rising ventricular tension, when heart volume and muscle fiber length remain unchanged, represents the hearts isovolumetric contraction period. Blood ejects from the heart when ventricular pressure exceeds arterial pressure. With each contraction, the spiral and circular arrangement of bands of cardiac muscle literally wrings out blood from the ventricles.

## The Arterial System

The arteries compose the high-pressure tubing that propels oxygen-rich blood to the tissues. Figure 15.4 illustrates that arteries consist of layers of connective tissue and smooth muscle. No gaseous exchange takes place between arterial blood and surrounding tissues because of the thickness of these vessels. Blood pumped from the left ventricle into the highly muscular yet elastic aorta distributes in the body through an intricate and highly efficient network of arteries and smaller arterial branches called arterioles. The walls of arterioles contain circular layers of smooth muscle that either constrict or relax to regulate blood flow to the periphery. These resistance vessels dramatically alter their internal diameter to rapidly adjust blood flow through the vascular circuit. This redistribution function takes on added importance during exercise because blood rapidly diverts to active muscles from areas that temporarily compromise their blood supply. The inset table of Figure 15.4 lists average values for the diameter of blood vessels and corresponding velocities of blood flowing through them.


Figure 15.1 Left. Schematic view of the cardiovascular system indicating the heart and pulmonary and systemic vascular circuits. Red shading depicts oxygen-rich arterial blood; blue shading denotes deoxygenated venous blood. The situation reverses in the pulmonary circuit; oxygenated blood returns to the heart in the right and left pulmonary veins. Right. Main arteries that compose the adult systemic circulation. The inset table at top left shows the absolute and percentage distribution of total blood volume in the pulmonary and systemic vascular circuits of a typical adult male at rest.


Figure 15.2 Functional and structural characteristics and mode of activation of skeletal, cardiac, and smooth muscle. (From Moore KL, Dalley AF. Clinically oriented anatomy. 4th ed. Baltimore: Lippincott Williams \& Wilkins, 1999.)


## INTEGRATIVE QUESTION

What advantage does a closed circulatory system provide to the physically active individual?

## Blood Pressure

Each contraction of the left ventricle forces blood to surge through the aorta. Peripheral vessels do not permit blood to run off into the arterial system as rapidly as it ejects from the heart. Thus, the distensible aorta stores a portion of blood, which creates pressure within the entire arterial system causing a pressure wave to travel down the aorta to remote branches of the arterial tree. The characteristic pulse in superficial arteries occurs from the stretch and subsequent recoil of the arterial wall during a cardiac cycle. In healthy
individuals, identical values occur for pulse rate and heart rate. In essence, arterial blood pressure reflects the combined effects of arterial blood flow per minute (i.e., cardiac output) and resistance to that flow in the peripheral vasculature. The following equation expresses this relationship:

Blood pressure $=$ Cardiac output $\times$ Total peripheral resistance

Systolic Blood Pressure. At rest in normotensive individuals, the highest pressure generated by the heart averages 120 mm Hg during left ventricular contraction (termed systole). The brachial artery at the level of the right atrium usually serves as the point of reference for this measurement. Systolic blood pressure provides an estimate of the work of the heart and force that blood exerts against the arterial walls during ventricular systole. During the hearts relaxation phase when aortic valves close, the natural elastic recoil of the


Figure 15.3 A. The heart, its great vessels, and one-way blood flow through valves, as indicated by the arrows. B. In diastole, the aortic and pulmonary valves snap closed; shortly thereafter, the mitral and tricuspid valves open and blood flows into the ventricular cavities. C. Initiation of systole and ventricular emptying closes the tricuspid and mitral valves, while the aortic and pulmonary valves open.


Figure 15.4 The structure of the walls of the blood vessels. A single layer of endothelial cells lines each vessel. Fibrous tissue wrapped in several layers of smooth muscle surrounds the arterial walls. A single layer of muscle cells sheathes the arterioles; capillaries consist of only one layer of rolled up endothelial cells often less than 1 micron ( $\mu \mathrm{m}$ ) thick, with a flat surface area of 300 to $1200 \mu \mathrm{~m}^{2}$. In the venule, fibrous tissue encases the endothelial cells; veins also possess a layer of smooth muscle. The inset table displays the average values for vessel diameter and corresponding values for blood flow velocity. A vessels resistance $(R)$ to flow depends on its radius. Decreasing vessel radius ( $r$ ) by one-half increases resistance 16-fold.
arterial system maintains a continuous head of pressure. This provides a steady blood flow into the periphery until the next surge of blood.

Diastolic Blood Pressure. During the relaxation phase of the cardiac cycle (termed diastole), arterial blood pressure decreases to 60 to 80 mm Hg . Diastolic blood pressure
indicates peripheral resistance or the ease that blood flows from the arterioles into the capillaries. With high peripheral resistance, pressure within the arteries after systole does not rapidly dissipate. Instead, it remains elevated for a larger portion of the cardiac cycle. The In a Practical Sense feature below illustrates the measurement of systolic and diastolic blood pressure by the common auscultation method.

## IN A PRACTICAL SENSE

## Blood Pressure Measurement, Classifications, and Recommended Follow-Up

Blood pressure represents the force exerted by blood against the arterial walls during a cardiac cycle. Systolic blood pressure, the higher of the two pressure measurements, occurs during ventricular contraction (systole) as the heart propels 70 to 100 mL of blood into the aorta. Following systole, the ventricles relax (diastole), the arteries recoil, and arterial pressure continually declines as blood flows into the periphery and the heart refills with blood. The lowest pressure attained during ventricular relaxation represents diastolic blood pressure. Pulse pressure refers to the difference between systolic and diastolic pressures. Systolic blood pressure in a typical adult varies between 110 and 140 mm Hg ; diastolic pressure varies between 60 and 90 mm Hg . Elevated systolic or diastolic blood pressure (termed hypertension) is defined as a resting systolic blood pressure above 140 mm Hg and diastolic pressure exceeding 90 mm Hg (stage 1 hypertension). Stage 2 hypertension relates to systolic blood pressures of 160 mm Hg and higher and diastolic pressures of 100 mm Hg and higher. Blood pressure readings that fall in the prehypertension range should be treated with lifestyle changes that include reducing excess weight, exercising more, quitting smoking, cutting back on salt, having no more than one or two alcoholic drinks a day, and eating more fruits, vegetables, and low-fat dairy products.

## MEASUREMENT PROCEDURES

Blood pressure, measured indirectly by auscultation (listening to sounds; described in 1902 by Russian vascular surgeon Nikolai S. Korotkoff, 1874 1920), uses a stethoscope and sphygmomanometer (consisting of a blood pressure cuff and an aneroid or mercury column pressure gauge). A typical measurement sequence occurs as follows:

1. Subject, seated in a quiet room, exposes upper right arm.
2. Locate the brachial artery at the inner side of the upper arm, approximately 1 inch above the bend in the elbow.
3. Take the free end of the cuff, gently slide it through the metal loop (or wrap over exposed Velcro), and flap it back over so the cuff wraps around the upper arm at heart level. Align the arrows on the cuff with the brachial artery. Secure the Velcro parts of the cuff. To obtain accurate readings, fit the sphygmomanometer cuff snugly (but not tightly). Use appropriate-sized cuffs for children and obese persons.
4. Place the stethoscope bell below the antecubital space over the brachial artery.
5. The cuff should now have the connecting tube (from the sphygmomanometer bulb and gauge) exit the cuff toward the arm.
6. Before inflating the cuff, ensure that the air-release switch remains closed (turn the knob clockwise).
7. Inflate the cuff with quick, even pumps to 180 to 200 mm Hg .
8. Gradually release cuff pressure (about 35 mm per s) by slowly opening the air-release knob (counterclockwise turn) and note


## IN A PRACTICALSENSE

Classification and Recommended Follow-up of Initial Blood Pressure Screening in Adults ${ }^{a}$

| Systolic <br> ( mm Hg ) | Diastolic ( mm Hg ) | Category | Follow-up |
| :---: | :---: | :---: | :---: |
| $<120$ | <80 | Optimal |  |
| <130 | <85 | Normal | Recheck in 2 y |
| 130139 | 8589 | High normal | Recheck in 1 y |
| 140159 | 9099 | Stage 1 hypertension | Confirm within 2 months |
| 160179 | 100109 | Moderate (Stage 2) hypertension | Begin treatment within 1 month if blood pressure is consistently high |
| 180209 | 110119 | Severe (Stage 3) hypertension | Begin treatment within 1 week |
| $>210$ | 120 | Very severe (Stage 4) hypertension | Treat immediately |

${ }^{a}$ Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressure categories vary, the higher reading determines the blood pressure classification. For example, a reading of $152 / 82 \mathrm{~mm} \mathrm{Hg}$ is classified as stage 1 hypertension.
From National Institutes of Health. The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. NIH Pub. no. 98-4080, 1997.

Continued
the pressure when you hear the first sound. Turbulence from the sudden rush of blood produces the sound as the formerly closed artery briefly opens during the highest pressure in the cardiac cycle. The first appearance of sound represents systolic blood pressure.
9. Continue to reduce cuff pressure, noting when the sound muffles (4th phase diastolic pressure) and when the sound disappears (5th phase diastolic pressure). Clinicians usually record the 5th phase as diastolic blood pressure.
10. If the measured pressure exceeds $140 / 90 \mathrm{~mm} \mathrm{Hg}$, allow a 10-minute period of quiet rest and repeat the procedure.
See the following URL for full explanation: http://www.nhlbi.nih. gov/guidelines/hypertension/express.pdf

## Classification of Blood Pressure (BP) for Adults

| Classification | Systolic BP <br> $(\mathbf{m m ~ H g})$ | Diastolic BP <br> $(\mathbf{m m ~ H g})$ |
| :--- | :--- | :--- |
| Normal | $<120$ | and $<80$ |
| Prehypertension | 120139 | or 8089 |
| Stage 1 Hypertension | 140159 | or 9099 |
| Stage 2 Hypertension | $\geq 160$ | or $\geq 100$ |

From National Institutes of Health. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Pub. no. 03-5233, 2003.

Mean Arterial Pressure. Systolic blood pressure typically averages 120 mm Hg , and the diastolic pressure equals 80 mm Hg in young, healthy adults at rest. The average or mean arterial pressure (MAP) is slightly lower than the arithmetic average of systolic and diastolic pressures because the heart remains in diastole longer than in systole. MAP averages 93 mm Hg at rest; this represents the average force exerted by the blood against the arterial walls during a cardiac cycle. The following formula computes MAP:
MAP = Diastolic BP + [0.333 (Systolic - Diastolic BP)]

For a person with a diastolic blood pressure of 89 mm Hg and a systolic pressure of 127 mm Hg , MAP equals $89+$ [0.333 (127-89)] or 102 mm Hg .

## Cardiac Output and Total Peripheral Resistance.

 The hemodynamic equation that relates blood pressure to cardiac output and total peripheral resistance rearranges as follows to illustrate factors that determine either cardiac output or total peripheral resistance:Cardiac output $=$ MAP $\div$ Total peripheral resistance
Total peripheral resistance $=$ MAP $\div$ Cardiac output
MAP (computed from systolic and diastolic blood pressures) and cardiac output estimate the change in total
resistance to blood flow in the transition from rest to exercise. Suppose systolic blood pressure at rest equals 120 mm Hg , diastolic pressure equals $80 \mathrm{~mm} \mathrm{Hg}(\mathrm{MAP}=93.3 \mathrm{~mm} \mathrm{Hg})$, and cardiac output averages $5.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. Substituting these values in the formula for total peripheral resistance yields 18.7 mm Hg per liter of blood flow ( $93.3 \mathrm{~mm} \mathrm{Hg} \div 5.0 \mathrm{~L}$. $\mathrm{min}^{-1}$ ). Resistance to peripheral blood flow decreases dramatically during strenuous exercise, when systolic pressure increases considerably more than diastolic pressure and cardiac output increases six or seven times the resting value in an elite endurance athlete. For example, if exercise cardiac output equals $35.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ and MAP equals 130 mm Hg (systolic $=$ 210 mm Hg ; diastolic $=90 \mathrm{~mm} \mathrm{Hg}$ ), then resistance to blood flow in the systemic circulation averages 3.71 mm Hg per liter per minute, or five times less than the resting value.

## Capillaries

The arterioles branch and form smaller and less muscular vessels 10 to 20 microns ( $\mu \mathrm{m}$ ) in diameter called metarterioles. These vessels end in a meshwork of microscopically small blood vessels called capillaries, which generally contain $6 \%$ of the total blood volume. In skeletal muscle, with its widely varying oxygen requirements, each metarteriole interfaces with 8 to 10 capillaries. The average capillary diameter is

7 to $10 \mu \mathrm{~m}$ (approximately $1 / 100$ th of a millimeter). Figure 15.4 shows that the capillary wall usually consists of a single layer of rolled up endothelial cells. Some capillaries are so narrow (about $34 \mu \mathrm{~m}$ in diameter) that only one blood cell at a time can squeeze through. In many instances, the extensive proliferation of capillaries causes their walls to abut the membranes of the surrounding cells. Capillary density varies throughout the body, depending on a particular tissues location and function. Capillary density of human skeletal muscle averages between 2000 and 3000 capillaries per square millimeter of tissue. Capillary density is considerably greater in heart muscle where no cell lies farther than 0.008 mm from its nearest capillary.

## Blood Flow in Capillaries

The precapillary sphincter, a ring of smooth muscle that encircles the vessel at its origin, controls capillary diameter. Sphincter constriction and relaxation provide an important local means of blood flow regulation within a specific tissue to meet metabolic requirements. Chapter 16 discusses specific factors for autoregulation of local blood supply.

Figure 15.5 depicts a generalized view of the dynamics of capillary blood flow within muscle during rest and exercise. Fewer capillaries function at rest than are available. In this example for the gastrocnemius muscle at rest, blood flow each minute averages 5 mL for every 100 g of muscle tissue. For a muscle that weighs 600 g , approximately 30 mL of blood flows through it each minute. During exercise, blood flow increases rapidly as previously unused capillaries open. Two


Figure 15.5 Capillary blood flow during rest (A) and exercise (B). Capillary diameter, red blood cell size, and blood viscosity all affect capillary blood flow. The position of the dark red knobs indicate closure or opening dormant capillaries. The right figure shows the pulsatile pattern of blood flow at rest, during exercise, and when exercise stops. Dilation of the active muscles ar terioles provides the major mechanism for augmenting local blood flow.


Figure 15.6 Distribution of the superficial (dark blue) and deep (light blue) veins.
smaller veins in the lower portion of the body eventually empty into the inferior vena cava, the bodys largest vein (Fig. 15.6). This large vessel returns blood to the right atrium from the abdomen, pelvis, and lower extremities. Venous blood from tributary vessels in the head, neck, shoulder regions, thorax, and part of the abdominal wall flows into the $7-\mathrm{cm}$ long superior vena cava to join the inferior vena cava at heart level. The mixture of blood that drains the upper and lower body, called mixed-venous blood, then enters the right atrium. From there it flows forcefully downward through the tricuspid valve into the right ventricle for pumping through the pulmonary artery to the lungs. Gas exchange takes place
in the alveolar capillary network of the lungs; oxygenated blood then returns in the pulmonary veins to the left side of the heart to once again begin passage throughout the body.

Figure 15.7 illustrates that blood pressure and blood flow vary considerably in the systemic circulation. During the cardiac cycle, resting blood pressure fluctuates between 120 and 80 mm Hg in the aorta and large arteries. The pressure then declines in direct proportion to the resistance encountered in the vascular circuit. Blood at the arteriole end of the capillaries, for example, exerts an average pressure of only 30 mm Hg . As blood enters the venules, it loses nearly all its impetus for


Figure 15.7 Blood flow and blood pressure in the systemic circulation at rest. Note that blood pressure within each portion of the arterial system inversely relates to the total area (resistance) in that section of the vascular tree. For example, when total vascular area approaches $5000 \mathrm{~cm}^{2}$, blood flow velocity is at its lowest level.
forward movement. The pressure decreases to approximately 0 mm Hg by the time blood reaches the right atrium. The venous system operates under relatively low pressure, so veins need only possess much thinner and less muscular walls than the thicker-walled and less distensible arteries (see Fig. 15.4).

## Venous Return

The low pressure of blood in the venous system poses a special problem that a unique characteristic of veins partly solves. Figure 15.8 shows that thin, membranous, flaplike valves spaced at short intervals within the vein allow blood to flow in only one direction toward the heart. This now seems so logical, but in 1759 when Harvey in England first proposed the idea to his colleagues during a medical lecture and demonstration, he was vilified for daring to contradict almost two thousand years of prior medical dogma since ancient physician Galen posited that blood sloshed back and forth through the heart and blood vessels.

The low pressure in the venous circuit means that the smallest muscular contractions, or even minor pressure
changes within the thoracic cavity with breathing, readily compress the veins. ${ }^{17}$ The alternate compression and relaxation of veins, including the one-way action of their valves, provides a milking or wringing action, similar to heart action, that propels blood back to the heart. Without valves, blood would stagnate as it sometimes does in veins of the extremities. People would faint every time they stood up because of reduced venous return and cerebral blood flow. In ancient Rome, when suspending people from a cross with nails through the ends of the extremities was the ultimate punishment, death occurred mainly from blood pooling in the lower extremities and pulmonary edema, and not by excruciating physical torture as often assumed.

## A Question of an Active Vasculature

Physiologists have debated the role of the venous system as an active vasculature for mobilizing blood volume. The systemic venous vessels normally contain $65 \%$ of the total blood volume at rest; the veins thus represent capacitance vessels that serve as blood reservoirs. This has led to speculation


Figure 15.8 The valves in veins (A) prevent the back flow of blood, but (B) do not hinder the normal one-way flow of blood. (C) Blood moves through veins by the action of nearby active muscle (muscle pump) or (D) contraction of smooth muscle bands within the veins.
about the role of veins as an active blood reservoir to either retard or facilitate blood delivery to the systemic circulation. Physiologists who take this position maintain that any increase in tension or tone of the vessels smooth muscle layer alters the diameter of the venous tree. If true, this would initiate rapid redistribution of blood from peripheral veins toward the central blood volume that returns to the heart. In contrast, physiologists who oppose this position believe that only the veins in the splanchnic and cutaneous regions are innervated richly enough to contribute to blood mobilization. They posit that skeletal muscle veins do not receive neural input, and whatever brief venoconstriction occurs in other regions would do little to contribute to blood redistribution. Current opinion maintains that the major contribution to blood mobilization in exercise occurs by active muscle pump action and the passive effect of arterial vasoconstriction (not visceral venoconstriction), which reduces downstream venous pressure. ${ }^{41}$

## Varicose Veins

Sometimes the valves within a vein fail to maintain their one-way blood flow, a defective condition termed varicose veins. This condition usually occurs in the surface veins of
the lower extremities. Consequently, blood gathers in them so they become excessively distended and painful, which impairs circulation from the affected area. In severe cases, the venous wall becomes inflamed and progressively deterioratesacondition called phlebitis. This necessitates vessel removal either surgically or nonsurgically by injecting solutions that irritate the vessels surface membranes (sclerotherapy). This procedure and laser ablation cause a portion of the vein to collapse, fuse, and eventually shrivel up. Blood then reroutes to the deeper veins.

Individuals with varicose veins should avoid static, straining-type exercises that accompany resistance training. During sustained, nonrhythmic muscle actions, the muscle and ventilatory pumps contribute little to venous return.
Increased intrathoracic and abdominal pressures (Valsalva maneuver) with straining also impede venous return. These factors act to pool blood in the veins of the lower body, which can aggravate an existing varicose vein condition. Exercise training does not prevent varicose veins; regular and rhythmic physical activity can minimize complications because repeated muscle actions continually propel blood toward the heart.

## Venous Pooling

The rhythmic action of muscular activity and consequent compression of the vascular tree (i.e., the muscle pump) contribute so much to venous return that many people faint when forced to maintain an upright posture without movement. The classic tilt table experiment demonstrates this point. A subject lies supine, secured on a table that pivots to different positions from the horizontal. Heart rate and blood pressure stabilize if the person remains horizontal. When the table tilts vertically, an uninterrupted column of blood exists from the heart to toes. This creates a hydrostatic force of 80 to 100 mm Hg that causes blood to pool in the lower extremities. Fluid backs up in the capillary bed and seeps into the surrounding tissues, causing them to swell (edema). Reduced venous return reduces cardiac output and arterial blood pressure; simultaneously, heart rate accelerates and blood mobilizes from the splanchnic region by upstream vasoconstriction (causing passive mobilization from downstream veins). Some active venoconstriction to counter the effects of venous pooling also may occur. Forcing the person to maintain the upright position induces fainting from insufficient cerebral blood supply. Tilting the person either horizontally or head down immediately restores circulation and consciousness. In Chapter 27, we discuss a variation of the tilt table experiment applied in microgravity research to induce symptoms and responses to weightlessness when subjects remain in a slight tilt-down position for weeks at a time.

The pressurized suits worn by test pilots and special support stockings for individuals with varicose veins reduce hydrostatic shifts of blood to the veins of the lower extremities in the upright position. A swimming pool provides a similar supportive effect in upright exercise because the waters external support facilitates venous return.

The Active Cool Down. The preceding discussion of venous pooling provides a sound rationale for continuing to walk or jog at a slow pace following strenuous exercise. Moderate exercise in recovery (cooling down) facilitates blood flow through the vascular circuit including myocardial vessels. In Chapter 7, we discuss how active recovery facilitates lactate removal from the blood. Continuation of mild exercise in recovery also may blunt potential deleterious effects on cardiac function from elevated catecholamines (epinephrine and norepinephrine) released during exercise. ${ }^{8,9}$

INTEGRATIVE QUESTION
The ancient Romans executed individuals by tying their arms and legs to a cross mounted in the vertical position. Discuss the physiologic responses that cause death under these circumstances.

## HYPERTENSION

Systolic pressure at rest can exceed 300 mm Hg in individuals whose arteries (1) have become hardened with fatty materials deposited within their walls or because the vessels connective tissue layer has thickened or (2) offer excessive resistance to peripheral blood flow because of neural hyperactivity or kidney malfunction. Diastolic pressure also can exceed 100 mm Hg under these conditions. Abnormally high blood pressure, termed hypertension, chronically strains the cardiovascular system and, untreated, damages arterial vessels and leads to arteriosclerosis, heart disease, stroke, and kidney failure. ${ }^{24}$ Figure 15.9 shows the percentages of the United States population with hypertension (systolic pressure $>140 \mathrm{~mm} \mathrm{Hg}$; diastolic pressure $>90 \mathrm{~mm} \mathrm{Hg}$ ) and its increased prevalence with age. The risk of becoming hypertensive increases with age such that the lifetime risk exceeds $80 \%$. More than one-half of those 60 to 69 years old and three quarters of those 70 years and older are hypertensive. ${ }^{7}$ An elevated systolic blood pressure provides a more reliable and accurate predictor of the risk associated with hypertension (and need for treatment) than diastolic blood pressure, particularly in middle age. ${ }^{26}$

## A Prevalent Disorder

As America ages and continues to become more overweight and overfat, the rate of hypertension increases to alarmingly high levels. The number of hypertensive Americans has increased to 73 million from 50 million a decade ago (See Fig. 15.9). One of every three to four Americans and a billion people worldwide experience chronic hypertension some time during their lifetime. A relatively high prevalence of hypertension exists among African Americans, who exhibit a higher risk of hypertension and ischemic stroke than Caucasians. ${ }^{39}$ Their predisposition for hypertension reflects reduced sensitivity to the vasodilating action of nitric oxide (see Chapter 16, p. 334). ${ }^{6,42}$ Only two-thirds of hypertensive


Figure 15.9 Prevalence of hypertension by age, race, and gender in the United States. (Data from the American Heart Association, 2004.)
persons know of their disease, only half receive treatment, and only a quarter have their blood pressure under control. Each year, an additional 2 million people become hypertensive. An individual on medication for hypertension still classifies as hypertensive, even if blood pressure remains within the normal range. Uncorrected hypertension often leads to congestive heart failure, kidney disease, myocardial infarction, or stroke. Blood pressure reduction, on the other hand, effectively prevents stroke and other vascular events including heart failure, even among the elderly. ${ }^{4}$ Lowering systolic blood pressure just 2 mm Hg reduces deaths from stroke by $6 \%$ and heart disease by $4 \%$. Lowering high blood pressure also may reduce the progression of dementia and cognitive impairment, which are more common in people


Figure 15.10 Recommended pharmacologic therapies for the treatment of hypertension following an initial 6 to 12 months of treatment with diet, weight loss, reduced alcohol intake, and regular exercise. A chronically overactive renin angiotensin mechanism also causes certain forms of high blood pressure.
with hypertension. Figure 15.10 shows recommended pharmacologic therapies for treating hypertension after initial nonpharmacologic approaches prove ineffective. Also presented is the renin angiotensin mechanism. Chapter 20 discusses that a prolonged overresponse of this mechanism with a resulting excess output of aldosterone causes hypertension.

## Effective Treatment Strategies

Preventing a chronic rise in blood pressure serves a crucial function. Even when elevated blood pressure normalizes (through lifestyle changes or medication), the disease risk remains higher than if the person had never become hypertensive in the first place. Blood pressure should be checked periodically because hypertension often progresses unnoticed for years. Effective prevention strategies include lifestyle changesregular physical activity (daily exercise
for at least 30 minutes at a moderate level), modest weight loss (for the overweight and obese), stress management, smoking cessation, reduced sodium and alcohol consumption, and adequate potassium, calcium, and magnesium intake. ${ }^{1,2,22,35,49,51}$ Regular aerobic physical activity lowers systolic and diastolic blood pressure while more vigorous exercise produces a greater lowering effect on diastolic pressure than more moderate exercise. ${ }^{44}$ Cardiorespiratory fitness remains a significant predictor of hypertension risk, whereas the effect of body weight emerges only in the overweight range. ${ }^{38}$ In addition to lifestyle changes, hypertension treatment also combines medications that reduce either extracellular fluid volume or peripheral resistance to blood flow. Lower odds of having to take medication for hypertension relate to both an increase in physical activity level and physical fitness level. ${ }^{52}$ A prudent diet, weight control, and regular, moderate physical activity should precede pharmacologic
treatment for stage 1 hypertension ( 140 to 159 mm Hg systolic; 90 to 99 mm Hg diastolic) and stage 2 hypertension ( 160 to 179 mm Hg systolic; 100 to 109 mm Hg diastolic). This is because of possible harmful side effects of drug therapy on other coronary artery disease risk factors.

The inset table in In a Practical Sense on p. 310 gives current classifications and recommended follow-up in initial blood pressure screening for adults. Chapter 32 discusses the role of regular aerobic exercise and resistance exercise to treat moderate hypertension.

## Lifestyle Choices That Lower Blood Pressure

| Advice | Details | Drop in Systolic <br> Blood Pressure |
| :--- | :--- | :--- |
| Lose excess weight | For every 20 pounds you lose | 5 to 20 mm Hg |
| Follow a DASH diet | Eat a lower-fat diet rich in vegetables, fruits, and low-fat dairy foods | 8 to 14 mm Hg |
| Exercise daily | Get 30 minutes a day of aerobic activity (like brisk walking) | 4 to 9 mm Hg |
| Limit sodium | Eat no more than 2400 mg a day (1500 mg is better) | 2 to 8 mm Hg |
| Limit alcohol | Have no more than 2 drinks a day (men), 1 drink a day (women) <br> (1 drink $=12$ oz. beer, 5 oz. wine, or 1.5 oz. 80 -proof whiskey) | 2 to 4 mm Hg |
|  |  |  |

From The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (www.nhlbi.nih.gov/guidelines/hypertension).

## BLOOD PRESSURE RESPONSE TO EXERCISE

The blood pressure response to exercise varies with the exercise mode.

## Resistance Exercise

Straining exercise, particularly the concentric (shortening) and/or static phase of muscle actions, mechanically compresses the peripheral arterial vessels that supply active muscles. Arterial vascular compression dramatically increases total peripheral resistance and reduces muscle perfusion. Muscle blood flow decreases proportionally to the percentage of maximum force capacity exerted. In an attempt to restore muscle blood flow, substantial increases occur in sympathetic
nervous system activity, cardiac output, and MAP. The magnitude of the hypertensive response relates directly to the intensity of effort and quantity of muscle mass activated. ${ }^{14,19,33}$ Young and older healthy adults have similar short-term hemodynamic responses to resistance exercise. ${ }^{30,31}$

A study from one of our laboratories measured blood pressure of normotensive subjects directly with a pressure transducer connected to a catheter inserted into the femoral artery. Measurements were made during three forms of exercise: (1) isometric bench press performed at $25,50,75$, and $100 \%$ of the maximal voluntary contraction (MVC); (2) freeweight bench press performed at 25 and $50 \%$ of the isometric MVC; and (3) hydraulic resistance bench press exercise performed all out for 20 seconds at slow and fast speeds. The results, displayed in Table 15.1, show clearly that the three exercise modes substantially increased arterial blood pressure

TABLE 15.1 Comparison of Peak Systolic and Diastolic Blood Pressure at Various Percentages of a Maximum Voluntary Contraction (MVC) During Isometric Exercise and Free-Weight and Hydraulic Bench Press Exercise

| Condition | Isometric ${ }^{\text {a }}$ (\% MVC) |  |  |  | Free-Weight Bench Press ${ }^{b}$ (\% MVC) |  | Hydraulic Bench Pess ${ }^{\text {c }}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 25 | 50 | 75 | 100 | 25 | 50 | Slow | Fast |
| Peak systolic, mm Hg | 172 | 179 | 200 | 225 | 169 | 232 | 237 | 245 |
| Peak diastolic, mm Hg | 106 | 116 | 135 | 156 | 104 | 154 | 101 | 160 |

[^30]

Figure 15.11 Heavy-resistance exercise magnifies the exercise blood pressure response (higher with legs than arms) compared with rhythmic, continuous aerobic exercise. The height of the bar indicates pulse pressure.
and the hearts corresponding workload (see Rate Pressure Product, p. 320). Other studies also show that exercise that activates a large muscle mass and requires relatively great muscle strain elicits dramatic blood pressure increases. ${ }^{12,25,29,34}$ As we point out in Chapter 16, this exacerbated blood pressure response results from the combined effect of (1) greater stimulation of the cardiovascular center by the active areas of the motor cortex and (2) large peripheral feedback to this center from the contracting muscle mass.

The acute cardiovascular strain with heavy-resistance exercise could prove harmful to individuals with heart and vascular disease, particularly individuals unfamiliar in this exercise mode. Figure 15.11 presents generalized responses for blood pressure during rhythmic aerobic exercise and heavy-resistance exercises that activate either a relatively small or relatively large muscle mass. In addition, intraocular pressure increases considerably during resistance exercise, which increases the risk for eye damage. The effect is further magnified with breath holding during the lift. ${ }^{47,48}$

## Steady-Rate Exercise

During rhythmic muscular activity (e.g., jogging, swimming, bicycling), vasodilation in the active muscles reduces total peripheral resistance to enhance blood flow through large portions of the peripheral vasculature. Alternate muscle contraction and relaxation also provide an effective force to propel blood through the vascular circuit and return it to the heart. Increased blood flow during rhythmic, steady-rate exercise rapidly increases systolic pressure during the first few minutes of exercise. Blood pressure then levels off at 140 to 160 mm Hg for healthy men and women. As exercise continues, systolic pressure gradually declines because the arterioles in the active muscles continue to dilate, further reducing peripheral resistance to blood flow. Diastolic blood pressure remains unchanged throughout exercise.

## INTEGRATIVE QUESTION

Explain how regular resistance-exercise training that disproportionately elevates blood pressure during exercise can ultimately blunt the blood pressure response to performing a 2-arm curl with 80 pounds?

## Graded Exercise

Figure 15.12 reveals the general pattern for systolic and diastolic blood pressures during continuous, graded treadmill exercise. After an initial rapid rise from the resting level, systolic blood pressure increases linearly with exercise intensity, while diastolic pressure remains stable or decreases slightly at the higher exercise levels. Healthy, sedentary and endurance-trained subjects demonstrate similar blood pressure responses. During maximum exercise by healthy, fit men and women, systolic blood pressure may increase to 200 mm Hg or higher, despite reduced total peripheral resistance. ${ }^{33}$ This level of blood pressure most likely reflects the hearts large cardiac output during maximal exercise by individuals with high aerobic capacity.

## Blood Pressure in Upper-Body Exercise

Exercise with the arms produces considerably higher systolic and diastolic blood pressures (and consequently greater cardiovascular strain) than leg exercise performed at a given percentage of $\mathrm{VO}_{2 \text { max }}$ in each form of exercise (Table 15.2). ${ }^{36,45}$ This occurs because the smaller arm muscle mass and vasculature offer greater resistance to blood flow than the larger leg


[^31]Figure 15.12 Generalized response for systolic and diastolic blood pressures during continuous, graded treadmill exercise up to maximum.

| TABLE 15.2 | Comparison of Systolic and Diastolic Blood Pressure During Dynamic Arm and Leg Exercise at Similar Percentages of $\mathrm{VO}_{2 \text { max }}$ |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Percentage of $\mathrm{VO}_{2 \text { max }}$ | Systolic Pressure ( mm Hg ) |  | Diastolic <br> Pressure <br> ( mm Hg) |  |
|  | Arms | Legs | Arms | Legs |
| 25 | 150 | 132 | 90 | 70 |
| 40 | 165 | 138 | 93 | 71 |
| 50 | 175 | 144 | 96 | 73 |
| 75 | 205 | 160 | 103 | 75 |

From strand PO, et al. Intraarterial blood pressure during exercise with different muscle groups. J Appl Physiol 1965;20:253.
mass and blood supply. Individuals with cardiovascular dysfunction should exercise relatively large muscle groups (walking, bicycling, and running) in contrast to exercise that engages a limited muscle mass (shoveling, overhead hammering, or arm-crank exercise). ${ }^{13,32}$ Chapter 17 further discusses the cardiovascular adjustments to upper-body exercise.

## In Recovery

Upon completion of a single bout of submaximal exercise, blood pressure temporarily falls below preexercise levels for normotensive and hypertensive individuals from an unexplained peripheral vasodilation. ${ }^{18,21,23,27}$ The hypotensive response to exercise can last up to 12 hours. It occurs in response to either low- or moderate-intensity aerobic exercise or resistance exercise. ${ }^{28,36}$ One explanation for postexercise hypotension proposes that a significant quantity of blood remains pooled in the visceral organs and/or skeletal muscle vascular beds during recovery. ${ }^{5,10}$ Venous pooling reduces central blood volume, which in turn decreases atrial filling pressure and lowers systemic arterial blood pressure. A prolonged increase in splanchnic, renal, or cutaneous blood flow in recovery probably plays only a limited contributory role in the postexercise hypotensive response. ${ }^{37,50}$ Also, release of atrial natriuretic peptide hormone, a potent vasodilator, does not account for postexercise hypotension. ${ }^{28}$ Regardless of the mechanism, postexercise reductions in blood pressure further support moderate exercise as a nonpharmacologic treatment for hypertension. Relatively prolonged reductions in postexercise blood pressure justify recommending multiple periods of physical activity interspersed throughout the day.

## THE HEART S BLOOD SUPPLY

Each day, nearly 2000 gallons of blood flow through the hearts chambers. None of the blood, however, passes directly into the myocardium because no direct circulatory channels
lead from the chambers into the tissues. Instead, the heart muscle maintains its own elaborate circulatory network. Figure 15.13 shows that these vessels form a visible, crownlike network called the coronary circulation that arises from the top portion of the heart.

The right and left coronary arteries emerge from the upper part of the ascending aorta. Their openings form just above the semilunar valves at a point where oxygenated blood leaves the left ventricle. These arteries then curl around the hearts surface. The right coronary artery supplies predominantly the right atrium and right ventricle. The greatest volume of blood flows in the left coronary artery to the left atrium and left ventricle and small sections of the right ventricle. These vessels divide and eventually form a dense capillary network within the myocardium. Blood leaves the tissues of the left ventricle through the coronary sinus; blood from the right ventricle exits via the anterior cardiac veins, which empty directly into the right atrium.

The driving force of each ventricular systole pushes some blood into the coronary arteries. Normal blood flow to the myocardium at rest equals 200 to 250 mL per minute; this represents approximately $5 \%$ of the hearts total output.

## Myocardial Oxygen Supply and Use

At rest, the myocardium uses considerable oxygen relative to its blood flow; it extracts about 70 to $80 \%$ of the oxygen from the blood in the coronary vessels. The magnitude of myocardial oxygen extraction differs considerably from most other tissues, which use only about one-fourth of their available oxygen at rest. Consequently, a proportionate increase in coronary blood flow in exercise essentially provides the sole mechanism to increase myocardial oxygen supply. During vigorous exercise, coronary blood flow increases four to six times above the resting level. Blood flow increases because elevated myocardial metabolism dilates coronary vessels. Sympathetic-mediated arteriolar vasodilation provides some contribution to increased coronary blood flow during exercise, but the local feedback control mechanism remains unknown. ${ }^{46}$ Arterial blood pressure also facilitates coronary blood flow. Increased aortic pressure during exercise forces a proportionately greater volume of blood into the coronary circulation. The ebb and flow of blood in the coronary vessels consistently fluctuates with each phase of the cardiac cycle. On average, about 2.5 times more blood flows during diastole than systole.

## Effects of Impaired Blood Supply

The myocardium depends on an adequate oxygen supply because, unlike skeletal muscle, this tissue has limited anaerobic energy-generating capacity. Extensive vascular perfusion supplies at least one capillary to each of the hearts muscle fibers. Tissue hypoxia provides a potent stimulus to myocardial blood flow. Impaired coronary blood flow usually produces


Figure 15.13 Anterior and posterior views of the coronary circulation including the SA and AV nodes (upper inset). Arteries are shaded red and veins blue, with the exception of the pulmonary circulation where colors reverse. The lower inset illustrates a myocardial infarction from the blockage of a coronary vessel.
chest pains termed angina pectoris. More pronounced pain occurs during exercise because the heart s energy requirements increase considerably. Fortunately, the stress of exercise provides an effective way to evaluate adequacy of myocardial blood flow. A blood clot, or thrombus, lodged in a coronary vessel usually impairs normal heart function. This form of heart attack, or more specifically myocardial infarction, may be mild; a more complete blockage severely damages the myocardium and causes death. Chapters 31 and 32 provide the details about coronary heart disease, exercise stress testing, and the role of regular exercise as preventive and rehabilitative medicine.

## Rate Pressure Product: An Estimate of Myocardial Work

One common estimate of myocardial workload (and resulting oxygen consumption) uses the product of peak systolic blood pressure (SBP), measured at the brachial artery, and heart rate (HR). This index of relative cardiac work termed the double product or rate pressure product (RPP), relates closely to directly measured myocardial oxygen consumption and coronary blood flow in healthy subjects over a
wide range of exercise intensities. RPP computes as follows:

$$
\mathrm{RPP}=\mathrm{SBP} \times \mathrm{HR}
$$

Changes in heart rate and blood pressure contribute equally to changes in RPP. Typical values for RPP range from 6000 at rest $\left(\mathrm{HR}=50 \mathrm{~b} \cdot \mathrm{~min}^{-1} ; \mathrm{SBP}=120 \mathrm{~mm} \mathrm{Hg}\right)$ to $40,000\left(\mathrm{HR}=200 \mathrm{~b} \cdot \mathrm{~min}^{-1} ; \mathrm{SBP}=200 \mathrm{~mm} \mathrm{Hg}\right)$ or above, depending on intensity and exercise mode. Resistance training and upper-body exercise produce substantially higher heart rate and blood pressure responses (hence higher RPPs) than more rhythmic exercise with the lower body. This added myocardial work poses an unnecessary risk for coronary heart disease patients with compromised myocardial oxygen supply.

Research with heart disease patients shows a physiologic correlation between RPP and onset of angina pectoris and electrocardiographic abnormalities during exercise. The RPP thus provides an objective yardstick to evaluate the effects on cardiac performance of various clinical, surgical, or exercise interventions. The well-documented lowering of exercise heart rate and systolic blood pressure (hence lower RPP and myocardial oxygen requirement) with training helps to explain the improved exercise capacity of cardiac patients following exercise training. Prolonged, high-intensity aerobic training
also allows cardiac patients to achieve a higher exercise RPP. ${ }^{11,16}$ In nine patients followed over a 7 -year training period, RPP increased by $11.5 \%$ before ischemic symptoms appeared during graded exercise testing. ${ }^{40}$ These findings provide indirect evidence for improved myocardial oxygenation, probably from greater coronary vascularization or reduced obstruction from the training adaptation.

INTEGRATIVE QUESTION
Explain why a training-induced increase in the rate pressure product before a patient experiences angina or electrocardiographic abnormalities during exercise implies enhanced myocardial oxygenation.

## FOCUS ON RESEARCH

## Required Exercise Intensity to Improve Fitness

Karvonen MJ, et al. The effects of training on heart rate: a longitudinal study. Ann Med Exp Biol Fenn 1957;35:307.
> For many years, research focused on the best ways to develop and maintain cardiorespiratory fitness. Exercise frequency, intensity, type, and time (FITT) all influence the exercise prescription, but the most important variable remains exercise intensity. Experts cannot agree about which method best determines optimal exercise intensity for inducing a training response. The study by Karvonen and colleagues provided a simple method based on heart rate to gauge the minimum training threshold.

The researchers used different exercise intensities to determine the influence of resting, exercise, and maximal heart rate on the training response of six young adult (20to 23 -year-old) male medical students. The studys unique aspect included constancy of exercise mode (treadmill running), duration ( 30 min ), frequency ( 4 or 5 days per week), and length of training ( 4 weeks). Three different heart rates served as criterion measures: (1) training heart rate (THR), heart rate measured during each exercise session; (2) resting heart rate (RHR), measured every morning in bed before rising; and (3) maximal heart rate (MHR), determined before and after the 4 -week training period.

The study aimed to keep relative training intensity constant by adjusting running speed so THR did not decrease as cardiovascular fitness improved (top panel of figure). The researchers method for calculating THR, now known as the Karvonen method or HR reserve method, applies the subjects exercise HR increase above RHR to the range between MHR and RHR. The following formula applies these data to establish THR at a percentage of training intensity $\left(\% \mathrm{~T}_{\mathrm{INT}}\right)$ :

$$
\mathrm{THR}=\left[(\mathrm{MHR}-\mathrm{RHR}) \times \% \mathrm{~T}_{\mathrm{INT}}\right]+\mathrm{RHR}
$$

The following formula computes $\% \mathrm{~T}_{\text {INT }}$ at a known THR as follows:

$$
\% \mathrm{~T}_{\mathrm{INT}}=(\mathrm{THR}-\mathrm{RHR}) \div(\mathrm{MHR}-\mathrm{RHR}) \times 100
$$

For example, if a woman wished to know her THR at $\% \mathrm{~T}_{\text {INT }}=70 \%$ and knows that her MHR equals $170 \mathrm{~b} \cdot \min ^{-1}$ and RHR equals $52 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, then THR equals $135 \mathrm{~b} \cdot \mathrm{~min}^{-1}:[(170-52) \times 0.70]+52=135$. Conversely, knowing THR enables one to calculate the $\% \mathrm{~T}_{\text {INT }}:(135-52) \div(170-52) \times 100=70 \%$.

The researchers showed that when heart rate established training intensity, the borderline between effective and ineffective training slightly exceeded $60 \%$ of the percentage training intensity. The researchers recommended that THR must reach at least $60 \% \mathrm{~T}_{\text {INT }}$ and preferably $70 \% \mathrm{~T}_{\text {INT }}$. The inset figure for a representative subject shows that THR averaged $136 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, or $71 \%$ of the available heart rate range. The top panel displays the change in running speed required to maintain a constant THR throughout the 4-week training period.


The concept and computations developed by Karvonen for establishing effective training intensity threshold using HR significantly affected the future study of exercise training.

## MYOCARDIAL METABOLISM

The myocardium relies almost exclusively on energy released in aerobic reactions; not surprisingly then, myocardial tissue has a threefold higher oxidative capacity than skeletal muscle. Its muscle fibers contain the greatest mitochondrial concentration of all tissues, with exceptional capacity for long-chain fatty acid catabolism as a primary means for ATP resynthesis.

Figure 15.14 shows the specific substrate use (on a percentage basis) by the myocardium during rest and moderate and intense exercise. Glucose, fatty acids, and lactate formed from glycolysis in skeletal muscle provide the energy for myocardial functioning. ${ }^{3,20}$ At rest, these three substrates contribute to ATP resynthesis, with the most energy from free fatty acid breakdown ( $60 \%$ to $70 \%$ ). ${ }^{15,43}$ Following a meal, glucose becomes the preferred energy substrate. In essence, the heart uses for energy whatever substrate it sees on a physiologic level. During intense exercise when lactate efflux from active skeletal muscle into the blood increases dramatically, the heart derives its major energy by oxidizing circulating lactate. In more moderate exercise, equal amounts of fat and carbohydrate provide the energy fuel. In prolonged submaximal exercise (not illustrated), myocardial metabolism of free fatty acids rises to almost $80 \%$ of the total energy requirement. Similar patterns of myocardial metabolism exist for trained and untrained individuals. An endurance-trained person, however, demonstrates considerably greater myocardial reliance on fat catabolism in submaximal exercise. This difference, similar to the effect for skeletal muscle, illustrates the carbohydratesparing effect of aerobic training.


Figure 15.14 Generalized pattern of myocardial substrate use at rest and in relation to exercise intensity.

## Summary

1. Striated fibers of the myocardium interconnect to make portions of the heart contract in a unified manner.
2. The heart functions as two separate pumps: One pump receives blood from the body and pumps it to the lungs for aeration (pulmonary circulation), while the other receives oxygenated blood from the lungs and pumps it throughout the systemic circulation.
3. Pressure changes created during the cardiac cycle act on the hearts valves to provide one-way blood flow in the vascular circuit.
4. The surge of blood with ventricular contraction (and subsequent runoff of blood in relaxation) creates pressure changes within the arterial vessels. Ventricular contraction generates systolic blood pressure, the highest pressure during the cardiac cycle. Diastolic pressure represents the lowest pressure before the next ventricular contraction.
5. The dense capillary network provides a large and effective surface for exchange of chemicals between the blood and surrounding tissues. These minutediameter blood vessels possess autoregulatory capacity to exquisitely adjust blood flow in response to the tissues metabolic activity.
6. The venous tree contains the largest portion of central blood volume at rest, but an increase in venous tone (venoconstriction) probably contributes little to the redistribution of blood during exercise.
7. Compression and relaxation of the veins by skeletal muscle action impart considerable energy to facilitate venous return. This muscle pump mechanism provides additional justification for active recovery immediately following vigorous exercise.
8. One of every three to four persons experiences chronic, abnormally high blood pressure sometime during his or her life. Hypertension imposes a chronic cardiovascular stress that eventually damages arterial vessels and leads to arteriosclerosis, heart disease, stroke, and kidney failure.
9. Systolic blood pressure increases in proportion to oxygen consumption and blood flow during graded exercise, whereas diastolic pressure remains relatively unchanged or decreases slightly. At the same relative and absolute exercise levels, upper-body exercise produces a greater rise in systolic pressure than leg exercise.
10. Following exercise, blood pressure decreases below the preexercise level and may remain lower for up to 12 hours.
11. During isometric, free-weight, and hydraulic resistance exercises, peak systolic and diastolic blood pressures mirror a hypertensive state. Performing high-intensity resistance exercises pose a risk to individuals with hypertension or heart disease.
12. At rest, the myocardium extracts approximately $80 \%$ of the oxygen flowing through the coronary
arteries. An increase in coronary blood flow primarily provides for myocardial oxygen needs in exercise.
13. The myocardium requires a continual and adequate oxygen supply. Coronary blood flow impairment initiates chest pains (angina); blockage of a coronary artery causes irreversible damage to the heart muscle (myocardial infarction).
14. Myocardial workload can be estimated from the rate pressure product (heart rate $\times$ systolic blood pressure).
15. The energy supply to maintain myocardial function comes from the metabolism of glucose, fatty acids, and circulating lactate. Their percentage use varies with the severity and duration of exercise and the individuals training status.

1, References are available online at , http://thepoint.lww.com/mkk7e.

On the Internet
Nova Online: Map of the Human Heart www.pbs.org/wgbh/nova/eheart/human.html www.pbs.org/wgbh/nova/heart/heartmap.html
JNC 7 Express: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

## CHAPTER 16



## Cardiovascular Regulation and Integration

## CHAPTER OBJECTIVES

- Explain how intrinsic and extrinsic factors regulate heart rate during rest and exercise
> Draw a normal electrocardiogram (ECG) tracing and identify and describe its major components
- Describe how local metabolic factors regulate blood flow during rest and exercise
- Explain the role of central command in cardiovascular regulation during exercise
- Describe the effects of aerobic exercise training on neural regulation of heart rate
> Outline the contributions of chemoreceptors, mechanoreceptors, and the metaboreflex in cardiovascular regulation during exercise
> Indicate how each component of Poiseuille s law affects blood flow
- Summarize the dynamics of blood flow to diverse tissues at exercise onset and as exercise progresses in duration and intensity
- Describe the proposed mechanisms for nitric oxide $s$ regulation of local blood flow
> Outline the heart transplant patient s cardiovascular response to exercise

Complex mechanisms continually interact to dynamically balance systemic blood pressure and blood flow to different tissues under various conditions. Neurochemical factors regulate heart rate and the internal opening of blood vessels. Finely regulated cardiovascular responses provide rapid control of heart function and the proper distribution of blood flow throughout the body. At rest, the skin receives approximately $5 \%$ of the 5 L of blood pumped by the heart each minute. This contrasts to exercise in a hot, humid environment when up to $20 \%$ of the total blood flow diverts to the body s surface for one major purpose-to dissipate heat. Shunting of blood and regulating blood pressure occur only within a closed vascular system. This dynamic allows a near-immediate increase and redistribution of blood flow to meet changing metabolic and physiologic needs and environmental challenges in the cold and heat, underwater, at high altitude, and in the condition of weightlessness.

## INTRINSIC REGULATION OF HEART RATE

Cardiac muscle, unlike other tissues, maintains its own rhythm. If left to its inherent rhythmicity, the heart would beat steadily at about 100 beats $\cdot \min { }^{1}$. Situated within the posterior wall of the right atrium lies a small ( $3-\mathrm{mm}$ wide and $1-\mathrm{cm}$ long) mass of specialized muscle tissue called the sinoatrial node, or SA node. This node spontaneously depolarizes and
repolarizes to provide the innate stimulus for heart action. For this reason, the term pacemaker describes the SA node. Figure 16.1 (left) shows the normal route for impulse transmission within the myocardium.

## The Hearts Electrical Activity

Electrochemical rhythms originating at the SA node spread across the atria to another small knot of tissue situated close to the tricuspid valve known as the atrioventricular node, or AV node. Figure 16.1 (right) illustrates the time sequence of the propagation of the electrical impulse from the SA node throughout the myocardium.

A 0.10 -second delay occurs after the electrical impulse spreads through the atria to allow them to contract and propel blood into the ventricles below. The AV node gives rise to the 1-cm long AV bundle, also called the bundle of His, named after the Swiss-born anatomist and cardiologist Wilhelm His, Jr. (1863 1934), who first described this tissue in 1893. The AV bundle transmits the impulse rapidly through the ventricles over specialized conducting fibers referred to as the Purkinje system (named for Czech [Bohemian] anatomist/physiologist/ biologist Jan Evangelista von Purkinje [1787 1869]). These fibers form distinct bundle branches that penetrate the right and left ventricles. Purkinje system fibers transmit the impulse about 6 times faster than normal ventricular muscle fibers. The passage of the impulse into the ventricles stimulates each


Figure 16.1 Left. The red arrows denote the normal route for excitation and conduction of the cardiac impulse. The impulse originates at the SA node, travels to the AV node, and then spreads throughout the ventricular mass. Right. Time sequence in seconds for electrical impulse transmission from the SA node throughout the myocardium.
ventricular cell within 0.06 seconds. This allows a unified and simultaneous subsequent contraction of both ventricles. The transmission of the cardiac impulse flows as follows:

$$
\begin{gathered}
\text { SA node } \rightarrow \text { Atria } \rightarrow \text { AV node } \rightarrow \text { AV bundle } \\
\text { (Purkinje fibers) } \rightarrow \text { Ventricles }
\end{gathered}
$$

## Electrocardiogram

Like all nerve and muscle tissue, the outer surface of myocardial cells (fibers) maintains a more positive electrical charge than inside. Upon stimulation prior to contraction, polarity reverses and the myocardial cells inside becomes more positive than outside. During the diastolic phase of the cardiac cycle, the membranes repolarize to reestablish the normal resting membrane potential.

The myocardium s electrical activity creates an electrical field throughout the body. The salty bodily fluids provide an excellent conducting medium, so electrodes placed on the skin s surface readily detect voltage changes from the sequence of electrical events before and during each cardiac
cycle. Figure 16.2 graphically displays the normal cycle of the heart s electrical activity by the electrocardiogram, or simply ECG (see also In a Practical Sense, p. 327). Its patterns of electrical deflection are referred to as P, QRS, and T waves.

The $\mathbf{P}$ wave represents depolarization of the atria. It lasts approximately 0.15 second and heralds atrial contraction. The relatively large QRS complex follows the P wave; it signals electrical changes from ventricular depolarization. At this point, the ventricles contract. Atrial repolarization follows the P wave; it produces a wave so small that the large QRS complex usually obscures it. The T wave represents ventricular repolarization that occurs during ventricular diastole. The heart s relatively long depolarization period of 0.20 to 0.30 seconds prevents initiation of the next myocardial impulse (and subsequent contraction). This rest or brief time-out refractory period allows sufficient time for ventricular filling between beats.

The ECG also objectively monitors heart rate during exercise. Radiotelemetry transmits the ECG while a person


Figure 16.2 Different phases of the normal ECG from atrial depolarization (upper left) to ventricular repolarization (lower middle).

## IN A PRACTICAL SENSE

## Placing Electrodes for Bipolar and 12-Lead ECG Recordings

Recording the heart s electrical activity began in 1841, when Italian physicist Carlo Matteuci (1811 1868) documented the electrical properties of frog muscles proposed by biologist Luigi Galvani (1737 1798). Seven years later, following considerable experiments also with frogs, world-renowned German electrophysiologist Emil Dubois-Reymond (1818 1868) described the experimental setups, instruments, and frog preparations to explain the properties of electrical transmission through biologic tissues. In 1890, British physiologists Sir William Maddock Bayliss (1860 1924) and Edward Starling (1866 1927) of University College, London, connected the terminals from a capillary electrometer to the right hand and skin over the apex beat. This setup produced a pattern that showed a triphasic variation accompanying (or rather preceding) each beat of the heart.

The electrocardiogram (ECG) represents a composite record of the hearts electrical events during a cardiac cycle. These events provide a way to monitor heart rate during different physical activities and exercise stress testing. The ECG can detect contraindications to exercise, including previous myocardial infarction, ischemic S-T segment changes, conduction defects, and left ventricular enlargement (hypertrophy). A valid ECG tracing requires proper electrode placement. The term ECG lead indicates the specific placement of a pair of electrodes on the body that transmits the electrical signal to a recorder. The record of electrical differences across different ECG leads creates the composite electrical picture of myocardial activity.

## SKIN PREPARATION

Proper skin preparation reduces extraneous electrical noise (interference and skeletal muscle artifact). Abrade the skin with fine sandpaper or commercially available pads and alcohol to remove surface epidermis and oil; the skin should appear red, slightly irritated, dry, and clean.

## BIPOLAR (3-ELECTRODE) CONFIGURATION

The top figure shows the typical electrode placement for a 3-lead bipolar configuration. This positioning provides less sensitivity for diagnostic testing but proves useful for routine ECG monitoring in functional exercise testing and radiotelemetry of the ECG during physical activity. The ground (green or black) electrode attaches over the sternum; the positive (red) electrode attaches on the left side of the chest in the $\mathrm{V}_{5}$ position (level of the fifth intercostal space adjacent to the midaxillary line); and the positive (white) electrode attaches on the right side of the chest just below the nipple at the level of the fifth intercostal space. Placement of the positive electrode can be altered to optimize the recording (e.g., third and fourth intercostal spaces, anterior portion of the right shoulder, or near the clavicle). Correct electrode placement can be remembered as follows: white to right, green to ground, red to left.

## MODIFIED 12-LEAD (10-ELECTRODE TORSO-MOUNTED) CONFIGURATION FOR EXERCISE STRESS TESTING

The standard 12-lead ECG consists of three limb leads, three augmented unipolar leads, and six chest leads. For improved exercise ECG recordings, electrodes mounted on the torso (abdominal level) replace the conventional ankle (leg) and wrist electrodes. This torso-mounted limb lead system (bottom figure) reduces electrical artifact introduced by limb movement during exercise.

## ELECTRODE POSITIONING IN THE MODIFIED 10-ELECTRODE, TORSO-MOUNTED SYSTEM

1. RL (right leg): just above right iliac crest on midaxillary line
2. LL (left leg): just above left iliac crest on midaxillary line
3. RA (right arm): just below right clavicle medial to deltoid muscle
4. LA (left arm): just below left clavicle medial to deltoid muscle
5. $\mathrm{V}_{1}$ : on right sternal border in fourth intercostal space
6. $V_{2}$ : on left sternal border in fourth intercostal space
7. $V_{3}$ : at midpoint of a straight line between $V_{2}$ and $V_{4}$
8. $\mathrm{V}_{4}$ : on midclavicular line in fifth intercostal space
9. $\mathrm{V}_{5}$ : on anterior axillary line and horizontal to $\mathrm{V}_{4}$
10. $\mathrm{V}_{6}$ : on midaxillary line and horizontal to $\mathrm{V}_{4}$ and $\mathrm{V}_{5}$

Phibbs B, Buckels L. Comparative yields of ECG leads in multistage stress testing. Am Heart J 1985;90:275.


Modified 12-Lead
configuration

performs any physical activity like football, weightlifting, basketball, ice hockey, dancing, swimming, and diving, to space extravehicular activity. As discussed in Chapter 31, electrocardiography furnishes a vital diagnostic tool to uncover abnormalities in heart function, particularly abnormalities related to cardiac rhythm, electrical conduction, myocardial oxygenation, and tissue damage.

## EXTRINSIC REGULATION OF HEART RATE AND CIRCULATION

Changes in heart rate occur rapidly through nerves that directly supply the myocardium and chemical messengers that circulate in blood. These extrinsic controls of cardiac function accelerate the heart in anticipation before exercise begins, and then rapidly adjust to the intensity of physical effort. To a large extent, extrinsic regulation can decrease heart rate to 25 to $30 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ under normal ambulatory conditions in highly trained endurance athletes and exceed $200 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ in maximal exercise in trained and untrained persons. ${ }^{6}$

Figure 16.3 illustrates neural mechanisms for cardiovascular regulation before and during exercise. Input from the brain and peripheral nervous system continually bombards the cardiovascular control center in the ventrolateral medulla. This center regulates the heart s output of blood and blood s preferential distribution to all the body s tissues.

## Sympathetic and Parasympathetic Neural Input

Neural influences can override the inherent rhythm of the myocardium. These influences originate in the cardiovascular center and flow through the sympathetic and parasympathetic components of the autonomic nervous system (see Chapter 19). These two divisions operate in parallel but act by distinctly different structural pathways and transmitter systems. Figure 16.4 illustrates the distribution of sympathetic and parasympathetic nerve fibers within the myocardium. Large numbers of sympathetic and parasympathetic neurons innervate the atria, whereas the ventricles receive sympathetic fibers almost exclusively.

## Sympathetic Influence

Stimulation of the sympathetic cardioaccelerator nerves releases the catecholamines epinephrine and norepinephrine. These neurohormones accelerate SA node depolarization, causing the heart to beat faster (chronotropic effect). The term tachycardia describes heart rate acceleration, usually to rates that exceed $100 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ at rest. Catecholamines also increase myocardial contractility (inotropic effect) to augment how much blood the heart pumps with each beat. The force of ventricular contraction nearly doubles under maximum sympathetic stimulation. Epinephrine, released into the blood from the medullary portion of the adrenal glands during general sympathetic activation, produces a similar but slower acting tachycardia effect on cardiac function.

Sympathetic stimulation also profoundly affects blood flow throughout the body to produce vasoconstriction except in the coronary vasculature. ${ }^{8,47}$ Figure 16.5 schematically depicts the distribution of sympathetic and parasympathetic outflow. The sympathetic system s preganglionic axons emerge only from the thoracic and lumbar segments of the spinal cord. The preganglionic neurons of the sympathetic nervous system lie within the cord s gray matter. Their axons emerge through the ventral roots and synapse in the ganglia of the sympathetic chain adjacent to the spinal column. Postganglionic sympathetic nerve fibers end in the smooth muscle layers of small arteries, arterioles, and precapillary sphincters. Norepinephrine acts as a general vasoconstrictor released by specific sympathetic neurons termed adrenergic fibers. Some adrenergic constrictor nerves remain continually active. Thus, certain blood vessels always exhibit a state of constriction or vasomotor tone even within active muscle during intense exercise. Dilation of blood vessels under adrenergic influence occurs more from reduced vasomotor tone (decreased adrenergic activity) than from increased activity of cholinergic sympathetic or parasympathetic dilator fibers (see next section). In addition, powerful vasodilation induced by byproducts of local metabolism overrides any sympathetically activated vasoconstriction in active tissue (see Factors Within Active Muscle, p. 333). Heart rate accelerates during exercise from humoral feedback from metabolites released to the circulation from active muscles. ${ }^{26}$

## Parasympathetic Influence

Preganglionic axons of the parasympathetic division emerge only from the brainstem and the cord s sacral segments. The parasympathetic and sympathetic systems thereby complement each other anatomically. The preganglionic parasympathetic neurons lie within brainstem tissue and the lower spinal cord. Their axons travel farther than sympathetic axons because their ganglia lie adjacent to or within target organs. Parasympathetic fibers distribute to the head, neck, and body cavities (except for erectile tissues of genitalia) and never emerge in the body wall and limbs. When stimulated, parasympathetic neurons release acetylcholine, which retards the rate of sinus discharge to slow heart rate. A reduced heart rate (bradycardia) results largely from stimulation of the pair of vagus nerves whose cell bodies originate in the medulla $s$ cardioinhibitory center. The vagus nerves, the only cranial nerves that exit the head and neck region, descend to the thorax and abdominal regions. These nerves carry approximately $80 \%$ of all parasympathetic fibers. Vagal stimulation exerts no effect on myocardial contractility. Parasympathetic nerve fibers leave the brainstem and spinal cord to affect diverse body areas. Like sympathetic function, parasympathetic stimulation excites some tissues (e.g., muscles of the iris, gallbladder and bile ducts, bronchi, and coronary arteries) and inhibits other tissues (muscles of gut sphincters, intestines, and skin vasculature). Except for sweat glands, parasympathetic stimulation induces glandular secretion.


| Condition | Activator | Response |
| :---: | :---: | :---: |
| Pre-exercise "anticipatory" response | Activation of central command from the motor cortex and higher areas of the brain causes an increase in sympathetic outflow and reciprocal inhibition of parasympathetic activity. | Acceleration of heart rate; increased myocardial contractility; vasodilation in skeletal and heart muscle (cholinergic fibers); vasoconstriction in other areas, especially skin, gut, spleen, liver, and kidneys (adrenergic fibers); increase in arterial blood pressure. |
| Exercise | Parasympathetic withdrawal at onset and during low-intensity exercise; progressive sympathetic stimulation in more intense exercise; reflex feedback from peripheral mechanical and chemical receptors that monitor muscle action; alterations in local metabolic conditions due to hypoxia, $\downarrow \mathrm{pH}$, $\uparrow \mathrm{PcO}_{2}, \uparrow \mathrm{ADP}, \uparrow \mathrm{Mg}^{2+}, \uparrow \mathrm{Ca}^{2+}$, and $\uparrow$ temperature cause autoregulatory vasodilation in active muscle. | Further dilation of muscle vasculature. |
|  | Continued sympathetic adrenergic outflow in conjunction with epinephrine and norepinephrine from the adrenal medulla. | Concomitant constriction of vasculature in inactive tissues to maintain adequate perfusion pressure throughout arterial system. Action of the muscle pump and visceral vasoconstiction combine to facilitate venous return and maintain central blood volume. |

Figure 16.3 Neural regulation of the cardiovascular system during exercise. (Modified from Mitchell JH, Raven PB. Cardiovascular adaptation to physical activity. (In: Bouchard C, et al., eds. Physical activity, fitness, and health. Champaign, IL: Human Kinetics, 1994.)


Figure 16.4 Distribution of sympathetic and parasympathetic nerve fibers to the myocardium. Sympathetic nerve fiber endings secrete epinephrine. Sympathetic fibers supply the SA and AV nodes and the muscle of the atria and ventricles. Parasympathetic nerve endings secrete acetylcholine. These fibers concentrate in the atria, including the SA and AV nodes.

At the start of and during low-to-moderate intensity exercise, heart rate increases by inhibition of parasympathetic stimulation largely through central command activation (see next section). Heart rate in strenuous exercise increases by additional parasympathetic inhibition and direct activation of sympathetic cardioaccelerator nerves. The magnitude of heart rate acceleration relates directly to physical activity intensity and duration.

## Central Command: Input from Higher Centers

Impulses originating in the brain s higher somatomotor central command center continually modulate medullary activity. The motor center recruits muscles required for physical activity. Impulses from the feed-forward central command descend via small afferent nerves through the cardiovascular center in the medulla. This neural input coordinates the rapid adjustment of the heart and blood vessels to optimize tissue perfusion and maintain central blood pressure. This type of neural control operates during the preexercise anticipatory period and during the early stage of exercise. Motor cortex stimulation of the medulla increases with the size of the muscle mass activated in exercise. Central command provides the greatest control over heart rate during exercise. 34,52

Figure 16.6 shows the influence of the central command on heart rate when exercise begins. In this experiment,
radiotelemetry continuously monitored the heart rate of trained sprint runners at rest, at the starting commands, and during 60-, 220-, and 440-yard races. Heart rate averaged $148 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ at the starting commands in anticipation of the 60 -yard sprint; this represented $74 \%$ of the total heart rate adjustment to the run before exercise even began. The longer sprint events elicited successively lower anticipatory heart rates. This pattern also occurred for longer-duration endurance events. For example, anticipatory heart rates of four athletes trained for the 880 -yard run averaged $122 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, whereas heart rates averaged $118 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ during the starting commands of the 1 -mile run and $108 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ immediately before the 2 -mile run. A high neural outflow from central command in anticipation of exercise and immediately at the start seems desirable for intense sprint activity to rapidly mobilize physiologic reserves. In contrast, revving the body s engine might prove wasteful before distance events. Interestingly, muscle blood flow also increases in anticipation of exercise. The response demonstrates training specificity because the magnitude of the preexercise increases in mean arterial pressure and decreases in skeletal muscle vascular resistance varies with exercise intensity, duration, and specific mode of prior training. ${ }^{2,13}$

The heart rapidly turns on during exercise by decreasing parasympathetic inhibitory input and increasing stimulating input from the brains central command. Accelerator input as exercise begins also comes from activation of receptors in


Figure 16.5 Schematic view of the chemical, anatomic, and functional organization of the sympathetic and parasympathetic divisions of the autonomic nervous system. The preganglionic inputs of both divisions use acetylcholine (ACh; red) as the neurotransmitter. The postganglionic parasympathetic innervation to the visceral organs also uses ACh, but postganglionic sympathetic innervation uses norepinephrine (NE; blue), with the exception that ACh innervates sweat glands. The adrenal medulla receives preganglionic sympathetic innervation and secretes epinephrine into the bloodstream when activated. In general, sympathetic stimulation produces catabolic effects that prepare the body to fight or flee, while parasympathetic stimulation produces anabolic responses that promote normal function and conserve energy. (Modified from Bear MF, et al. Neuroscience: exploring the brain. Baltimore: Lippincott Williams \& Wilkins, 2006.)


## Anticipation $\square 60 \mathrm{yd} \Gamma 220 \mathrm{yd} \square 440 \mathrm{yd}$

Figure 16.6 Heart rate response of sprint-trained runners. The largest increase in anticipatory heart rate (HR immediately before exercising) occurred in the short-sprint events and was successively smaller before the longer sprints. (From McArdle WD, et al. Telemetered cardiac response to selected running events. J Appl Physiol 1967;23:566.)
active joints and muscles (see following section). The much slower contribution to heart rate increase from the sympathetic nervous system-triggered by reflex activity and not central command-does not occur until achieving moderate exercise intensity. Even in so-called nonsprint events, heart rate reaches $180 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ within 30 seconds of 1 - and 2-mile runs. Further heart rate increases progress gradually with several plateaus during the run. Almost identical results occur for heart rate measured by telemetry during competitive swimming events except for lower maximum heart rates during swimming.

Central command involvement in cardiovascular regulation also explains how variations in emotional state affect cardiovascular response. Such neural input creates difficulty obtaining true resting values for heart rate and blood pressure. ${ }^{5}$

## INTEGRATIVE QUESTIONS

Give a physiologic rationale for biofeedback and relaxation techniques to treat hypertension and stress-related disorders.

## Peripheral Input

The cardiovascular center receives reflex sensory input (feedback) from peripheral receptors in blood vessels, joints, and muscles. Chemoreceptors and mechanoreceptors within muscle and its vasculature monitor its chemical and physical state. Afferent impulses from these receptors-slow-conducting, thin-fiber group III and IV afferents from pacinian corpuscles and unencapsulated nerve-ending receptors-provide rapid
feedback. This input modifies either vagal (parasympathetic) or sympathetic outflow to bring about appropriate cardiovascular and respiratory responses to various intensities of physical activity. ${ }^{17,19,21,43}$ Activation of chemically sensitive afferents within the muscle s interstitium helps to regulate sympathetic neural activation of muscle during submaximal exercise. Metabolites produced primarily during the concentric phase of muscular activity stimulate this metaboreflex. ${ }^{11}$ Three mechanisms continually assess the nature and intensity of exercise and the mass of muscle activated:

1. Reflex neural input from mechanical deformation of type III afferents within active muscles
2. Chemical stimulation of type IV afferents within active muscles (exercise pressor reflex)
3. Feed-forward outflow from the motor areas of the central command

Specific mechanoreceptor feedback governs central nervous system s regulation of blood flow and blood pressure during dynamic exercise. ${ }^{46}$ The aortic arch and carotid sinus contain pressure-sensitive baroreceptors, while cardiopulmonary mechanoreceptors assess mechanical activity in the left ventricle, right atrium, and large veins. These receptors function as negative feedback controllers to (1) inhibit sympathetic outflow from the cardiovascular center and (2) blunt an inordinate rise in arterial blood pressure. ${ }^{40,53}$ As blood pressure increases, stretching of the arterial vessels activates the baroreceptors to slow the heart reflexly and dilate the peripheral vasculature. This decreases blood pressure toward more normal levels. During exercise, blood pressure remains effectively regulated but at higher levels. This probably occurs from an override of the arterial baroreflex feedback mechanism or an upward resetting of its threshold and/or sensitivity (i.e., reduced baroreflex gain), partly from central command activation. ${ }^{32,41}$ The baroreceptors more than likely serve as a brake to curtail abnormally high blood pressure levels during exercise.

## Carotid Artery Palpation

External pressure against the carotid artery sometimes slows the heart rate from direct baroreceptor stimulation at the bifurcation of the carotid artery. The potential for bradycardia from carotid artery palpation is important to exercise specialists because this location is routinely used to determine exercise heart rate. Consistently low heart rate estimation with carotid artery palpation in susceptible individuals would push the person to a higher exercise level-certainly an undesirable effect for cardiac patients.

Although research in the late 1970s suggested that carotid artery palpation slowed postexercise heart rate and occasionally produced electrocardiographic abnormalities, ${ }^{51}$ later reports indicated rather convincingly for healthy adults and cardiac patients that carotid artery palpation caused little or no heart rate alteration during rest or exercise and recovery. ${ }^{36,44}$ Vascular disease can affect carotid sinus sensitivity and produce falsely low heart rate values. An excellent substitute
location uses pulse rate at the radial artery (thumb side of wrist) or temporal artery (side of head at temple) as even firm palpation of these vessels does not affect heart rate.

## Local Factors

The byproducts of energy metabolism provide an autoregulatory mechanism within the muscle to augment perfusion during physical activity. We discuss the local control of circulation in the following sections.

## DISTRIBUTION OF BLOOD

If fully dilated, the body s blood vessels could hold approximately 20 L of blood, four times more than the actual average total blood volume of 5 L . Thus, maintenance of blood flow and blood pressure, particularly during exercise, requires a finely regulated balance between vascular dilation and vascular constriction. The capacity of large portions of the vasculature to constrict or dilate provides rapid blood redistribution to meet metabolic requirements. It also optimizes blood pressure throughout the vascular circuit.

## Physical Factors Affecting Blood Flow

Blood flows through the vascular circuit generally following physical laws of hydrodynamics applied to rigid, cylindrical vessels. The volume of flow in any vessel relates to two factors:

1. Directly to the pressure gradient between the two ends of the vessels, not to the absolute pressure within the vessel
2. Inversely to the resistance encountered to fluid flow

Friction between the blood and internal vascular wall creates resistance or force that impedes blood flow. Three factors determine resistance:

1. Blood thickness or viscosity
2. Length of the conducting tube
3. Blood vessel radius (probably the most important factor)

An equation, referred to as Poiseuilles law (experimentally derived in 1838 by French physician and physiologist Jean Louis Marie Poiseuille (1797 1869); the unit of viscosity [resistance to flow] is named the poise in his honor), ties these factors together to express the general relationship among pressure differential, resistance, and flow as follows:

$$
\begin{aligned}
\text { Flow }=\text { Pressure gradient } \times \text { Vessel radius }^{4} \div \text { Vessel length } & \times \text { Fluid viscosity }
\end{aligned}
$$

In the body, the transport vessel length remains constant, while blood viscosity varies only slightly under most circumstances. The radius of the conducting tube affects blood flow the most because resistance to flow changes with the vessel s radius raised to the fourth power. For example, halving a vessel s radius decreases flow 16 -fold. Conversely, doubling the radius increases volume 16 -fold. With the pressure differential within
the vascular circuit remaining constant, a small change in vessel radius dramatically alters blood flow. Physiologically, constriction and dilation of the smaller arterial blood vessels provide the crucial mechanism to regulate regional blood flow.

## Effect of Exercise

Any increase in energy expenditure requires rapid adjustments in blood flow that impact the entire cardiovascular system. For example, nerves and local metabolites act on smooth muscle bands of arteriole walls to alter their internal diameter almost instantaneously to meet blood flow demands. Visceral vasoconstriction and muscle pump action divert a large flow of blood into the central circulation.

At exercise onset, the vascular component of active muscles increases by dilation of local arterioles. These small feed arteries to skeletal muscle normally possess well-developed flow-mediated and myogenic regulatory mechanisms. They require little modification through exercise training to adequately supply the blood flow requirements of vigorous physical activity. ${ }^{22}$ Concurrently, other vessels to tissues that can temporarily compromise their blood supply constrict, or shut down. Two examples include the splanchnic and renal areas. Here, blood flow decreases in proportion to relative exercise intensity (i.e., $\% \mathrm{VO}_{2 \text { max }}$ ). Blood flow shifts from the abdominal viscera to active muscles even during relatively light exercise (HR $\leq 90 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ ). ${ }^{37}$ Two factors contribute to reduced blood flow to nonactive tissues: (1) increased sympathetic nervous system outflow (central and peripheral mechanisms) and (2) local chemicals that directly stimulate vasoconstriction or enhance the effects of other vasoconstrictors. ${ }^{29,30,33}$

The kidneys vividly illustrate regional blood flow adjustment and conservation of bodily fluids via sympathetic vasoconstriction of its vasculature. Renal blood flow at rest normally averages 1100 mL per minute ( $20 \%$ of the total cardiac output), among the highest blood flow to any organ as either a percentage of cardiac output or relative to organ weight. During maximal exercise, however, renal blood flow decreases to 250 mL per minute or only $1 \%$ of the total exercise cardiac output. A large but temporary reduction in blood flow also occurs in the liver, pancreas, and gastrointestinal tract. ${ }^{43}$

## Factors Within Active Muscle

Skeletal muscle blood flow closely couples to metabolic demands. Regulation occurs from the interaction of neural vasoconstriction activity and locally derived vasoactive substances within active tissues vascular endothelium and red blood cells. ${ }^{12}$ At rest, only one of every 30 to 40 capillaries in muscle tissue remains open. The opening of dormant capillaries in exercise serves three important functions:

1. Increases total muscle blood flow
2. Delivers a large blood volume with only a minimal increase in blood flow velocity
3. Increases the effective surface for gas and nutrient exchange between the blood and muscle fibers

Vasodilation occurs from local factors related to tissue metabolism that act directly on the smooth muscle bands of small arterioles and precapillary sphincters. This rapid response adjusts precisely to the muscles force output and metabolic needs. Decreased tissue oxygen supply serves as a potent local stimulus for vasodilation in skeletal and cardiac muscle. Additionally, local increases in blood flow, temperature, carbon dioxide, acidity, adenosine, magnesium and potassium ions, and nitric oxide production (see next section) by the endothelial cells lining the blood vessels trigger the discharge of relaxing factors that enhance regional blood flow. ${ }^{14,18,28}$ The venous system may also increase local blood flow by assessing increases in the metabolic needs of active muscle and releasing vasodilatory factors (from venular endothelial cells) that diffuse to and dilate the adjacent arteriole. ${ }^{20}$ The autoregulatory mechanisms for blood flow make sense physiologically because they reflect elevated tissue metabolism and increased oxygen need. Local regulation provides such strong control that it maintains adequate regional blood flow even in patients whose nerves to the blood vessels have been surgically removed. Local metabolite stimulation of chemoreceptors also provides the peripheral neural reflex input for medullary control of the heart and vasculature.

Nitric Oxide and Autoregulation of Tissue Blood Flow. Nitric oxide (NO) serves as an important signal molecule that dilates blood vessels and decreases vascular resistance. This gas is a common, unstable industrial and automotive air pollutant formed when nitrogen burns. Most living organisms naturally produce it from its precursor L-arginine. Stimuli from diverse signal chemicals (including neurotransmitters) and sheering stress and vessel stretch from
increased blood flow through the vessel lumen provoke NO synthesis and release by the vascular endothelium to serve its role as a vascular gatekeeper. Formerly termed endotheliumderived relaxing factor by 1998 physiology or medicine Nobel Prize corecipient Robert F. Furchgott (1916 2009; for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system), NO rapidly spreads through underlying cell membranes to smooth muscle cells within the arterial wall. Here it binds with and activates guanylyl cyclase, an enzyme important in cellular communication and signal transduction. This initiates a cascade of reactions that attenuate sympathetic vasoconstriction and induce arterial smooth muscle relaxation to increase blood flow in neighboring blood vessels. NO exerts its potent vasodilator effect on skeletal muscle (including the diaphragm), spongelike vascular tissues, skin, and myocardial tissue (Fig. 16.7). ${ }^{4,48}$

NO mediates bodily functions as diverse as olfaction, inhibition of blood clot formation, and enhanced immune response regulation, and acts as an interneuron or signaling messenger. It also contributes to cutaneous active vasodilation during heat stress and rapidly dilates the coronary vasculature as an early adaptation to moderate exercise training. ${ }^{24,45,49}$ Vascular wall receptors for NO contribute to blood pressure regulation in response to central cardiovascular stimulation during emotionally stressful situations including exercise. Racial differences in resting blood pressure relate to a lower sensitivity to NOs dilating action in blacks than in whites. ${ }^{10}$ In coronary artery disease, the endothelium produces less NO. Reduced NO bioavailability explains the potent beneficial effect of exogenous nitroglycerin treatment (which releases NO gas) to reverse chest discomfort or pain (angina pectoris) from coronary vessel disease.


## Role of Nitric Oxide

- Endothelial cells within blood vessels release nitric oxide (NO) gas, which initiates a cascade of events that attenuate sympathetic vasoconstriction and induce arterial smooth muscle relaxation to increase blood flow
- NO is either released by autonomic neurons
and synthesized by the vascular endothelium or from drugs like Viagra or nitroglycerin (and related heart drugs), which cause vasodilation by stimulating NO gas release.
- Vasodilation occurs when NO penetrates smooth muscle cells.

Figure 16.7 Mechanism for how nitric oxide regulates local blood flow.

## Hormonal Factors

Sympathetic nerves terminate in the medullary portion of the adrenal glands. With sympathetic activation, this glandular tissue secretes large quantities of epinephrine and a smaller amount of norepinephrine into the blood. These hormonal chemical messengers induce a generalized constrictor response, except in blood vessels of the heart and skeletal muscles. Hormonal control of regional blood flow plays a relatively minor role during exercise compared with the more local, rapid, and potent sympathetic neural drive.

## INTEGRATIVE EXERCISE RESPONSE

The neural command center above the medullary region initiates cardiovascular changes immediately before and at exercise onset. Heart rate and myocardial contractility increase from feed-forward input from this center, which also suppresses parasympathetic activation. Concurrently, predictable alterations in regional blood flow occur in proportion to exercise severity. Modulation of vascular dilation and constriction optimizes blood flow to areas in need while maintaining blood pressure throughout the arterial system. As exercise continues, reflex feedback to the medulla from peripheral mechanical and chemical receptors in active tissue appraises tissue metabolism and circulatory needs. Local metabolic factors act directly to dilate resistance vessels in active muscles. Vasodilation reduces peripheral resistance for greater blood flow in these areas. Arterial blood flow through active muscles progresses in pulsatile oscillations that favor enhanced flow during eccentric (lengthening) muscle actions and/or the recovery phases of concentric (shortening) actions. ${ }^{42}$ Centrally mediated constrictor adjustments also occur in the vasculature of nonexercising tissues (skin, kidneys, splanchnic region, and inactive muscle). Constrictor action maintains adequate perfusion pressure within exercising muscle while simultaneously increasing blood supply to meet metabolic demands.

Factors that affect venous return are equally as important as those that regulate arterial blood flow. Muscle and ventilatory pump actions and visceral vasoconstriction immediately return blood to the right ventricle when exercise begins and continue to facilitate venous return as cardiac output increases. These adjustments balance venous return with cardiac output. In upright exercise, gravity impedes return of blood from the extremities thus making venous blood flow regulation crucial.

## INTEGRATIVE QUESTION

Explain the following statement: Task-specific, regular aerobic exercise not only trains the cardiovascular system, but also trains the neuromuscular system to facilitate physiologic adjustments to the specific exercise mode.

## EXERCISING AFTER CARDIAC TRANSPLANTATION

Patients with left ventricular dysfunction-ejection fraction less than $20 \%$, referred to as end-stage heart disease-show poor long-term prognosis. For these patients, cardiac transplantation becomes their only hope of survival. Figure 16.8A shows the number of transplants per calendar year reported to the registry of the International Society for Heart and Lung Transplantation (www.ishlt.org/), beginning with the first human transplant nearly 45 years ago. The steady decline in transplants after 1995 results from a reduction in donor availability. ${ }^{27}$ As of June 15, 2007, the one-year survival rate for heart transplant patients was $87.4 \%$ for males and $85.5 \%$ for females; five-year survival rate averaged $72.3 \%$ for males and $67.6 \%$ for females.

Cardiac transplantation, also called orthotopic transplantation, illustrates the importance of extrinsic neural control of exercise heart rate. The procedure removes donor and recipient hearts by transection at the midatrial level-preserving the recipient s pulmonary venous connections of the posterior wall of the left atrium-and transection of the aorta just above the semilunar valves. Transplantation eliminates neural innervation of the myocardium, although hormonal feedback from circulating catecholamines largely from the adrenal medulla remains intact (Fig. 16.9A).

## Improved Function but Altered Circulatory Dynamics

Following successful transplantation, patients generally report a favorable quality of life, and approximately $50 \%$ of individuals return to work. In general, a transplant patient demonstrates prolonged oxygen uptake kinetics, impaired exercise capacity, and diminished physiologic and hemodynamic function that rarely exceeds 45 to $70 \%$ of normal. ${ }^{1,7,16,35,50}$ This does not necessarily represent the rule for younger, previously active patients who adhere to rehabilitation. ${ }^{38}$ In general, heart transplant recipients can perform relatively intense exercise training, and often achieve performance values of moderately trained healthy subjects. ${ }^{39}$

Figure 16.10A C illustrates peak oxygen consumption $\left(\mathrm{VO}_{2 \text { peak }}\right)$ for an initial pool of 140 patients evaluated prior to transplantation and up to 9 years after the procedure. Cardiac transplantation produced an average $50 \%$ improvement in $\mathrm{VO}_{2 \text { peak }}$ (Fig. 16.10A) from $14.2 \mathrm{~mL} \cdot \mathrm{~kg}^{1} \cdot \min { }^{1}$ before to $21.4 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1} 11.2$ months after surgery. The patients maintained improved aerobic capacity up to 9 years postsurgery (Fig. 16.10B). Figure 16.10C shows that younger patients exhibited the greatest improvement following transplantation.

## Sluggish Circulatory Response

The short-term exercise response for transplant patients classifies as abnormal. These patients demonstrate limited cardiac output and oxygen consumption during exercise, with

## FOCUS ON RESEARCH

## Age-Related Changes in Exercise-Induced Cardiovascular Function

## Robinson S. Experimental studies of physical fitness in relation to age. Arbeitsphysiologie 1938;10:18.

$>$ Robinson s classic comprehensive cross-sectional study documents the relationship of aging to physiologic responses during rest and exercise in 93 healthy, nonathletic males aged 6 to 91 years. Measurement variables included resting and exercise oxygen consumption $\left(\mathrm{VO}_{2}\right)$, lung volume, heart rate (HR), arterial blood pressure, submaximal treadmill walking performance at $5.6 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ at an $8.6 \%$ incline for 15 minutes, and a 2 - to 5 -minute treadmill run to exhaustion.

The top figure shows that $\mathrm{HR}_{\max }$ in older men is nearly $20 \%$ lower compared to young boys. The younger individuals also showed greater variability in HR response to exercise and more rapid HR acceleration at the start of exercise; their HRs returned to baseline more rapidly in recovery than older subjects. In the middle figure, $\mathrm{VO}_{2 \text { peak }}$ increased from age 8 to 10 years, declined for the next few years, then increased further until about age 17, and decreased steadily thereafter. Interestingly, Robinson suggested that the $\mathrm{VO}_{2 \text { peak }}$ decrease with age was probably related to a reduced level of general physical activity and was not necessarily true aging. Thus, recognition of the deleterious effects of a sedentary lifestyle on cardiovascular function occurred as early as 1938. The bottom figure depicts pulmonary ventilation relative to body mass (BM; $\mathrm{V}_{\mathrm{E}} \cdot \mathrm{kg} \mathrm{BM}{ }^{-1}$ ), breathing rate (breaths $\cdot \min ^{1}$ ), and tidal air volume (TV) expressed as a percentage of forced vital capacity (TV $\times 100 \div$ FVC) during maximal exercise. Measures of ventilatory function declined with age, and older men used a greater fraction of FVC as TV than younger men. Boys increased ventilation over resting values principally by increasing breathing frequency; adults increased ventilation by increasing breathing rate and tidal volume.

This pioneering cross-sectional study demonstrated an age- and sedentary lifestyle related decline in cardiovascular and pulmonary function variables during rest and throughout the full range of exercise intensity. Subsequent research verified Robinson s assertion that a significant component of the functional capacity decline with aging coincides more with lifestyle characteristics than chronologic age per se.


Breathing rate $\square \dot{\mathrm{V}}_{\mathrm{E}} / \mathrm{kg}$ BM $\square$ TV • 100 / FVC
Top. $\mathrm{HR}_{\max }\left(\mathrm{b} \cdot \min { }^{1}\right)$ versus age. Middle. $\mathrm{VO}_{2 \text { peak }}$ versus age. Bottom. Pulmonary minute ventilation $\left(\mathrm{V}_{\mathrm{E}}\right)$, breathing rate, and tidal volume (TV) versus age.


```
1982-1988(n=9148) \ 1989-1993(n=17,898) \1994-1998 (n=18,714) \ 1999-2003 (n=13,480)
```

Figure 16.8 A. Number of hearts transplanted by year and mean donor age (green line) from 1982 to 2006 as reported by the International Society for Heart and Lung Transplantation (www.ishlt.org/). B. Survival of heart transplantation by era. Half-life survival (time when one-half of those who underwent transplantation had died) was 9.4 years between 1994 and 1998 compared to 8.1 years between 1982 and 1988. Modified from data based on results reported in J Heart Lung Transplant 2005;24:945 and Internet sources.
accompanying reduced left ventricular ejection capacity. Figure 16.9B reveals that circulatory sluggishness results from the denervated heart $s$ inability to accelerate significantly with increasing exercise demands (often by only 20 to $\left.40 \mathrm{~b} \cdot \mathrm{~min}^{-1}\right) .^{3,15,31}$ The exercise response of the denervated transplanted heart does improve over the 12 -month postsurgery period, yet the adaptations exert no meaningful effect on submaximal or peak exercise oxygen consumption.

In healthy individuals, stroke volume increases up to approximately $50 \%$ of $\mathrm{VO}_{2 \max }$ and then plateaus; further increases in cardiac output come mainly from increases in heart rate. Transplant patients, in contrast, have no stroke volume plateau during graded exercise; instead, stroke volume progressively increases by the Frank-Starling mechanism (i.e., progressive increases in cardiac filling) throughout the exercise range. Chapter 32 discusses the effects of exercise training for the heart transplant patient.

## INTEGRATIVE QUESTION

If heart transplantation surgically removes all nerves to the myocardium, explain how heart rate can increase for these patients during physical activity.

## Summary

1. The cardiovascular system provides rapid heart rate regulation and effective distribution of blood through the vascular circuit (while maintaining blood pressure) in response to overall metabolic and physiologic needs.
2. The cardiac rhythm originates at the SA node. The impulse then travels across the atria to the AV node and, after a brief delay, spreads across the large ventricular mass. This normal conduction pattern initiates



## $\square$ Before transplant $\square$ After transplant

Figure 16.9 A. Regulation of heart rate under normal conditions. Heart transplantation produces cardiac denervation by removing vagal and sympathetic efferent stimulation to the myocardium. Circulating epinephrine from the adrenal medulla provides the primary mechanism to regulate exercise heart rate. B. Heart rate response of a patient during graded exercise before and after orthotopic cardiac transplantation. Note the elevated resting heart rate and delayed and depressed heart rate response following transplantation. (Figure B from Squires RW. Exercise training after cardiac transplantation. Med Sci Sports Exerc 1991;23:686.)

$\square$ Before cardiac transplantation $\square$ Normal population $\square$ After cardiac transplantation

Figure 16.10 Long-term effects of heart transplantation (TX) on aerobic functional capacity. $\mathrm{A} . \mathrm{VO}_{2 \text { peak }}$ before and 11.2 months after cardiac transplantation in 43 patients who underwent testing at both intervals. Post-TX average is significantly higher than pre-TX. B. Significant improvements in peak oxygen consumption ( $\mathrm{VO}_{2 \text { peak }}$ ) and percentage improvement occurred as early as 6 months after transplantation and remained improved up to 9 years after the transplant procedure. C. Impact of age on improvement in $\mathrm{VO}_{2 \text { peak }}$ in 43 patients who underwent exercise testing before and 1 year after cardiac transplantation. (From Osada N, et al. Long-term cardiopulmonary exercise performance after heart transplantation. Am J Cardiol 1997;79:451.)
atrial and ventricular contractions to provide impetus for blood flow.
3. The electrocardiogram (ECG) records the sequence of the heart s electrical events during the cardiac cycle. The ECG detects various heart function abnormalities during rest and increasing exercise intensity.
4. Epinephrine and norepinephrine accelerate heart rate and increase myocardial contractility. Acetylcholine acts through the vagus nerve to slow heart rate.
5. The heart turns on in the transition from rest to exercise from increased sympathetic and decreased parasympathetic activity integrated with central command input.
6. Cortical influence in anticipation before and during the initial stage of physical activity governs a substantial part of the heart rate adjustment to exercise.
7. Reflex sensory input from peripheral receptors in blood vessels, joints, and muscles provides the cardiovascular center with continual feedback about the physical and chemical state of active muscles.
8. Neural and hormonal extrinsic factors modify the heart s inherent rhythm. The heart rate rapidly accelerates in anticipation of exercise and can reach about $200 \mathrm{~b} \cdot \min ^{1}$ in maximal exercise.
9. Carotid artery palpation accurately accesses heart rate during and immediately after exercise in healthy individuals.
10. Nerves, hormones, and local metabolic factors act on the smooth muscle bands in blood vessels to alter the vessels internal diameter and regulate blood flow to metabolic demands.
11. Blood flow changes with the vessels radius raised to the fourth power in accord with Poiseuille s law.
12. Nitric oxide, an extraordinarily important and potent endothelium-derived relaxing factor, facilitates blood vessel dilation and decreases vascular resistance.
13. The kidneys and splanchnic regions dramatically compromise their blood flow in exercise to augment delivery of blood to the muscles and maintain systemic blood pressure.
14. Patients who successfully undergo orthotopic transplantation have a depressed cardiovascular response to exercise; the denervated heart cannot accelerate rapidly to meet the increased demands of physical activity.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

The International Society for Heart \& Lung Transplantation www.ishlt.org/

## CHAPTER 17



## Functional Capacity of the Cardiovascular System

## CHAPTER OBJECTIVES

- Discuss the advantages and disadvantages of the direct Fick, indicator dilution, and $\mathrm{CO}_{2}$ rebreathing methods to measure cardiac output
> Compare cardiac output during rest and maximal exercise for an endurance-trained and sedentary person
- Explain the influence of each component of the Fick equation on $\mathrm{VO}_{2 \text { max }}$
> Discuss two physiologic mechanisms that influence exercise stroke volume
> Contrast the components of cardiac output during rest and maximal exercise for sedentary and endurance-trained individuals
> Discuss the contribution of the Frank-Starling mechanism to augment cardiac output during different exercise modes
> Outline the dynamics and proposed mechanisms for cardiovascular drift
> Outline cardiac output distribution to major body tissues during rest and intense aerobic exercise
- Describe the relationship between maximal cardiac output and $\mathrm{VO}_{2 \text { max }}$ among individuals who vary in aerobic fitness
- Indicate factors that contribute to expanding the $\mathrm{a}-\mathrm{vO}_{2}$ difference during graded exercise
> Contrast cardiovascular and metabolic dynamics during upper-body versus lower-body graded exercise


## CARDIAC OUTPUT

Cardiac output $(\mathbf{Q})$ expresses the amount of blood pumped by the heart during a 1-minute period. The maximal value reflects the functional capacity of the cardiovascular system. Output from the heart, as with any pump, depends on its rate of pumping (heart rate, HR) and quantity of blood ejected with each stroke (stroke volume, SV). Cardiac output computes as follows:

$$
\text { Cardiac output }=\text { Heart rate } \times \text { Stroke volume }
$$

## Measuring Cardiac Output

The output from a hose, pump, or faucet is determined by opening the valve and collecting and measuring the volume of fluid ejected over a given time. To more fully understand cardiac output dynamics, it is instructive to describe methods of measurement. Three common methods assess cardiac output of a closed circulatory system in humans: (1) direct Fick, (2) indicator dilution, and (3) $\mathrm{CO}_{2}$ rebreathing.

## Direct Fick Method

Two factors determine the output of fluid from a pump in a closed circuit:

1. Change in concentration of a substance between the outflow and inflow ports of the pump
2. Total quantity of that substance taken up (or given off) by the fluid in a given time

For cardiovascular dynamics, calculating cardiac output requires knowledge of two variables: (1) average difference between the oxygen content of arterial and mixed-venous blood ( $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference) and (2) oxygen consumption during 1 minute $\left(\dot{\mathrm{V}}_{2}\right)$. The question then becomes how much blood circulates during the minute to account for the observed oxygen consumption given the observed $a-\bar{v} \mathrm{O}_{2}$ difference. The Fick equation, derived by noted German mathematician/ physiologist/physicist Adolph Fick (1829 1901; first to devise a technique for measuring cardiac output) and published in 1870 , expresses the relationships among cardiac output, oxygen consumption, and $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference. These variables could not be determined in humans until the perfection of cardiac catheterization as a clinical tool in 1940.

$$
\underset{\left(\mathrm{mL} \cdot \min ^{-1}\right)}{\text { Cardiac output }}=\frac{\dot{\mathrm{V}} \mathrm{O}_{2} \mathrm{~mL} \cdot \mathrm{~min}^{-1}}{\left(\mathrm{a}-\overline{\mathrm{V}} \mathrm{O}_{2}\right. \text { difference }} \times 100
$$

Figure 17.1 illustrates the Fick principle to determine cardiac output. The person in this example consumes 250 mL of oxygen during 1 minute at rest, and the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference during this time averages 5 mL of oxygen per 100 mL (deciliter [dL]) of blood. Cardiac output computes as follows by substituting these values in the Fick equation:

$$
\underset{\left(\mathrm{mL} \cdot \mathrm{~min}^{-1}\right)}{\text { Cardiac output }}=\frac{250 \mathrm{~mL} \mathrm{O}_{2}}{5 \mathrm{~mL} \mathrm{O}_{2}} \times 100=5000 \mathrm{~mL} \text { blood }
$$

Although straightforward in principle, the actual Fick method to determine cardiac output requires complex methodology usually performed in a hospital. Measuring oxygen consumption involves open-circuit spirometry methods (see Chapter 8). Measuring $a-\bar{v} \mathrm{O}_{2}$ difference remains the more difficult task. A representative sample of arterial blood can come from any convenient systemic artery (e.g., femoral, radial, brachial). These arteries are easily located, but arterial puncture has high risk, and sampling mixed-venous blood presents additional difficulties because the blood in each vein only reflects the metabolic activity of the specific area it drains. An accurate estimate of the average oxygen content of all venous blood requires sampling from an anatomic mixing chamber such as the right atrium, right ventricle, or most accurately, the pulmonary artery. Such sampling requires threading a small flexible catheter through the antecubital vein in the arm into the superior vena cava that drains into the right heart. Arterial and mixed-venous blood are then sampled simultaneously with measurement of oxygen consumption.

Numerous studies of cardiovascular dynamics have applied the direct Fick method under various experimental conditions. The method generally serves as the criterion standard to validate other techniques for cardiac output measurement. The invasive nature of the Fick method can alter normal cardiovascular dynamics during the measurement period that may not reflect the person s usual cardiovascular response.

## Indicator Dilution Method

The indicator dilution method involves venous and arterial punctures but does not require cardiac catheterization. A known quantity of an inert dye such as indocyanine green whose concentration curve can be measured in blood by light absorption is injected into a large vein. The indicator material remains in the vascular stream, usually bound to plasma proteins or red blood cells. It then mixes in the blood as the blood travels to the lungs and returns to the heart before ejection throughout the systemic circuit. A photosensitive device continually assesses arterial blood samples. The area under the dilution concentration curve (obtained by repetitive sampling) reflects the average concentration of indicator material in blood leaving the heart. Cardiac output computes as follows from the dilution of a known quantity of dye in an unknown quantity of blood:

$$
\frac{\text { Cardiac }}{\text { output }}=\frac{\text { Quantity of dye injected }}{\begin{array}{l}
\text { Average dye concentration in blood for } \\
\text { duration of curve } \times \text { Duration of curve }
\end{array}}
$$

## $\mathrm{CO}_{2}$ Rebreathing Method

One can determine cardiac output by substituting $\mathrm{CO}_{2}$ values for $\mathrm{O}_{2}$ values in the Fick equation. ${ }^{18,35}$ The same opencircuit spirometry method for determining oxygen consumption in the typical Fick technique determines $\mathrm{CO}_{2}$ production in the rebreathing method. Using a rapid $\mathrm{CO}_{2}$ gas analyzer and making reasonable assumptions about gas exchange provides valid estimates of mixed-venous and arterial $\mathrm{CO}_{2}$


Figure 17.1 The Fick principle to measure cardiac output per minute (Q).
levels. This noninvasive, or bloodless, technique requires breath-by-breath $\mathrm{CO}_{2}$ analysis, a technique common in today s exercise physiology laboratories. Values for $\mathrm{CO}_{2}$ production and mixed-venous and arterial $\mathrm{CO}_{2}$ concentrations (derived from expired $\mathrm{CO}_{2}$ obtained during different times) provide the data to compute cardiac output in accordance with the Fick principle as follows:

$$
\begin{array}{r}
\text { Cardiac output } \\
\left(\mathrm{mL} \cdot \min ^{-1}\right)
\end{array}=\frac{\mathrm{VCO}_{2}}{\overline{\mathrm{v}}-\mathrm{a} \mathrm{CO}} 2 \text { difference } \times 100
$$

The $\mathrm{CO}_{2}$ rebreathing method offers obvious advantages over the direct Fick and indicator dilution methods, particularly during exercise. It does not require blood sampling or close medical supervision and only minimally interferes with the subject during movement. One limitation of $\mathrm{CO}_{2}$ rebreathing requires that subjects exercise under steady-rate aerobic metabolism. This restricts the method s use during maximal and supermaximal exercise and in the transition from rest to exercise.

## INTEGRATIVE QUESTION

In what way does the Fick equation fully explain the physiologic components that determine $\mathrm{VO}_{2 \max }$ ?

## CARDIAC OUTPUT AT REST

Cardiac output varies considerably during rest. Influencing factors include emotional conditions that alter cortical outflow (central command) to the cardioaccelerator nerves and nerves that modulate arterial resistance vessels. Each minute, the left ventricle pumps the entire 5-L blood volume of a representative $70-\mathrm{kg}$ adult male. A 5-L cardiac output at rest represents an average value for trained and untrained males. Resting cardiac output for a representative $56-\mathrm{kg}$ woman averages nearly $4.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ (see next section).

## Untrained Individuals

For the average sedentary person at rest, an average heart rate of $70 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ usually sustains the $5-\mathrm{L}$ cardiac output. Substituting this heart rate value in the cardiac output equation, the heart s calculated stroke volume equals 0.714 L , or $71.4 \mathrm{~mL}(\mathrm{SV}=\mathrm{Q} \div \mathrm{HR})$. Stroke volume and cardiac output for women average about $25 \%$ below values for men; in women, the stroke volume at rest averages 50 to 60 mL . This gender difference generally relates to the average woman s smaller body size.

## Endurance Athletes

Endurance training brings the heart s sinus node under greater influence of acetylcholine, the parasympathetic hormone that slows heart rate. At the same time, resting sympathetic activity decreases. This training adaptation partially explains the low resting heart rates of many elite endurance athletes. Relatively brief training periods exert only a minimal lowering effect on resting heart rate. ${ }^{1,39}$

Heart rates in healthy endurance athletes generally average $50 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ at rest, although heart rates below $30 \mathrm{~b} \cdot$ $\min ^{-1}$ have been reported, but infrequently. Consequently, the endurance athlete $s$ resting cardiac output of $5 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ circulates with the relatively large stroke volume of 100 mL . The following summarizes average values for cardiac output, heart rate, and stroke volume for endurance-trained and untrained men at rest:

$$
\underset{\text { Cardiac }}{\text { output }}=\begin{gathered}
\text { Rest } \\
\text { Heart } \\
\text { rate }
\end{gathered} \times \begin{gathered}
\text { Stroke } \\
\text { volume }
\end{gathered}
$$

Untrained: $5000 \mathrm{~mL} \cdot \mathrm{~min}^{-1}=70 \mathrm{~b} \cdot \mathrm{~min}^{-1}=71 \mathrm{~mL}$
Trained: $5000 \mathrm{~mL} \cdot \mathrm{~min}^{-1}=50 \mathrm{~b} \cdot \mathrm{~min}^{-1}=100 \mathrm{~mL}$
Two factors likely explain the large stroke volume and low heart rate of endurance-trained athletes:

1. Increased vagal tone and decreased sympathetic drive, both of which slow the heart
2. Increased blood volume, myocardial contractility, and compliance of the left ventricle, all of which augment the heart s stroke volume

## CARDIAC OUTPUT DURING EXERCISE

Systemic blood flow increases directly with exercise intensity. Cardiac output increases rapidly during the transition from rest to steady-rate exercise. Thereafter, cardiac output rises gradually until it plateaus when blood flow meets the exercise metabolic requirements.

In sedentary, college-aged males, cardiac output during maximal exercise increased four times above the resting level to 20 to $22 \mathrm{~L} \cdot \min ^{-1}$. Maximum heart rate for these young adults averaged $195 \mathrm{~b} \cdot \mathrm{~min}^{-1}$. Consequently, the stroke volume generally ranged between 103 and $113 \mathrm{~mL}(20,000 \mathrm{~mL}$. $\min ^{-1} \div 195 \mathrm{~b} \cdot \mathrm{~min}^{-1}=103 \mathrm{~mL} \cdot \mathrm{~b}^{-1} ; 22,000 \mathrm{~mL} \cdot \mathrm{~min}^{-1} \div$ $195 \mathrm{~b} \cdot \min ^{-1}=113 \mathrm{~mL}$ ). In contrast, world-class endurance athletes achieve maximum cardiac outputs of 35 to 40 L . $\min ^{-1}$. This high value assumes greater significance when one considers that the trained person generally achieves a slightly lower maximum heart rate than a sedentary person of similar age. The endurance athlete achieves a large maximal cardiac output solely through a large stroke volume. For example, the cardiac output of an Olympic medal winner in cross-country skiing increased to $40 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ in maximum exercise (almost 8 times above rest); the stroke volume was 210 mL . This nearly doubled the maximum volume of blood pumped per beat by a sedentary counterpart. As a point of comparison among species, thoroughbred racehorses achieve cardiac outputs of $600 \mathrm{~L} \cdot \min ^{-1}$ (accompanying a 120 to $150 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ ). ${ }^{7,24}$

The following summarizes average values for cardiac output, heart rate, and stroke volume for endurance-trained and untrained men during maximal exercise:

| Maximal Exercise |  |  |  |
| :---: | :---: | :---: | :---: |
| Cardiac | Heart | $\times$ | Stroke |
| output |  |  |  |

Untrained: $22,000 \mathrm{~mL}=195 \mathrm{~b} \cdot \mathrm{~min}^{-1}=113 \mathrm{~mL}$
Trained: $35,000 \mathrm{~mL}=195 \mathrm{~b} \cdot \mathrm{~min}^{-1}=179 \mathrm{~mL}$
The importance of stroke volume in differentiating among people with high and low $\mathrm{V}_{2 \text { max }}$ is shown in Table 17.1. These data were obtained from three groups: athletes, healthy but sedentary men, and patients with mitral stenosis, a valvular disease of the left ventricle. The differences in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$

TABLE 17.1 Maximal Values for Oxygen Consumption, Heart Rate, Stroke Volume, and Cardiac Output in Three Groups with Very Low, Normal, and High Aerobic Capacities

|  | Max <br> $\left(\mathbf{V O} \mathbf{m a x}^{2}\right.$ <br> Heart Rate | Max <br> $\left(\mathbf{B} \cdot \mathbf{m i n}^{-\mathbf{1}}\right)$ | Stroke Volume <br> $(\mathbf{m L})$ | Max <br> Cardiac Output <br> $\left(\mathbf{L} \cdot \mathbf{m i n}^{-\mathbf{1}}\right)$ |
| :--- | :---: | :---: | :---: | :---: |
| Group | 1.6 | 190 | 50 | 9.5 |
| Mitral stenosis | 3.2 | 200 | 100 | 20.0 |
| Sedentary | 190 | 160 | 30.4 |  |
| Athlete | 5.2 |  |  |  |

among groups closely relate to differences in maximal stroke volume. Patients with mitral stenosis had an aerobic capacity and maximum stroke volume that was half that of the sedentary subjects. The relationship was also apparent in comparisons between healthy subjects. The $\dot{\mathrm{VO}}_{2 \text { max }}$ of athletes averaged $62.5 \%$ larger than the sedentary group. This was paralleled by a $60 \%$ larger stroke volume. Because the maximal heart rates of all groups were similar, differences in cardiac output (and $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ ) were almost entirely due to differences in maximal stroke volume.

## Enhancing Stroke Volume: Diastolic Filling Versus Systolic Emptying

Three physiologic mechanisms increase the heart s stroke volume during exercise.

1. The first, intrinsic to the myocardium, involves enhanced cardiac filling in diastole followed by a more forceful systolic contraction.
2. Neurohormonal influence governs the second mechanism that involves normal ventricular filling with a subsequent forceful ejection and emptying during systole.
3. The third mechanism comes from training adaptations that expand blood volume and reduce resistance to blood flow in peripheral tissues. ${ }^{9,14,36}$

## Enhanced Diastolic Filling

Any factor that increases venous return or slows the heart produces greater ventricular filling (preload) during the cardiac cycle s diastolic phase. An increase in end-diastolic volume stretches myocardial fibers and initiates a powerful ejection stroke during contraction. This ejects the normal stroke volume plus any additional blood that entered the ventricles in diastole and stretched the myocardium.

Two researchers, German physiologist Otto Frank (1865 1944; investigated the isometric and isotonic contractile behavior of the heart) and British physiologist Ernest Henry Starling (1866 1927; first to use the term hormone), described the relationship between contractile force and the resting length
of the heart s muscle fibers. This phenomenon, termed the Frank-Starling law of the heart (also known as Starling s law or the Frank-Starling mechanism) remains a fundamental principle of cardiac architecture. It states: Within physiological limits, the force of contraction is directly proportional to the initial length of the muscle fiber. The principle operates during the cardiac cycle and applies to all of the heart s chambers. For years, physiologists taught that the Frank-Starling mechanism provided the modus operandi for all stroke volume increases during exercise. They believed that venous return in exercise facilitated greater cardiac filling. The preload stretched the ventricles in diastole to produce a more forceful ejection stroke. More than likely, this response pattern for stroke volume operates during the transition from rest to exercise or as a person moves from an upright to recumbent position. Enhanced diastolic filling also occurs in swimming because the body s horizontal position optimizes venous return. A more optimal arrangement of the sarcomere s myofilaments as the muscle fiber stretches enhances contractility.

The data in Table 17.2 show the effect of body position on circulatory dynamics. The horizontal position produces the largest and most stable cardiac output and stroke volume. Stroke volume remains near maximum in this position at rest and increases only slightly during exercise. In contrast, in the upright position, gravity counters the return flow of blood to the heart (decreased preload) to diminish stroke volume and cardiac output. During upright exercise of increasing intensity, stroke volume approaches the maximum stroke volume in the supine position.

## Greater Systolic Emptying

In most modes of upright exercise, the heart does not fill to increase cardiac volume to the extent it does in the recumbent position. Despite research inconsistencies on this topic, the progressive increase in stroke volume during graded upright exercise in both children and adults most likely results from the combined effect of enhanced diastolic filling and more complete emptying during systole. ${ }^{5,12,23,33}$ Greater systolic ejection occurs despite increased resistance to blood flow in the arterial circuit from exercise-induced elevation of systolic blood pressure (afterload).

TABLE 17.2 The Effect of Body Position on Cardiac Output, Stroke Volume, and Heart Rate at Rest and During Exercise in Physically Active Subjects ${ }^{\text {a }}$

|  | Rest |  | Moderate Exercise |  | Strenuous Exercise |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Supine | Upright | Supine | Upright | Supine | Upright |
| Cardiac output, $\mathrm{L} \cdot \mathrm{m}^{-1}$ | 9.2 | 6.6 | 19.0 | 16.9 | 26.3 | 24.5 |
| Stroke volume, mL | 141 | 103 | 163 | 149 | 164 | 155 |
| Heart rate, beats $\cdot \mathrm{m}^{-1}$ | 65 | 64 | 115 | 112 | 160 | 159 |
| Oxygen consumption, $\mathrm{L} \cdot \mathrm{m}^{-1}$ | 345 | 384 | 1769 | 1864 | 3364 | 3387 |

Data from Beveg rd, ., et al.: Circulatory studies in well-trained athletes at rest and during heavy exercise, with special reference to stroke volume and the influence of body position. Acta Physiol Scand, 57:26, 1963.

Enhanced systolic ejection, with or without increased end-diastolic volume, occurs because the ventricles always contain a functional residual blood volume. At rest in the upright position, approximately $40 \%$ or 50 to 70 mL of the total end-diastolic blood volume remains in the left ventricle following systole. Catecholamine release in exercise enhances myocardial contractile force to augment stroke power and facilitate systolic emptying.

Endurance training likely increases compliance of the left ventricle (reduced cardiac stiffness) to facilitate acceptance of blood in the diastolic phase of the cardiac cycle. ${ }^{19,42}$ Whether endurance training enhances the myocardium s innate contractile state remains unclear. ${ }^{10,24}$ If this adaptation does occur, it too would contribute to a larger stroke volume effect.

## Cardiovascular Drift: Reduced Stroke Volume and Increased Heart Rate During Prolonged Exercise

Submaximal exercise performed for more than 15 minutes (particularly in the heat and accompanied with increases in core body temperature) produces progressive water loss through sweating and a fluid shift from plasma to tissues. A rise in core temperature also redistributes blood to the periphery for body cooling. Concurrently, the progressive fall in plasma volume decreases central venous cardiac filling pressure (preload) to reduce stroke volume. A reduced stroke volume initiates a compensatory heart rate increase to maintain a nearly constant cardiac output as exercise progresses and body temperature increases. ${ }^{8}$ The term cardiovascular drift describes the gradual time-dependent downward drift in several cardiovascular responses, most notably stroke volume (with concomitant heart rate increase) during prolonged steady-rate exercise, particularly during high ambient temperatures. ${ }^{15}$ Under these circumstances, a person must exercise at lower intensity than if these cardiovascular dynamics (cardiovascular drift) did not occur. ${ }^{3,11,41}$

One explanation for cardiovascular drift suggests the effects of a progressive increase in cutaneous blood flow as core temperature rises in prolonged exercise. Increased redistribution of blood to the periphery for heat dissipation increases the skin s venous volume, ultimately reducing ventricular filling pressure and stroke volume. An alternative explanation exists for the stroke volume decline during cardiovascular drift in prolonged exercise. Figure 17.2 shows responses for heart rate, stroke volume, and cutaneous blood flow (CBF) for seven active men during 60 minutes of submaximal cycling in a thermoneutral environment. In one exercise trial, the men received a placebo; at the onset of exercise in the other trial, they received a small dose of a $\beta_{1}$-adrenoceptor blocker (atenolol) to prevent the heart rate increase that normally occurs after 15 minutes of exercise (i.e., cardiovascular drift). Fifteen minutes into exercise, heart rate and stroke volume remained similar during control and $\beta_{1}$-adrenoceptor blockade conditions. From 15 to 55 minutes during the control trial, a $13 \%$ decrease in stroke volume accompanied an $11 \%$ heart rate increase, while cutaneous blood flow showed no increase


## Control $\lceil$ Adrenoceptor-blockade

Figure 17.2 Stroke volume, heart rate, and cutaneous blood flow (CBF) during 60 minutes of exercise under $\beta_{1}$-adrenoceptor blockade and control treatments. (From Fritzsche RG, et al. Stroke volume decline during prolonged exercise is influenced by the increase in heart rate. J Appl Physiol 1999;86:799.)
from 20 to 60 minutes of exercise. In contrast, from 15 to 55 minutes of exercise under blockade conditions (when atenolol prevented a heart rate increase), stroke volume failed to decline compared with control conditions despite similar levels of cutaneous blood flow in both trials. Cardiac output
remained stable at about $16 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ under both conditions. These observations confirm that a decline in stroke volume during prolonged exercise in a thermoneutral environment primarily results from increased exercise heart rate and not increased cutaneous blood flow as body temperature rises. ${ }^{2}$ The progressive increase in heart rate with cardiovascular drift during exercise more than likely decreases end-diastolic volume, thus reducing the heart s stroke volume.

## INTEGRATIVE QUESTION

Increasing the bloods hemoglobin concentration increases $V O_{2 \max }$ during maximal exercise at sea level. According to this effect, what component of the Fick equation limits maximal oxygen consumption? Discuss.

## CARDIAC OUTPUT DISTRIBUTION

Blood generally flows to tissues in proportion to their metabolic demands. Blood flow to the kidneys, skin, and splanchnic areas also varies with the metabolic demands of skeletal muscle during physical activity.

## Blood Flow at Rest

At rest in a thermoneutral environment, the typical 5-L cardiac output generally distributes in the proportions shown in Figure 17.3A. Approximately one fifth of the cardiac output
flows to muscle tissue, while the digestive tract, liver, spleen, brain, and kidneys receive major portions of the remaining blood.

## Redistribution of Blood Flow During Exercise

Figure 17.3B illustrates the percentage distribution of cardiac output during strenuous exercise. Environmental stress, level of fatigue, and exercise mode and intensity affect regional blood flow, but the major portion of the exercise cardiac output diverts to active muscles. Approximately 4 to 7 mL of blood flows each minute to each 100 g of muscle at rest. This flow increases steadily in graded exercise, with active muscle receiving up to 50 to 75 mL per 100 g of tissue each minute of maximal exertion. ${ }^{28,29}$ Blood flow within active muscle is highly regulated. The greatest quantity of blood diverts to the oxidative portions of the muscle at the expense of those areas with high glycolytic capacity. ${ }^{4,16}$ Thus, peak blood flow in a small portion of active quadriceps muscle reaches values as high as 300 to $400 \mathrm{~mL} 100 \mathrm{~g}^{-1} \cdot \mathrm{~min}^{-1} .{ }^{26}$ During big muscle activities such as running and cycling at maximum intensity, muscle blood flow accounts for 80 to $85 \%$ of the total cardiac output. ${ }^{30}$

Blood flow to muscle also increases disproportionately relative to flow to other tissues. For trained individuals, blood redistribution-from one organ to another by vasoconstriction in one and vasodilation in the other-begins in the anticipatory period just prior to exercise. ${ }^{4}$ Two factors, hormonal vascular regulation and local metabolic conditions, cause blood to route through active muscles from areas that temporarily tolerate


## A Distribution of cardiac output during rest

B Distribution of cardiac output during strenuous exercise
Figure 17.3 (A) Relative distribution of cardiac output during rest and (B) strenuous endurance exercise. The number in parentheses indicates percentage of the total cardiac output. The large absolute mass of muscle tissue at rest receives about the same quantity of blood as the much smaller kidneys. In strenuous exercise, approximately $84 \%$ of the cardiac output diverts to the active musculature.
compromised blood flow. ${ }^{20}$ Blood redistribution among specific tissues occurs primarily during high-intensity exercise. For example, blood flow to the skin, the primary heatexchange organ, increases during light and moderate exercise in response to the rise in core temperature. ${ }^{13,43}$ During nearmaximal effort, the skin restricts its blood flow, redirecting it to active muscle, even in a hot environment. ${ }^{27}$

The kidneys and splanchnic tissues consume only 10 to $25 \%$ of the oxygen in their normal blood supply. These tissues tolerate a considerably reduced blood flow before oxygen demand exceeds supply and compromises function. ${ }^{22}$ Renal blood flow can decrease up to four-fifths of the blood supply at rest. Increased oxygen extraction from the available blood supply generally maintains the oxygen needs of tissues with reduced blood flow. The visceral organs sustain a substantially reduced blood supply for more than 1 hour during intense exercise. Redistribution of 2 to 3 L of blood away from these tissues frees up to 600 mL of oxygen each minute for use by active muscles. Sustained blood flow reduction to the liver and kidneys, however, may contribute to fatigue often experienced during prolonged submaximal exercise. Regular aerobic training diminishes the typical vasoconstrictor response to splanchnic and renal tissues with exercise. ${ }^{20,34}$ An improved capacity to maintain blood flow to the liver and kidneys during sustained exercise probably contributes to improved endurance.

## Blood Flow to the Heart and Brain

Heart and brain tissue cannot tolerate a compromised blood supply (see Fig. 17.3). At rest, the myocardium normally uses approximately $75 \%$ of the oxygen in the blood flowing through the coronary circulation. With such a limited margin of reserve, increased coronary blood flow primarily supplies the increased myocardial oxygen needs with exercise. Thus, a four- to fivefold increase in coronary circulation accompanies a similar increase in myocardial work during exercise; this amounts to a blood flow of about $1 \mathrm{~L} \cdot \min { }^{1}$ during maximum exercise. Cerebral blood flow also increases during exercise by approximately 25 to $30 \%$ compared with the resting flow. ${ }^{37}$

## CARDIAC OUTPUT AND OXYGEN TRANSPORT

## Rest

Arterial blood carries about 200 mL of oxygen per liter in a person with a normal hemoglobin level (see Chapter 13). If resting cardiac output each minute equals 5 L , potentially 1000 mL of oxygen becomes available to the body ( 5 L blood $\times 200 \mathrm{~mL} \mathrm{O} \mathrm{O}_{2}$ ). The resting oxygen consumption typically averages 250 to $300 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$, allowing 750 mL of oxygen to return unused to the heart. This does not reflect an unnecessary waste of blood flow. Instead, the extra oxygen circulating above the resting requirement represents oxygen in reservea margin of safety when a tissue s metabolism rapidly and dramatically increases.

## Exercise

A healthy, young adult with a maximum heart rate of $200 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ and stroke volume of $80 \mathrm{~mL}(0.08 \mathrm{~L})$ generates a maximum cardiac output of $16 \mathrm{~L} \cdot \mathrm{~min}^{-1}(200 \times$ $0.08 \mathrm{~L})$. Even during maximal exercise, hemoglobin saturation with oxygen remains nearly complete, so each liter of arterial blood carries about 200 mL of oxygen. Consequently, 3200 mL of oxygen circulates each minute via a $16-\mathrm{L}$ cardiac output ( $16 \mathrm{~L} \times 200 \mathrm{~mL} \mathrm{O}_{2} \cdot \mathrm{~L}^{-1}$ ). Even if the tissues could extract all of the oxygen from all of the blood as it traveled throughout the body, the $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ could not exceed 3200 mL . This represents a purely theoretical value because the oxygen demands of some tissues such as the brain and skin do not increase markedly with exercise, yet they still require a substantial blood supply.

Based on the preceding example, increasing the heart s stroke volume from 80 to 200 mL while maintaining the maximum heart rate at $200 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ dramatically increases maximum cardiac output to $40 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. This represents a 2.5 -fold increase in oxygen circulated during each minute of exercise (from 3200 to 8000 mL ). An increase in maximum cardiac output clearly produces a proportionate increase in capacity to circulate oxygen and profoundly impacts an individuals maximal oxygen consumption.

## Close Association Between Maximum Cardiac Output and $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$

Figure 17.4 depicts the close relationship between maximum cardiac output and the capacity for a high level of aerobic exercise metabolism. $\dot{\mathrm{V}}{ }_{2 \text { max }}$ values represent averages for the


Figure 17.4 Relationship between maximal cardiac output and maximal oxygen consumption $\left(\mathrm{VO}_{2 \max }\right)$ in endurance trained and untrained individuals. Maximal cardiac output relates to $\mathrm{VO}_{2 \text { max }}$ in the ratio of about 6:1.
sedentary person to the elite endurance athlete. An unmistakable association exists-a low maximal oxygen consumption corresponds closely with a low maximum cardiac output, whereas a 5- or $6-\mathrm{L} \dot{\mathrm{V}} \mathrm{O}_{2 \max }$ invariably accompanies a 30 - to 40-L cardiac output.

A 5- to 6-L increase in blood flow accompanies each 1-L increase in oxygen consumption above the resting value; this relationship remains essentially unchanged regardless of exercise mode over a broad range of dynamic exercises. High levels of maximal oxygen consumption and cardiac output provide distinguishing characteristics for preadolescent and adult endurance athletes. An almost proportionate increase in maximum cardiac output accompanies increases in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ with endurance training (see Chapter 21).

## Cardiac Output Differences Among Men and Women and Children

Cardiac output and oxygen consumption remain linearly related during graded exercise for boys and girls and men and women. However, teenage and adult females generally exercise at any level of submaximal oxygen consumption with a 5 to $10 \%$ larger cardiac output than males. ${ }^{25}$ The $10 \%$ lower hemoglobin concentration in women than in men explains this apparent gender difference in submaximal cardiac output. A proportionate increase in submaximal cardiac output compensates for this minor decrease in the blood s oxygen-carrying capacity.

Higher heart rates in children than in adults during submaximal treadmill and cycle ergometer exercise do not fully compensate for their smaller stroke volume. This produces a smaller cardiac output for children at a given submaximal exercise oxygen consumption. ${ }^{32,38}$ As such, the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference expands to meet the oxygen requirements. The biologic significance remains unclear of this difference in central circulatory function between children and adults. Comparisons of cardiac responses (stroke volume, aortic peak blood flow velocity, systolic ejection time) between prepubertal children and adults fail to demonstrate any age-related exercise impairment. ${ }^{31}$

## Oxygen Extraction: The $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ Difference

If only blood flow increased tissue oxygen supply, then increasing cardiac output from $5 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at rest to $100 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ during maximum exercise would achieve the 20 -fold oxygen consumption increase common among endurance athletes. Fortunately, strenuous exercise does not require this large cardiac output. Instead, hemoglobin releases a considerable quantity of its reserve oxygen from blood that perfuses active tissues. Exercise oxygen consumption increases by two mechanisms:

1. Increased total quantity of blood pumped by the heart (i.e., increased cardiac output)
2. Greater use of the already existing relatively large quantity of oxygen carried by the blood (i.e., expanded $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference)

Rearranging the Fick equation summarizes the important relationship among cardiac output, $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference, and $\dot{\mathrm{V}} \mathrm{O}_{2}$ as follows:

$$
\dot{\mathrm{V}} \mathrm{O}_{2}=\dot{\mathrm{Q}} \times \mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2} \text { difference }
$$

## $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ Difference During Rest

Resting metabolism uses about 5 mL of oxygen from the 20 mL of oxygen in each deciliter of arterial blood ( 50 mL per liter) that passes through the tissue capillaries. This represents an $a-\bar{v} \mathrm{O}_{2}$ difference of 5 mL of oxygen per deciliter of blood perfusing the tissue-capillary bed. Thus, 15 mL of oxygen or $75 \%$ of the blood s original oxygen load still remains bound to hemoglobin.

## INTEGRATIVE QUESTION

Explain how factors that influence the $a-\bar{v} O_{2}$ difference in maximal exercise account for the specificity of $\mathrm{VO}_{2 \text { max }}$ improvement with different modes of aerobic training,

## $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ Difference During Exercise

Figure 17.5 shows a progressive expansion of the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference from rest to maximal exercise for physically active men. A similar pattern emerges for women, except that arterial


[^32]Figure 17.5 Changes in $a-\bar{v} \mathrm{O}_{2}$ difference from rest to maximal exercise in physically active men.

## IN A PRACTICAL SENSE

## Predicting $\mathrm{VO}_{2 \text { max }}$ Using Running and Swimming

The 1.5 -mile run and the 12 -minute swim provide reliable and valid tests to predict $\dot{V}_{2 \text { max }}$. The tests are effective for mass testing in schools and with recreational runners and swimmers. We do not recommend these tests for unconditioned beginners, men over age 40 and women over age 50 without proper medical clearance, symptomatic individuals, and those with known disease or coronary heart disease risk factors. The swim test assumes relatively high-level swimming skill.

| TABLE | 1 Predicted $\mathrm{VO}_{2 \text { max }}$ ( $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \min ^{-1}$ ) for 1.5-mile Walk-Run Test (min:s) |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Time | $\stackrel{\mathrm{V}}{ } \mathrm{O}_{2 \text { max }}$ | Time | $\dot{\mathrm{V}}^{2}{ }_{\text {2max }}$ | Time | $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ |
| 6:10 | 80.0 | 10:30 | 48.6 | 14:50 | 34.0 |
| 6:20 | 79.0 | 10:40 | 48.0 | 15:00 | 33.6 |
| 6:30 | 77.9 | 10:50 | 47.4 | 15:10 | 33.1 |
| 6:40 | 76.7 | 11:00 | 46.6 | 15:20 | 32.7 |
| 6:50 | 75.5 | 11:10 | 45.8 | 15:30 | 32.2 |
| 7:00 | 74.0 | 11:20 | 45.1 | 15:40 | 31.8 |
| 7:10 | 72.6 | 11:30 | 44.4 | 15:50 | 31.4 |
| 7:20 | 71.3 | 11:40 | 43.7 | 16:00 | 30.9 |
| 7:30 | 69.9 | 11:50 | 43.2 | 16:10 | 30.5 |
| 7:40 | 68.3 | 12:00 | 42.3 | 16:20 | 30.2 |
| 7:50 | 66.8 | 12:10 | 41.7 | 16:30 | 29.8 |
| 8:00 | 65.2 | 12:20 | 41.0 | 16:40 | 29.5 |
| 8:10 | 63.9 | 12:30 | 40.4 | 16:50 | 29.1 |
| 8:20 | 62.5 | 12:40 | 39.8 | 17:00 | 28.9 |
| 8:30 | 61.2 | 12:50 | 39.2 | 17:10 | 28.5 |
| 8:40 | 60.2 | 13:00 | 38.6 | 17:20 | 28.3 |
| 8:50 | 59.1 | 13:10 | 38.1 | 17:30 | 28.0 |
| 9:00 | 58.1 | 13:20 | 37.8 | 17:40 | 27.7 |
| 9:10 | 56.9 | 13:30 | 37.2 | 17:50 | 27.4 |
| 9:20 | 55.9 | 13:40 | 36.8 | 18:00 | 27.1 |
| 9:30 | 54.7 | 13:50 | 36.3 | 18:10 | 26.8 |
| 9:40 | 53.5 | 14:00 | 35.9 | 18:20 | 26.6 |
| 9:50 | 52.3 | 14:10 | 35.5 | 18:30 | 26.3 |
| 10:00 | 51.1 | 14:20 | 35.1 | 18:40 | 26.0 |
| 10:10 | 50.4 | 14:30 | 34.7 | 18:50 | 25.7 |
| 10:20 | 49.5 | 14:40 | 34.3 | 19:00 | 25.4 |

## THE TESTS

## 1.5-Mile Walk Run Test

1. Testing site: a school track (each lap measures $1 / 4$ mile) or premeasured 1.5 -mile course.
2. Warm up for at least 3 minutes (easy stretching, mild calisthenics, and jogging in place).
3. Walk, jog, and/or run the 1.5 -mile distance as fast as possible.
4. Record run time in min:s.
5. Allow a 5-minute cool-down upon test completion.
6. Refer to TABLE 1 for predicting $\dot{\mathrm{VO}}_{2 \text { max }}$.

Cooper KH. A means of assessing maximal oxygen uptake. JAMA 1968;203:201.

## 12-Minute Swim Test

Individuals swim as far as possible in 12 minutes, with distance measured in yards. Differences in skill level, swim conditioning, and body composition greatly affect oxygen consumption (exercise economy), thus making $\dot{\mathrm{VO}}_{2 \text { max }}$ predictions less valid than those based on walking and running (with smaller variation in economy).

1. Warm up for at least 3 minutes with easy stretching and mild calisthenics followed by several laps of easy swimming.
2. Swim as many laps as possible in 12 minutes; paced swimming is preferred to intervals of fast and slow effort.
3. Determine total distance swam in yards; if the test ends in the middle of the pool, estimate distance; find swim fitness and $\dot{\mathrm{VO}}_{2 \text { max }}$ prediction in TABLE 2.

Cooper KH. The aerobics program for total well-being. New York: Bantam Books, 1982.

| TABLE $2 \quad 1$ | 12-Minute Swim Test Fitness Categories (Age 1829 Years) |  |  |
| :---: | :---: | :---: | :---: |
| Distance (YD) | Fitness Category | Estimated $\mathrm{VO}_{2 \text { max }}$ ( $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ ) |  |
|  |  | Males | Females |
| $\geq 700$ | Excellent | >52.5 | >41.0 |
| 500700 | Good | 46.552 .4 | 37.040 .0 |
| 400500 | Average | 42.546 .4 | 33.036 .9 |
| 200400 | Fair | 36.542 .4 | 29.032 .9 |
| $\leq 200$ | Poor | 33.036 .4 | 23.628 .9 |

## FOCUS ON RESEARCH

## Consequences of Stopping Endurance Exercise Training


#### Abstract

Coyle EF, et al. Time course of loss of adaptations after stopping prolonged intense endurance training. J Appl Physiol 1984;57:1857.


> Considerable research frames the understanding of physiologic and metabolic adaptations to diverse types of exercise training. Much less attention has focused on what happens when training stops. A clearer picture of the dynamics of detraining would clarify the importance of regular physical activity and the consequences of adapting a sedentary lifestyle.

Coyle and colleagues studied cessation of exercise training in seven highly trained runners or cyclists. Subjects had trained for 10 to 12 months at least 5 days weekly for 60 minutes daily at 70 to $80 \%$ of $\mathrm{VO}_{2 \text { max }}$. Fifty-seven sedentary subjects served as controls. Testing included muscle biopsies on the last day of training and on days 12, 21, 56, and 84 of detraining. Physiologic variables included oxygen consumption $\left(\dot{\mathrm{VO}}_{2}\right)$, cardiac output $(\mathrm{Q})$, heart rate (HR), stroke volume (SV), and arteriovenous oxygen difference (a- $\overline{\mathrm{v}} \mathrm{O}_{2}$ diff) during 15 minutes of exercise at $75 \%$ of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ and at $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$. Muscle biopsies included the left gastrocnemius for runners and vastus lateralis for cyclists.

Except for exercise during testing in the detraining period, subjects limited their physical activity to the minimal level required in their sedentary jobs and walked less than 500 m daily at a slow pace. The inset figure shows average changes in physiologic variables at each testing session. $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ decreased in all subjects, declining $7 \%$ below training levels after 12 days, $14 \%$ after 56 days, and $16 \%$ by day 84. Maximal values for $\mathrm{Q}, \mathrm{SV}$, and $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff each declined while HR increased during detraining. Stroke volume decreased by $11 \%$ during the first 12 days and stabilized at $86 \%$ of the trained value by day 56 . No further decreases occurred in the final 4 weeks. The increase in $\mathrm{HR}_{\max }$ partially compensated for the decrease in $\mathrm{SV}_{\max }$. Thus, $\mathrm{Q}_{\max }$
declined by only $8 \%$ during the initial 3 weeks of detraining, with an average total decrease of $10 \%$ over 84 days.

The muscle biopsy data also indicated impressive detraining changes. Citrate synthase and succinate dehydrogenase, key enzymes in aerobic respiration, declined in parallel to reach their lowest levels at day 56. Detraining did not affect myoglobin levels or muscle capillarization. Because capillary density did not change with detraining, the researchers attributed the decreased oxygen extraction (a- $\overline{\mathrm{V}} \mathrm{O}_{2}$ diff $_{\max }$ ) to reduced mitochondrial oxidative capacity reflected in depressed respiratory enzyme levels.

This study confirmed that decreases in maximum SV (central factor) and maximum a- $\overline{\mathrm{v}} \mathrm{O}_{2}$ diff (peripheral factor) contributed to reductions in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ with detraining. The results thus support the age-old dictum, use it or lose it.


Average changes in maximum heart rate $\left(\mathrm{HR}_{\max }\right)$, stroke volume, arteriovenous oxygen differences ( $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff max ), cardiac output, and $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ over 84 days of detraining.
oxygen content averages 5 to $10 \%$ lower because of lower hemoglobin concentrations. The figure includes values for oxygen content of arterial and mixed-venous blood during different exercise oxygen consumptions. Arterial blood oxygen content varies little from its value of $20 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ at rest throughout the full exercise intensity range. In contrast, mixedvenous oxygen content varies between 12 and $15 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ during rest to a low of 2 to $4 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ during maximal exercise. The difference between arterial and mixed-venous blood oxygen content at any discrete time (i.e., the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference) represents oxygen extraction from arterial blood as it circulates throughout the body.

The progressive expansion of the $a-\bar{v} \mathrm{O}_{2}$ difference to at least three times resting value results from a reduced venous oxygen content, which in maximal exercise approaches $20 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ in active muscle (all oxygen extracted). The oxygen content of a true mixed-venous sample from the pulmonary artery rarely falls below 2 to $4 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ because blood returning from active tissues mixes with oxy-gen-rich venous blood from metabolically less active regions.

Figure 17.5 also shows that the capacity of each deciliter of arterial blood to carry oxygen (yellow line) increases during exercise from an increased concentration of red blood cells (hemoconcentration). Hemoconcentration results from
the progressive movement of fluid from the plasma to the interstitial space with (1) increases in capillary hydrostatic pressure as blood pressure rises and (2) metabolic byproducts of exercise metabolism that osmotically draw fluid into tissue spaces from the plasma.

## Factors Affecting the Exercise $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ Difference

Central and peripheral factors interact to increase oxygen extraction in active tissue during exercise. Diverting a large portion of the cardiac output to active musculature influences the magnitude of the $a-\bar{v} \mathrm{O}_{2}$ difference in maximal exercise. Some tissues temporarily decrease their blood supply during exercise by redistributing blood to make more oxygen available for muscle metabolism. Exercise training redirects a greater portion of the central circulation to active muscle.

Increases in skeletal muscle microcirculation also increase tissue oxygen extraction. Muscle biopsy specimens from the quadriceps femor muscle show a relatively large ratio of capillaries to muscle fibers in individuals who exhibit large $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ differences during intense exercise. An increased capillary-to-fiber ratio reflects a positive endurance training adaptation that enlarges the interface for nutrient and metabolic gas exchange during exercise. Individual muscle cells ability to generate energy aerobically represents another important factor that governs oxygen extraction capacity.

Increasing the size and number of mitochondria and augmenting aerobic enzyme activity improve a muscle s metabolic capacity in exercise. Local vascular and metabolic improvements within muscle ultimately enhance its capacity to produce ATP aerobically. ${ }^{40}$ These local training adaptations translate to an increased oxygen extraction capacity.

INTEGRATIVE QUESTION
Present a physiologic rationale to support the relative importance of (1) central circulatory factors and (2) peripheral factors residing within the active muscle mass in limiting $V O_{2 \text { max }}$.

## CARDIOVASCULAR ADJUSTMENTS TO UPPER-BODY EXERCISE

Upper-body exercise creates different metabolic and cardiovascular responses than lower-body exercise that requires predominantly leg musculature activation.

## Maximal Oxygen Consumption

The highest oxygen consumption during arm exercise averages 20 to $30 \%$ lower than leg exercise. Similarly, arm exercise produces lower maximal values for heart rate and pulmonary ventilation. In large part, these differences relate to the relatively smaller muscle mass activated in arm exercise.


## Arms Legs

Figure 17.6 Arm exercise requires greater oxygen consumption than leg exercise at any submaximal power output throughout the comparison range. The largest differences occur during intense exercise. Data represent averages for men and women. (From Laboratory of Applied Physiology, Queens College, Flushing, NY.)

## Submaximal Oxygen Consumption

Submaximal exercise reverses the pattern for oxygen consumption between upper- and lower-body exercise observed in maximal effort. Figure 17.6 shows higher oxygen consumption during arm exercise at all submaximal power outputs. The small differences during light exercise become progressively larger as intensity increases. Two factors produce this additional oxygen cost at higher intensities of arm exercise:

1. Lower mechanical efficiency in upper-body exercise from the additional cost of static muscle actions that do not contribute to external work
2. Recruitment of additional musculature to stabilize the torso during arm exercise

## Physiologic Response

Any level of submaximal oxygen consumption (or percentage $\mathrm{VO}_{2 \max }$ ) or power output with upper-body exercise provides greater physiologic strain than lower-body exercise. Specifically, submaximal arm exercise produces higher heart rates, pulmonary ventilations, and perceptions of effort than comparable intensities of leg exercise. This also applies to blood pressure during arm versus leg exercise (see Chapter 15).

The elevated heart rate response in submaximal arm exercise probably results from two factors:

1. Greater feed-forward stimulation from the brain s central command to the medullary control center
2. Increased feedback stimulation to the medulla from peripheral receptors in active tissue

Upper-body exercise places a greater strain (i.e., greater force per unit muscle, greater percentage of maximum capacity, and more metabolic byproducts) on the relatively smaller upper-body musculature for any submaximum exercise level. Added strain augments peripheral feedback to the medulla, which increases heart rate and blood pressure. A smaller muscle mass reduces input to the medullary cardiovascular control center from the motor cortex, with less peripheral feedback from the smaller upper-body muscle mass, which may account for the lower maximum heart rate in upper-body exercise.

Implications. A standard submaximal exercise load (power output or oxygen consumption) with the upper body produces greater metabolic and physiologic strain than leg exercise. For this reason, exercise prescriptions based on running and bicycling do not apply to arm exercise. Low correlations often emerge between $\dot{\mathrm{V}}_{2 \text { max }}$ in arm versus leg exercise, so one should not expect to accurately predict aerobic capacity for arm exercise based on a test that uses the legs and vice versa. ${ }^{6,17}$ This lack of strong association between the two exercise modes further amplifies the specificity concept applied to aerobic fitness.

## Summary

1. Cardiac output reflects the functional capacity of the cardiovascular system. Heart rate and stroke volume determine the heart s output capacity expressed as follows: Cardiac output $=$ Heart rate $\times$ Stroke volume.
2. Several invasive and noninvasive methods measure cardiac output in humans. Each has specific advantages and disadvantages during exercise.
3. Cardiac output increases proportionally with exercise intensity, starting from approximately $5 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at rest to a maximum of 20 to $25 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ in untrained, college-aged men and 35 to $40 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ in elite male endurance athletes.
4. The large stroke volumes of endurance athletes explain the difference in maximum cardiac outputs compared with untrained persons.
5. Stroke volume increases during upright exercise from the interaction between greater ventricular filling during diastole and more complete emptying during systole.
6. Sympathetic hormones augment systolic ejection by increasing stroke power during systole.
7. Blood flows to specific tissues in proportion to their metabolic activity.
8. The kidneys and splanchnic regions temporarily compromise blood supply to redistribute blood to exercising muscles; most of the cardiac output diverts to active muscles during exercise.
9. Maximum cardiac output and maximum $a-\bar{v} \mathrm{O}_{2}$ difference determine maximal oxygen consumption. A large cardiac output clearly differentiates endurance athletes from untrained counterparts.
10. Arm exercise generates $25 \%$ lower $\dot{\mathrm{V}}_{2 \text { max }}$ than leg exercise.
11. Any level of submaximal oxygen consumption (or $\% \dot{\mathrm{~V}} \mathrm{O}_{2 \max }$ ) or power output with upper-body exercise provides greater physiologic strain than lowerbody exercise.


References are available online at http://thepoint.lww.com/mkk7e.


## CHAPTER 18

## Skeletal Muscle: Structure and Function

## CHAPTER OBJECTIVES

> Outline the levels of organization in the gross structure of skeletal muscle
> List four major protein constituents of skeletal muscle and their functions
> Draw and label the structures that characterize a skeletal muscle fibers striated appearance under the light microscope at low magnification
> Describe the different arrangements of individual muscle fibers along the long axis of skeletal muscle and explain the biomechanical advantage of each
> Draw and label a skeletal muscle fibers ultrastructural components
> Summarize the salient features of the sliding filament model of muscle contraction
$>$ Outline the sequence of chemical and mechanical events during skeletal muscle excitation contraction coupling and relaxation
> Discuss the function of the triad and T-tubule system
> Contrast slow-twitch and fast-twitch (including subdivisions) muscle fiber characteristics
> Outline the distribution patterns of muscle fiber type among diverse groups of elite athletes

- Discuss modifications in muscle fibers and fiber types with specific exercise training

The following sections present the architectural organization of skeletal muscle with focus on its gross and microscopic structures. We also highlight the sequence of chemical and mechanical events in muscle action and relaxation, including differences in muscle fiber characteristics among sedentary and elite athletes in different sports.

## GROSS STRUCTURE OF SKELETAL MUSCLE

Each of the bodys more than 660 skeletal muscles contains various wrappings of fibrous connective tissue. Figure 18.1 illustrates the gross structural details of a skeletal muscle and its thousands of cylindrical cells called fibers. These long, slender, multinucleated fibers (whose number probably remains largely fixed by the second trimester of fetal development) lie parallel to each other, with the force of action directed along the fibers long axis. Individual fiber length varies from a few millimeters in the eye muscles to nearly 30 cm in the large antigravity muscles of the leg (with width reaching 0.15 mm ).

## Levels of Organization

The endomysium, a fine layer of connective tissue, wraps each muscle fiber and separates it from neighboring fibers. Another layer of connective tissue, the perimysium, surrounds a bundle of up to 150 fibers called a fasciculus. A fascia of fibrous connective tissue, the epimysium, surrounds the entire muscle. This protective sheath tapers at its distal and proximal ends as it blends into and joins the intramuscular tissue sheaths to form the dense, strong connective tissue of the tendons. The tendons connect both ends of the muscle to the periosteum, the bones outermost covering.

The tissues of the tendon intermesh with the collagenous fibers within the bone. This forms a powerful link between muscle and bone that remains inseparable except during severe stress when it can sever or literally pull away from the bone. When the tendon attaches to the end of a long bone, the bone adapts by enlarging at that end to create a more stable union. Depending on bone size, the term tubercle, tuberosity, or trochanter describes this overgrowth.

The force of muscle action transmits directly from the connective tissue harness to the tendons, which then pull on the bone at the point of attachment. The forces exerted on the tendinous attachments under muscular exertion range from 20 to 50 newtons ( 197 to 492 kg ) per $\mathrm{cm}^{2}$ of cross-sectional areaforces often much larger than the muscle fibers themselves can tolerate. The muscles origin refers to the location where the tendon joins a relatively stable skeletal part, generally the proximal or fixed end of the lever system or that nearest the bodys midline; the point of distal muscle attachment to the moving bone represents the insertion. Figure 18.1B illustrates the tendons ultrastructural details. The protein collagen comprises about $70 \%$ of the tendons dry mass.

Beneath the endomysium and surrounding each muscle fiber lies the sarcolemma, a thin, elastic membrane that encloses the fibers cellular contents. It contains a plasma
membrane (plasmalemma) and a basement membrane. The plasma membrane, a bilayer lipid structure, conducts the electrochemical wave of depolarization over the surface of the muscle fiber. The membrane also insulates one fiber from another during depolarization. The basement membrane contains proteins and strands of collagen fibrils that fuse with the collagenous fibers in the outer covering of the tendon. Between the basement and plasma membranes lie myogenic stem cells known as satellite cells, the normally quiescent myoblasts that function in regenerative cellular growth, possible adaptations to exercise training, and recovery from injury. ${ }^{18,36,47}$ Incorporation of satellite cell nuclei into existing muscle fibers seems a likely explanation for exercise-induced muscle fiber hypertrophy. ${ }^{20}$

The fibers aqueous protoplasm ( sarcoplasm) contains enzymes, fat and glycogen particles, nuclei (approximately 250 per mm of fiber length) that contain the genes, mitochondria, and other specialized organelles. Figure 18.1C details the sarcoplasmic reticulum, an extensive longitudinal latticelike network of tubular channels and vesicles. This highly specialized system provides structural integrity to the cell. It allows the wave of depolarization to spread rapidly from the fibers outer surface to its inner environment through the Ttubule system to initiate muscle action. The sarcoplasmic reticulum that surrounds each myofibril contains biologic pumps that take up $\mathrm{Ca}{ }^{2+}$ from the fibers sarcoplasm. This produces a calcium concentration gradient between the sarcoplasmic reticulum (higher $\left[\mathrm{Ca}^{2+}\right]$ ) and the sarcoplasm surrounding the filaments (lower $\left[\mathrm{Ca}^{2+}\right]$ ).

## Chemical Composition

Water constitutes approximately $75 \%$ of skeletal muscle mass while protein composes $20 \%$. The remaining $5 \%$ contains salts and other substances, including high-energy phosphates; urea; lactate; the minerals calcium, magnesium, and phosphorus; various enzymes; sodium, potassium, and chloride ions; amino acids, fats, and carbohydrates. Myosin (approximately $60 \%$ of muscle protein), actin, and tropomyosin are the most abundant muscle proteins. Each 100 g of muscle tissue contains about 700 mg of the oxygen-binding, conjugated protein myoglobin.

## Blood Supply

Arteries and veins that lie parallel to individual muscle fibers provide a rich vascular supply. These vessels divide into numerous arterioles, capillaries, and venules to form a vast network in and around the endomysium. Extensive branching of blood vessels ensures each muscle fiber an adequate oxygenated blood supply from the arterial system and rapid removal of carbon dioxide in the venous circulation. During the most intense exercise for an elite endurance athlete, the muscles oxygen uptake increases nearly 70 times to approximately 11 mL per 100 g per minute or a total muscle $\dot{\mathrm{VO}}_{2}$ of $3400 \mathrm{~mL} \cdot \min ^{1}$. The local vascular bed delivers large quantities of blood through active tissues to accommodate this
 of skeletal muscle structures and arrangement of connective tissue wrappings. A. Endomysium covers individual fibers. Perimysium surrounds groups of fibers called fasciculi, and epimysium wraps the entire muscle in a sheath of connective tissue. The sarcolemma, a thin, elastic membrane, covers the surface of each muscle fiber. B. Details of tendon structure. The microfibril forms from five parallel tropocollagen molecules that unite to form fibrils and then collagen fibers. An endotendon encloses a bundle of fibers, and an epitendon sheath, known as a fascicle, surrounds a group of endotendons. The fascicles combine into a tendon that becomes surrounded by its own sheath, the paratendon ( $\mu \mathrm{m}=$ $10^{-6} \mathrm{~m} ; \mathrm{nm}=10^{-9} \mathrm{~m}$ ). C. Cross section of the sarcoplasmic reticulum and T-tubule system that surrounds the myofibrils. Note the close contact of the mitochondria and network of intracellular membranes and tubules.

## FOCUS ON RESEARCH

## A Tissue Responsive to Regular Exercise


#### Abstract

Tipton CM, et al. Influence of exercise on strength of medial collateral knee ligaments of dogs. Am J Physiol 1970;218:894.


$>$ Prior to 1970, evidence showing that exercise improved connective tissue strength came from studies with laboratory mice and rats. The pioneering study by Tipton and colleagues provides direct experimental evidence of exercise training benefits on the strength of either intact or surgically repaired medial collateral ligaments of dogs. These data provide an important framework to justify the current commonly accepted therapeutic use of exercisenot immobilizationto rehabilitate soft tissue injury and surgical repair.

Tipton studied more than 100 male mongrel dogs (age $>1$ year) to answer several questions, including the effects of 6 weeks of increased or decreased physical activity (exercise training, immobilization, normal cage activity, and sham surgical procedures) on intact knee ligament strength. A second goal described the effects of variations in exercise training, immobilization, and normal cage activity on the strength of surgically repaired ligaments, a question of primary interest in sports medicine.

In all evaluations of ligament strength, the plantaris, gastrocnemius, and extensor digitorum longus muscles were removed (along with the joints surrounding soft tissue), leaving the capsule and ligaments intact. A testing apparatus held the bone capsule bone preparation as the tibia was pulled from the femur at a constant speed of $0.25 \mathrm{~mm} \cdot \mathrm{~s}{ }^{1}$. The force ( kg ) necessary to separate the ligament from the bonethe stress strain measurementrepresented the separation force (SF). The SF-to-body mass ratio (SFR) adjusted for the animals differences in body mass. Exercise training included treadmill running at different speeds, grades, and durations for a maximum of 6 days weekly for 6 weeks; 3 days of endurance and 3 days of wind sprint training. By week 3, the animals were exercising 1 hour daily.

Immobilization involved fixing one of the hind legs with the knee flexed at 60 to 80 with pins placed through the femur and one through the tibia. A fast-drying plaster cast then secured the leg. Surgical repair of the left medial collateral ligament exposed the ligament by making an incision through its superficial and deep portions along the
joint line while preserving the blood supply. Two steelwire sutures reattached the ligament at its original location. Sham operations (no ligament cut) included pin insertion, skin incision, ligament exposure, and wound closure.

Figure 1 shows that strength of the intact knee ligament relates to the animals level of physical activity, with immobilization (group 2) producing the least strength (lowest SF) and 6 weeks of treadmill running (group 4) yielding the greatest strength. Strength of the surgically repaired ligaments (Fig. 2) depended on the time interval before sacrifice and the amount of activity performed by the experimental leg. Location of separation also varied between intact and repaired ligaments; intact ligaments separated from their tibial attachment, while surgically repaired ligaments invariably separated at the repair site.

The data indicated that physical activity markedly improves ligament strength. These important findings verified that connective tissue responds to the mechanical stress of exercise.

Tiptons innovative work provided the first experimental verification that ligaments from immobilized legs were weaker and weighed less than ligaments from normal


## $\square$ Group $1 \square$ Group $2 \square$ Group $3 \square$ Group 4

Figure 1 Physical activity levels and strength (separation force) of intact knee ligaments. Group 1, sham procedure on left leg; group 2, decreased physical activity by leg immobilization; group 3, normal cage activity; group 4, increased physical activity with exercise training. Group 2 data are significantly lower than other group means.

## FOCUS ON RESEARCH Contined


control and exercised legs. The study also cast doubt on the efficacy of immobilization following ligament surgery. Instead, the study supports exercise training as a first line of rehabilitation following soft tissue surgery.

Figure 2 Strength of surgically repaired ligaments related to duration of immobilization and physical activity level.
oxygen requirement. Blood flow distribution fluctuates in rhythmic activities such as running, swimming, or cycling. It decreases during the muscles contraction phase and increases during relaxation to provide a milking action that moves blood through the muscles and propels it back to the heart. The rapid dilation of previously dormant capillaries complements the pulsatile blood flow. Between 200 and 500 capillaries deliver blood to each square millimeter of active muscle cross section, with up to four capillaries directly contacting each fiber. In endurance athletes, five to seven capillaries surround each fiber; this adaptation ensures greater local blood flow and adequate tissue oxygenation when needed (see next section).

Physical activities that require straining present a somewhat different picture for muscle blood flow. When a muscle generates about $60 \%$ of its force-generating capacity for several seconds, elevated intramuscular pressure occludes local blood flow during the contraction. With a sustained highforce contraction, the intramuscular high-energy phosphates and glycolytic anaerobic reactions provide the main energy source for muscular effort.

## Capillarization

The trained muscles increased capillary-to-muscle fiber ratio helps to explain improved exercise capacity with endurance training. ${ }^{2,6}$ An enhanced capillary microcirculation expedites the removal of heat and metabolic byproducts from active tissues in addition to facilitating delivery of oxygen, nutrients, and hormones. Electron microscopy reveals the total number of capillaries per muscle (and capillaries per
$\mathrm{mm}^{2}$ of muscle tissue) averages about $40 \%$ higher in en-durance-trained athletes than untrained counterparts. This almost equals the $41 \%$ difference in $\dot{\mathrm{V}}_{2 \text { max }}$ between the two groups. A positive association also exists between $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ and average number of muscle capillaries. ${ }^{38}$ Enhanced vascularization on the capillary level proves particularly beneficial during exercise that requires a high level of steady-rate aerobic metabolism. Vascular stretch and shear stress on the vessel walls from increased blood flow during exercise stimulate capillary development with intense aerobic training. ${ }^{29}$

## SKELETAL MUSCLE ULTRASTRUCTURE

Electron microscopy, X-ray diffraction, histochemical staining, helium neon laser diffraction, in vitro motility assays, and optical tweezer technologies (see Chapter 33) reveal the microscopic anatomy (ultrastructure) of skeletal muscle. Figure 18.2 shows the different levels of gross and subcellular organization within a skeletal muscle fiber. A single multinucleated muscle fiber contains smaller functional units that lie parallel to the fibers long axis. These fibrils or myofibrils, approximately $1 \mu \mathrm{~m}(1 \mu \mathrm{~m}=1 / 1000 \mathrm{~mm})$ in diameter, contain even smaller subunits called filaments or myofilaments that lie parallel to the long axis of the myofibril. The myofilaments chiefly consist of ordered assemblages of the proteins actin and myosin that account for about $85 \%$ of the myofibrillar complex. Twelve to 15 other proteins either serve a structural function or affect protein filament interaction during muscle action. Examples include (1) tropomyosin, located along the actin filaments (5\%); (2) troponin (which consists of troponin ${ }^{1}$, T, C) located in the actin filaments

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Figure 18.2 - Gross and subcellular microscopic organization of skeletal muscle. A. Individual fibers constitute the whole muscle. B. Fibers consist of myofibrils with actin and myosin protein filament subdivisions. C-F. Details of a single sarcomere with the actin and myosin filaments, a microscopic view of the sarcomere (note the two Z lines), and a cross-sectional view of the filaments.


Figure 18.3 - Top. Structural position of the filaments in a sarcomere. The $Z$ line bounds a sarcomere at both ends. Bottom. Detailed view of a sarcomere, including the proteins listed in Table 18.1.
(3\%); (3) $\alpha$-actinin, distributed in the Z-band region (7\%); (4) $\beta$-actinin, found in the actin filaments (1\%); (5) M protein, identified in the region of the M lines within the sarcomere (less than $1 \%$ ); and (5) C protein (less than $1 \%$ ), which contributes to the sarcomere's structural integrity.

## The Sarcomere

At low magnification, the alternating light and dark bands along the length of the skeletal muscle fiber give it a characteristic striated appearance. Figure 18.3 (top) illustrates the structural details of this cross-striation pattern within a myofibril. The I band represents the lighter area and the darker zone the $A$ band. The $Z$ line bisects the I band and adheres to the sarcolemma; it provides stability to the entire structure. Optical properties denote the specific bands. When polarized light passes through the I band, it moves at the same velocity in all directions (isotropic). Light passing through the A band
does not scatter equally (anisotropic). The letter $Z$ indicates "between" (from German, zwischenscheibe); the letter M (mittelscheibe) denotes "middle"; and the letter H (hellerscheibe) denotes "a clear disk or zone."

The sarcomere consists of the basic repeating unit between two $Z$ lines. This structural entity comprises the functional unit of a muscle fiber. The actin and bipolar myosin filaments within the sarcomere contribute primarily to the mechanics of muscle contraction. Sarcomeres lie in series, and their filaments have a parallel configuration within a given fiber. In the resting state, the length of each sarcomere averages $2.5 \mu \mathrm{~m}$. Thus, a myofibril $15-\mathrm{mm}$ long contains about 6000 sarcomeres joined end to end. The length of the sarcomere largely determines a muscle's functional properties.

The position of thin actin and thicker myosin proteins in the sarcomere creates an interdigitating overlap of the two filaments. The center of the A band contains the $H$ zone, a region of lower optical density because this area has no actin filaments.

## TABLE 18.1 Twelve Proteins Associated with a Muscle Fibers Sarcomere and Their Proposed Functions

| Structure | Protein | Function |
| :---: | :---: | :---: |
| Thin filament | Actin | The main protein of actin that interacts with myosin during excitation contraction coupling |
|  | Tropomyosin | Transduces the conformational change of the troponin complex to actin |
|  | Troponin | Binds $\mathrm{Ca}^{2+}$ and affects tropomyosin; represents the switch that transforms the $\mathrm{Ca}{ }^{2+}$ signal into a molecular signal that induces crossbridge cycling |
|  | Nebulin | Present adjacent to actin and believed to control the number of actin monomers joined to each other in a thin filament |
| Thick filament C stripes | Myosin | Splits ATP and is responsible for the power stroke of the myosin head |
|  | C protein | Holds the myosin thick filaments in a regular array; may hold the H protein of adjacent thick filaments at an even distance during force generation; may also control the number of myosin molecules in a thick filament |
| M line | M protein | Helps hold thick filaments in a regular array |
|  | Myomesin | Provides a strong anchoring point for the protein titin |
|  | M-CK | Provides ATP from phosphocreatine; located proximal to the myosin heads |
| Z line | $\alpha$-actinin | Holds the thin filaments in place spatially |
|  | Desmin | Forms the connection between adjacent Z lines from different myofibrils; helps to keep the sarcomeres in register so they maintain their striated appearance |
| Elastic filament | Titin | Helps keep the thick filament centered between two Z lines during contraction; believed to control the number of myosin molecules contained in the thick filament |

The $M$ band bisects the central portion of the H zone, which delineates the sarcomeres center. The M band consists of the protein structures that support the arrangement of the myosin filaments. Figure 18.3 (bottom) shows a detailed view of a sarcomere and Table 18.1 lists proposed functions of a sarcomeres proteins.

## MUSCLE FIBER ALIGNMENT

The long axis of a muscle determines the arrangement of individual fibers from an imaginary line drawn through the origin and insertion, or the fiber angle relative to the force-generating axis. Differences in sarcomere alignment and length strongly affect a muscles force- and power-generating capacity (Fig. 18.4). Fusiform, or spindle-shaped, fibers run parallel to the muscles long axis (e.g., biceps brachii) and taper at the tendinous attachment. In contrast, pennate, or fan-shaped, fibers fasciculi (bundles of fibers) lie at an oblique pennation angle that varies up to 30 . In the soleus muscle, for example, the pennation angle averages 25 , whereas for the vastus medialis it equals 5 ; the sartorius muscle has no angle of pennation. Of functional significance, the degree of pennation directly impacts sarcomere number per cross-sectional muscle area (no fibers run full muscle length). In essence, pennation allows individual muscle fibers to remain short while the overall muscle may attain considerable length. A fusiform fiber has no pennation, so the fibers cross-sectional area represents the true anatomic cross section. In pennate muscle, the complex arrangement of connective tissue, tendons, and relatively short fibers creates a larger cross-sectional area than fusiform fibers because more sarcomeres pack into a given volume of muscle. The term physiologic cross-sectional area (PCSA) refers to the total cross-sectional areas of all fibers
within a particular muscle. An unusually large pennation angle of 30 results in only a $13 \%$ loss in an individual fibers force capacity; this makes for a huge increase in total fiber packing ability. ${ }^{30,40}$ Thus, pennation per se allows packing of a large number of fibers into a smaller cross-sectional area. Pennate muscles tend to generate considerable power. The bottom of Figure 18.4 illustrates the effect of pennation on fiber packing and force-generating capacity.

The fibers in a fusiform muscle run parallel to the muscles long axis. In this case, fiber length equals muscle length, and a fibers force generation transmits directly to the tendon. This arrangement facilitates rapid muscle shortening. A unipennate fiber arrangement, where muscle fibers lie at an oblique angle to the tendon, produces a larger effective cross-sectional area than in fusiform muscle. Other factors being equal, muscles with greater pennation, although slower in contractile velocity, generate greater force and power than fusiform muscles because more sarcomeres contribute to the muscle action. A bipennate muscle has two sets of fibers that lie obliquely on both sides of a common tendon (e.g., gastrocnemius and rectus femoris muscles). The multipennate deltoid muscle contains more than two sets of fibers that converge at different angles and insert directly into tendons at both their ends. Pennate muscles differ from fusiform fibers in three ways:

1. They generally contain shorter fibers.
2. They possess more individual fibers.
3. They exhibit less range of motion.

## Complex Fusiform Arrangement

The complex parallel muscle (series-fibered muscle) features individual fibers that run parallel to the muscles line of pull. Unlike the simple fusiform arrangement where a fiber runs the


Figure 18.4 Top. Various forms of fiber arrangement in human skeletal muscle. Bottom. Force development in a fusiform muscle with no angle of pennation ( $=0$ ) and when $=30$. A 30 angle of pennation produces a $13 \%$ loss of each fibers maximum force on the tendon, solely based on muscle mechanics. Pennation angle increases the number of fibers that pack into a given volume of muscle (bottom right). Muscle mass and the contractile capacity relate proportionately for a given muscle in comparisons among individuals. Because of the effect of pennation angle, it does not necessarily follow that muscle mass per se relates to an equivalent tension output among different muscle groups. (Modified from Lieber RL. Skeletal muscle structure, function, and plasticity. The physiological basis of rehabilitation. 3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2009.)
entire muscle length, the complex parallel arrangement features muscle fibers that terminate in the muscles midbelly and taper to interact with the connective tissue matrix and/or adjacent muscle fibers. This arrangement enables parallel packing of relatively short fibers within a long muscle (e.g., the $50-\mathrm{cm}$ long sartorius). This structural specialization with diverse intrafascicular terminations also creates lateral tensioneither through connective tissue into tendon or through adjacent and series fibers into connective tissueat-various points along the fibers surface.

INTEGRATIVE QUESTION
List the advantages of a skeletal muscle organ system composed of muscles whose fibers vary in architectural design.

## Fiber Length Muscle Length Ratio

The ratio of individual fiber length to a muscles total length usually varies between 0.2 and 0.6 . This means that individual fibers in the longest muscles such as the upper and lower limbs remain significantly shorter than the muscles overall length. Figure 18.5 (left) illustrates the architectural properties of four lower limb muscles. On average, quadriceps muscle fibers maintain pennation angles that average 4.6 , a PCSA of approximately $21.7 \mathrm{~cm}^{2}$, with a fiber length that averages about 68 mm . This contrasts with the biceps femoris (hamstring) muscle with relatively long fibers ( 111 mm ) and an intermediate PCSA ( $11.7 \mathrm{~cm}^{2}$ ). Quadriceps muscles exhibit approximately $50 \%$ greater force capacity than hamstrings, whose design allows for rapid shortening. These design differences suggest susceptibility of the hamstrings to tearing as often


Figure 18.5 Left. Muscle architectural properties in the lower limb. The quadriceps and plantar flexors exhibit high force production from their low fiber length to muscle length (FL:ML) ratios and relatively large physiologic cross-sectional areas (PCSA). In contrast, the hamstrings and dorsiflexor muscles show architecture designed for high contractile velocity from their relatively high FL:ML and long FL. Right. Hypothetical pennate (short fibers) muscles and fusiform (long fibers) muscles of the same length and same amount of contractile machinery. The muscle force muscle length curve (A) shows the fusiform muscle with a longer working range and lower maximum force output than the pennate muscle. Lower force capacity (dorsiflexors and hamstrings) occurs because for a given change in muscle length, the individual sarcomeres lengthen less, with the change in muscle length distributed over more sarcomeres. A greater PCSA (C) produces a greater force output (quadriceps and plantar flexors). The muscle force muscle velocity curve (B) shows that the fusiform muscle with longer fibers exhibits higher contractile velocity but a lower maximum force output. (Modified from Lieber RL. Skeletal muscle structure, function, and plasticity. The physiological basis of rehabilitation. 3rd edition. Baltimore: Lippincott Williams \& Wilkins, 2009.)
occurs in sprint running when an abrupt force output imbalance occurs during maximal activation between the quadriceps and hamstrings. Part of the imbalance may be from a strength deficit between the hamstrings and quadriceps, which predisposes individuals to recurrent hamstring injuries and discomfort. ${ }^{10}$ The hamstring-to-quadriceps strength ratio typically computes by dividing the maximal knee flexor (hamstring) moment by the maximal knee extensor (quadriceps) moment. ${ }^{1}$ Specific exercise training at preset velocities designed to improve this ratio serves as an integral part of functional rehabilitation of hamstring-to-quadriceps deficits. ${ }^{8,14,31}$

Figure 18.5 (right inset, $A$ and $B$ ) shows the generalized muscle force muscle length and muscle force muscle velocity relationships for fusiform and pennate muscles with the same amount of contractile protein and identical muscle fiber type. In this hypothetical example, the muscle force muscle length curve for fusiform muscle shows a longer working range and lower maximum force output because of longer individual fibers and a smaller PCSA (Fig. 18.5C). The opposite occurs for pennate muscle with shorter fibers and larger PCSAthese fibers generate about double the force of fusiform muscles. For the muscle force muscle velocity
curve, the fusiform muscle with longer fibers exhibits a higher contractile velocity but lower force output capacity.

## ACTIN MYOSIN ORIENTATION

Thousands of myosin filaments lie along the line of actin filaments in a muscle fiber. Figure 18.6A illustrates the sarcomeres actin myosin orientation at resting length; Figure 18.6B shows the hexagonal arrangement of myosin and actin filaments. Myosin filaments consist of bundles of molecules with polypeptide tails and globular heads. Actin filaments have two twisted chains of monomers bound by tropomyosin polypeptide chains. Six relatively thin actin filaments, each about 50 in diameter and $1 \mu \mathrm{~m}$ long, encircle the thicker myosin filament ( $150 \quad$ in diameter and $1.5 \mu \mathrm{~m}$ long). This represents an extremely impressive substructural configuration. For example, a myofibril $1 \mu \mathrm{~m}$ in diameter contains approximately 450 thick filaments in the sarcomeres center and 900 thin filaments at each end. A muscle fiber $100 \mu \mathrm{~m}$ in diameter and 1 cm long contains approximately 8000 myofibrils; each myofibril consists of 4500 sarcomeres on average. In a single fiber, this arrangement consists of approximately 16 billion thick filaments and 64 billion thin filaments.

Figure 18.7 illustrates the spatial orientation of various components of contractile filaments. Projections, or crossbridges, spiral around the myosin filament in the region of overlap of the actin and myosin filaments. The crossbridges


## AResting sarcomere



Figure 18.6 A. Ultrastructure of actin myosin orientation within a resting sarcomere. B. Representation of electron micrograph through a cross section of myofibrils in a single muscle fiber. Note the hexagonal orientation of the smaller actin and larger myosin filaments, including crossbridges that extend from a thick to thin filament.


Figure 18.7 Details of the thick and thin protein filaments including tropomyosin, troponin complex, and M bridge. The globular heads of the myosin contain myosin ATPase; this active head frees the energy from ATP for muscle action.
repeat at intervals of approximately 450 along the filament. Globular lollipop-like myosin heads extend perpendicularly to latch onto the thinner double-twisted actin strands to create structural and functional links between myofilaments. The unique feature of myosins two heads concerns their opposite orientation at the ends of the thick filament. ATP hydrolysis activates the two heads, placing them in an optimal orientation to bind actins active sites, thus pulling the thin filaments and Z lines of the sarcomere toward the middle.

Tropomyosin and troponin are two other important constituents of the actin helical structure. These proteins regulate the make-and-break contacts between the myofilaments during muscle action. Tropomyosin distributes along the length of the actin filament in a groove formed by the double helix. Tropomyosin inhibits actin and myosin interaction (coupling) and thus prevents their permanent bonding. Troponin and its three-subunit proteins embedded at fairly regular intervals along the actin strands exhibit a high affinity for calcium ions $\left(\mathrm{Ca}^{2+}\right)$, a mineral that plays a crucial role in muscle action and fatigue. ${ }^{27}$ For example, $\mathrm{Ca}^{2+}$ and troponin trigger myofibrils to interact and slide past each other. During muscle fiber stimulation, troponin molecules undergo a conformational change that tugs on tropomyosin protein strands. Tropomyosin then moves deeper into the groove between the two actin strands, uncovering actins active sites so muscle action proceeds. Muscle fatigue relates to considerable reductions in $\mathrm{Ca}^{2+}$ concentration in the transverse tubules during intense exercise, in addition to intrinsic alterations in the contractile apparatus and sarcoplasmic reticulum function. ${ }^{7,46}$

The M band consists of transversely and longitudinally oriented proteins that maintain myosin filament orientation within a sarcomere. As Figure 18.7 illustrates, the perpendicularly oriented M bridges connect with six adjacent myosin filaments in a hexagonal pattern.


Figure 18.8 The complex highway tubule system within a muscle fiber.

An exciting area of muscle biochemistry, physiology, and mechanics involves the study of cytoskeletal proteins and structures that serve as an intermediate intracellular filament system. ${ }^{33}$ The intracellular cytoskeleton provides (1) structural integrity in the inactive muscle cell, (2) lateral force transmission to adjacent sarcomeres through interaction with actomyosin during muscle action, and (3) connections to the cells surface membrane. A better understanding of the role of the cytoskeleton, its diverse proteins, and the myofibrillar lattice structure should enhance current understanding of muscle action, including processes in muscle injury, repair, and overload.

## Intracellular Tubule Systems

Figure 18.8 illustrates the complex tubule system within a muscle fiber. The lateral end of each tubule channel terminates in a saclike vesicle that stores $\mathrm{Ca}^{2+}$. Another network of tubulesthe transverse tubule system, or T-tubule systemruns perpendicular to the myofibril. T tubules lie between the most lateral part of two sarcoplasmic channels; vesicles of these structures abut the T tubule. The term triad describes this repeating pattern of two vesicles and a T tubule in each Z line region. Each sarcomere contains two triads, with the pattern repeated regularly along the myofibrils length.

The T tubules pass through the fiber and open externally from the inside of the muscle cell. The triad and T-tubule system function as a microtransportation network by spreading
the action potential (wave of depolarization) from the fibers outer membrane inward to deeper cell regions. Propagation of the action potential stimulates the triad sacs to release $\mathrm{Ca}^{2+}$, which diffuses a short distance to activate the actin filaments. Muscle action begins when myosin filament crossbridges momentarily attach to active sites on the actin filaments. When electrical excitation ceases, $\mathrm{Ca}^{2+}$ concentration in cytoplasm decreases; this relates to muscle relaxation. To some extent, propagating an action potential (and countering fatigue in exercise) depends on maintaining continued steep gradients of $\mathrm{Na}^{+}$and $\mathrm{K}^{+}$across the sarcolemma. Decreased chemical gradients of these electrolytes (from a reduction in $\mathrm{Na}^{+} / \mathrm{K}^{+}$pump activity) severely affect muscle fiber excitability and consequent contractile performance of active muscles. ${ }^{32}$

## CHEMICAL AND MECHANICAL EVENTS DURING MUSCLE ACTION AND RELAXATION

Electron microscopy, X-ray diffraction, and biochemical methods have unraveled many secrets of cellular structure and kinetics, providing testable hypotheses about chemical and mechanical events during muscle activation and relaxation. Many pieces of the puzzle remain unanswered, but considerable evidence supports the sliding-filament model to explain muscle contraction. Proposed some 60 years ago to explain the
molecular movements that underlie muscle action, the model still fits nicely with the ever-expanding details about muscle ultrastructure and function. ${ }^{19}$

## Mechanics of Muscle Action: The Sliding-Filament Model

In the early 1950s, two British biologists, unrelated and working independently, Hugh Huxley (1924 ) and Sir Andrew Fielding Huxley (1917; 1963 cowinner of the Nobel Prize in Physiology or Medicine for work on ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane) proposed a sliding-filament model of muscle contraction. In 1957, A. Huxley extended the theory to include specifics of crossbridge behavior. ${ }^{20,21}$ The theory proposes that a muscle shortens or lengthens because the thick and thin filaments slide past each other without changing length. The myosin crossbridges, which cyclically attach, rotate, and detach from the actin filaments with energy from ATP hydrolysis, provide the molecular motor to drive fiber shortening. ${ }^{13,37}$ This produces a major conformational change in relative size within the sarcomeres zones and bands and produces a force at the Z bands. Figure 18.9 shows that the thin actin filaments move past the myosin myofilaments (translate over them by a preset amount) and into the A band region during shortening (and move out during the lengthening or relaxation phase). ${ }^{4,5}$ Thus, the major structural rearrangement during shortening occurs in the region of the I band. This band decreases as the Z bands are pulled toward the center of each sarcomere. No change


Figure 18.9 Structural rearrangement of actin and myosin filaments at rest (sarcomere length, $4.0 \mu \mathrm{~m}$ ) and during muscle shortening (contracted sarcomere length, $2.7 \mu \mathrm{~m}$ ).
occurs in the width of the A band, although the H zone can disappear when the actin filaments make contact at the sarcomere center. A static (isometric) muscle action generates force, but the fibers length remains unchanged; the relative spacing of I band and A band remains constant. In this case, the same molecular groups interact continuously. The A band widens in an eccentric action as the fiber lengthens during force generation.

## Mechanical Action of Crossbridges

Myosin plays both an enzymatic and structural role in muscle action. The globular head of the myosin crossbridge, which contains an actin-activated ATPase in its actin-binding site, provides the mechanical power stroke for the actin and myosin filaments to slide past each other. The cyclic, oscillating to-and-fro motion of the crossbridges (powered by ATP hydrolysis) moves like oars knifing through water (Fig. 18.10). But unlike oars, crossbridges do not all move synchronously. If they did, the muscle action would produce a series of uneven actions instead of finely graded, smoothly modulated movements and force outputs. During shortening, each crossbridge undergoes many repeated but independent cycles of asynchronous movement.

At any one time, approximately $50 \%$ of the crossbridges make contact with the actin filaments to form the protein complex actomyosin, which exhibits contractile properties. The remaining crossbridges move through other positions in their vibrating cycle. Figure 18.10 shows that each crossbridge action contributes only a small longitudinal displacement to the filaments full sliding action. The process resembles the movement of a person climbing a rope. The arms and legs represent the crossbridges. Climbing progresses by first reaching with the arms; then grabbing, pulling, and breaking contact while the legs extend; and then repeating this procedure throughout the climb as the person traverses from one point to the next point and so on.

The biochemical technique of in vitro motility assays quantifies the behavior of actin and myosin molecules. ${ }^{27}$ Careful experimentation has determined that myosin elicits a 1 to 10 piconewton ( $\mathrm{pN} ; 10^{2} \mathrm{~N}$ ) force, in which myosin movement ranges from 1 to 20 nanometers ( $\mathrm{nm} ; 10^{9} \mathrm{~m}$ ) over a 5 ms interval. Four elegant research tools determine the chemical and mechanical properties of the actomyosin complex.

1. Microneedles. A glass needle placed in contact with myosin molecules and an actin filament records the mechanical movements of the molecules. Researchers then deduce the forces produced by the myosin heads as they slide along the actin strand. ${ }^{22}$
2. Optical tweezers. This technique interfaces powerful laser technology with a microscope to isolate individual molecules and measure molecular movement one molecule at a time. ${ }^{12}$
3. Atomic force microscope. The displacement and forces from a probe (with actin and myosin molecules attached) interfaced with a specialized


Figure 18.10 Top. Relative positioning of actin and myosin filaments during crossbridge oscillation. Bottom. The action of each crossbridge contributes a small displacement of movement. For clarity, we show only one actin strand.
microscope yields quantitative data about actin myosin interaction. ${ }^{25}$
4. Fluorescent probes. Light-emitting probes quantify the kinetics of molecular binding and release between myosin and actin and how ATP releases energy when degraded to ADP and inorganic phosphate. ${ }^{15}$ The technique reveals how actin rotates slightly as it moves along myosin ${ }^{39}$ and how the myosin heads function during their power stroke. ${ }^{49}$

## INTEGRATIVE QUESTION

Discuss the meaning of molecular motor to describe how the myofilament crossbridges contribute to muscle fiber action.

## Sarcomere LengthIsometric Tension Curve in an Isolated Fiber

Figure 18.11 displays interactions between actin and myosin during isometric tension development in an isolated skeletal muscle preparation. British and Swedish researchers developed this length tension curve approximately 45 years ago by electrically stimulating a single frog muscle fiber ( 8 mm long and $75 \mu \mathrm{~m}$ in diameter) and plotting maximum tension output at selected muscle sarcomere lengths. ${ }^{11,17}$ The length of the sarcomere along the horizontal axis ranged from $1.6 \mu \mathrm{~m}$ at maximum overlap of the actin filaments (approximately $70 \%$ of maximum tension) to $3.6 \mu \mathrm{~m}$ when fully relaxed. Note that the crest of the upward curve for tension occurred at a sarcomere length between 2.0 and $2.25 \mu \mathrm{~m}$; this length for maximal tension represents the region of maximum actin and myosin filament interaction. Interestingly, the difference of $0.2 \mu \mathrm{~m}$ at this part of the curve equals precisely the width of the region where no change takes place in actin myosin interaction. The curve shifts downward when the sarcomere stretches beyond $2.2 \mu \mathrm{~m}$, thus indicating a decline in peak tension. This decline occurs from reduced overlap between actin and myosin filaments; less overlap produces less crossbridge interaction and diminished active tension development. The fiber fails to develop tension at the maximum point of stretch of $3.65 \mu \mathrm{~m}$ (maximum actin filament length, $2.0 \mu \mathrm{~m}$; maximum myosin filament length, $1.65 \mu \mathrm{~m}$ ). Crossbridge interaction cannot take place at a sarcomere length of $3.65 \mu \mathrm{~m}$ and above.

## Sarcomere Length/sometric Tension Curve in Human Muscle Fibers in Vivo

An elegant procedure determines the range over which sarcomeres in intact human muscle operate on their length tension curve. Figure 18.12 illustrates sarcomere action during different wrist position angles in patients who undergo surgery to correct chronic lateral epicondylitis (tennis elbow). The researchers compared the length tension characteristics of an animal preparation (Fig. 18.11) with those of human muscle in vivo. Figure 18.12 (top right) depicts the intraoperative helium neon laser to quantify sarcomere length. The laser, positioned beneath the lateral end of the extensor carpi radialis brevis muscle (ECRB), quantified sarcomere lengths at three different wrist positions: (1) full flexion to increase sarcomere length, (2) neutral, and (3) full extension to decrease sarcomere length. The top left of Figure 18.12 shows the laser diffraction pattern for computing sarcomere length. Biopsy specimens from the same muscle verified the laser determinations. An electron micrograph displayed behind the


Figure 18.11 Relationship between tension and sarcomere length in skeletal muscle during an isometric muscle action. Optimal sarcomere length (i.e., the one with the greatest interaction between actin and myosin filaments) occurs between 2.0 and $2.25 \mu \mathrm{~m}$ (light blue vertical band). Tension output decreases steadily as sarcomere length increases beyond the optimal length. Note the amount of overlap in the actin and myosin filaments at various regions of the tension length curve and how tension output varies at different sarcomere lengths. Thin filament thickness equals $1.0 \mu \mathrm{~m}$; thick filament thickness, $1.6 \mu \mathrm{~m}$.
length tension curve shows the actin and myosin filaments and A and I bands from a muscle biopsy sample. In this experiment, actin filament length equaled $1.30 \mu \mathrm{~m}$, while the myosin filaments were $1.66 \mu \mathrm{~m}$ long. The thicker blue portion for the plateau and downward parts of the curve show the operating range of the ECRB sarcomeres during both passive (2.6 $3.4 \mu \mathrm{~m}$ ) and active ( $2.443 .33 \mu \mathrm{~m}$ ) muscle actions. These data objectify the intrinsic relation between sarcomere length and muscle fiber force capacity (length tension curve) measured in vivo in human muscle.

## Link Between Actin, Myosin, and ATP

The interaction and movement of the protein filaments during muscle action require that myosin crossbridges continually undergo oscillatory movements by combining, detaching, and recombining with new sites along the actin strands (or the same sites in a static action). The myosin crossbridges detach from the actin filament when ATP molecules join the actomyosin complex. The myosin crossbridge in this chemical reaction returns to its original state ready to bind to a new active actin site. The dissociation of actomyosin occurs as follows:

$$
\text { Actomyosin }+ \text { ATP } \rightarrow \text { Actin }+ \text { Myosin-ATP }
$$

Energy from ATP hydrolysis transduces into mechanical force when ADP and inorganic phosphate end products form. One of the reacting sites on the globular head of the myosin
crossbridge binds to an actin reactive site. The other myosin active site serves as the actin-activated enzyme myofibrillar adenosine triphosphatase (myosin ATPase). This enzyme splits ATP to yield energy for muscle action. The rate of ATP splitting is relatively slow if myosin and actin remain apart; when they join, myosin ATPase reaction rates increase substantially. Energy released from ATP splitting activates the crossbridges, causing them to oscillate. This course of energy transfer produces a conformational change in myosins globular head so it interacts with the appropriate actin molecule. The actin filament slides forward from conformational change at multiple points of contact between myosin and actin.

Prior to muscle action, the elongated, pear-shaped, flexible myosin head literally bends around the energy-carrying ATP molecule and cocks like a spring. The myosin then interacts with the adjacent actin filament, splits a phosphate from ATP, and releases its stored mechanical energy as it straightens. This forces the sliding motion that generates muscle tension. The actin and myosin filaments slide past each other at speeds up to $15 \mu \mathrm{~m} \cdot \mathrm{~s}{ }^{13}{ }^{3}$

## Excitation Contraction Coupling

Excitation contraction coupling represents the physiologic mechanism whereby an electrical discharge at the muscle initiates chemical events at the cell surface, releasing intracellular


Figure 18.12 Changes in the length tension curve for sarcomeres in vivo during human wrist flexion and extension. The top insets illustrate the helium neon laser procedure (and view of the illumination prism) used during the surgery. The electron micrograph depicted behind the length tension curve shows the actin and myosin filaments and the A and I bands from biopsy samples of the extensor carpi radialis brevis muscle to verify sarcomere lengths. The thickened blue portion of a hypothetical length tension curve represents sarcomere length change during wrist flexion (causing sarcomere length increase) and wrist extension (causing sarcomere length decrease). The numbers over the curve represent the inflection points based on the measured filament lengths. (Modified from Lieber RL, et al. In vivo measurement of human wrist extensor muscle sarcomere length changes. J Neurophysiol 1994;71:874. Illustration of the experimental procedure, including the example of the laser diffraction pattern and electron micrograph courtesy of Dr. R. L. Lieber, Professor of Orthopaedics and Bioengineering, Biomedical Sciences Group, Muscle Physiology Laboratory, University of California, San Diego, CA; muscle.ucsd.edu/more_html/ bibliography.shtml)
$\mathrm{Ca}^{2+}$ and ultimately causing muscle action. Intracellular $\mathrm{Ca}^{2+}$ plays an intimate role in regulating a muscle fibers contractile and metabolic activity. $\mathrm{Ca}^{2+}$ concentration within a nonactive muscle fiber remains relatively low compared with the extracellular fluid that bathes the cell. Muscle fiber stimulation causes an immediate, small increase in intracellular $\mathrm{Ca}^{2+}$, which precedes contractile activity. Cellular $\mathrm{Ca}^{2+}$
increases when the action potential at the transverse tubules causes $\mathrm{Ca}^{2+}$ release from lateral sacs of the sarcoplasmic reticulum. The inhibitory action of troponin (prevents actin myosin interaction) rapidly dissipates when $\mathrm{Ca}^{2+}$ binds with this and other proteins in the actin filaments. In a sense, the muscle turns on for action.

$$
\text { Actin }+ \text { Myosin ATPase } \rightarrow \text { Actomyosin }+ \text { ATPase }
$$

Joining the active sites on actin and myosin activates myosin ATPase to split ATP. The energy generated causes myosin crossbridge movement to produce muscle tension.

$$
\text { Actomyosin ATP } \rightarrow \text { Actomyosin }+ \text { ADP }+\mathrm{Pi}+\text { Energy }
$$

The crossbridge uncouples from actin when ATP binds to the myosin crossbridge. Coupling and uncoupling continue when $\mathrm{Ca}^{2+}$ concentration remains high enough to inhibit the troponin tropomyosin system. When neural stimulation ceases, $\mathrm{Ca}^{2+}$ moves back into the lateral sacs of the sarcoplasmic reticulum. This restores the inhibitory action of troponin tropomyosin, and actin and myosin stay apart provided ATP concentration remains adequate. In rigor mortis, the muscles stiffen and become rigid soon after death because the cell no longer contains ATP. Without ATP, the myosin crossbridges and actin remain attached and do not separate. Figure 18.13 illustrates the interaction between actin and myosin filaments, $\mathrm{Ca}^{2+}$, and ATP in both a relaxed and shortened muscle fiber.

Stimulation produces a threefold rise in $\mathrm{Ca}^{2+}$ concentration and accompanying increase in the action potential in type II (fast-twitch) muscle fibers compared with type I (slow-twitch) muscle fibers in isolated muscle preparations. Such differences reflect faster $\mathrm{Ca}^{2+}$ transport through the sarcoplasmic reticulum and ultimately to the contractile proteins


Figure 18.13 Interaction among actin myosin filaments, $\mathrm{Ca}^{2+}$, and ATP in relaxed and shortened muscle. In the relaxed state, troponin and tropomyosin interact with actin, preventing the myosin crossbridge from coupling to actin. During muscle action, the crossbridge couples with actin from $\mathrm{Ca}^{2+}$ binding with troponin tropomyosin.
in type II fibers. During excitation contraction coupling, electrochemical events occur within the cell membrane at the site of excitation. The common pathway for precisely targeting the chemical signal to the contractile proteins depends mostly on ion channel regulators. These structures serve as selective gates or sensors to modulate ion passage between the intracellular and extracellular fluids before myofilament activation.

## Relaxation

When muscle stimulation ceases, $\mathrm{Ca}^{2+}$ flow stops and troponin frees up to inhibit actin myosin interaction. Recovery involves active pumping of $\mathrm{Ca}^{2+}$ into the sarcoplasmic reticulum where it concentrates in the lateral vesicles. Retrieval of $\mathrm{Ca}^{2+}$ from the troponin tropomyosin protein complex turns off the active sites on the actin filament. Deactivation serves two purposes: (1) prevents any mechanical link between the myosin crossbridges and actin filaments and (2) inhibits myosin ATPase activity, which curtails ATP splitting. Muscle relaxation occurs when the actin and myosin filaments return to their original states.

## Sequence of Events in Muscle Action

Figure 18.14 summarizes the main events in muscle activation, contraction, and relaxation. The sequence begins with the initiation of an action potential by the motor nerve. The impulse then propagates over the entire fiber surface (sarcolemma) as it depolarizes. The following nine steps correspond to the numbered sequence in Figure 18.14:

Step 1: Generation of an action potential in the motor neuron causes the small, saclike vesicles within the terminal axon to release acetylcholine (ACh). ACh diffuses across the synaptic cleft and attaches to specialized ACh receptors on the sarcolemma. Almost perfect symmetry exists between the imprint of the presynaptic vesicles that contain ACh and the imprint of the postsynaptic receptors that capture ACh.
Step 2: The muscle action potential depolarizes the transverse tubules at the sarcomeres A I junction.
Step 3: Depolarization of the T-tubule system causes $\mathrm{Ca}^{2+}$ release from the lateral sacs (terminal cisternae) of the sarcoplasmic reticulum.
Step 4: $\mathrm{Ca}^{2+}$ binds to troponin tropomyosin in the actin filaments. This releases the inhibition that prevented actin from combining with myosin.
Step 5: During muscle action, actin combines with myosin ATP. Actin also activates the enzyme myosin ATPase, which then splits ATP. The reactions energy produces myosin crossbridge movement and creates tension.
Step 6: ATP binds to the myosin crossbridge; this breaks the actin myosin bond and allows the crossbridge to dissociate from actin. The thick and thin


Figure 18.14 Schematic view of the nine main events in muscle contraction and relaxation. Numbers correspond to the sequence of nine steps outlined on $p$. 369. The neurotransmitter acetylcholine (ACh), released from saclike vesicles within the terminal axon, initiates transmission at the myoneural junction. Here, the electrochemical signal jumps across the 0.05- $\mu \mathrm{m}$ cleft between neuron and muscle fiber. The electrical impulse, traveling at a velocity of $1 \mathrm{~m} \cdot \mathrm{~s}^{1}$ or faster, spreads through the fibers architecturally elegant tubule system to the myofibrils inner contractile machinery.
filaments then slide past each other and the muscle shortens.
Step 7: Crossbridge activation continues when $\mathrm{Ca}^{2+}$ concentration remains high enough (from membrane depolarization) to inhibit the troponin tropomyosin system.
Step 8: When muscle stimulation ceases, intracellular $\mathrm{Ca}^{2+}$ concentration rapidly decreases as $\mathrm{Ca}^{2+}$ moves back into the lateral sacs of the sarcoplasmic reticulum through active transport that requires ATP hydrolysis.
Step 9: $\mathrm{Ca}^{2+}$ removal restores the inhibitory action of troponin tropomyosin. In the presence of ATP, actin and myosin remain in the dissociated, relaxed state.

## MUSCLE FIBER TYPE

Skeletal muscle does not simply contain a homogeneous group of fibers with similar metabolic and contractile properties. Rather, researchers have shown that skeletal muscle contains two main types of fibers that differ in the primary mechanisms they use to produce ATP, the type of motor neuron innervation and the type of myosin heavy chain expressed. The proportions of each type of muscle fiber vary from muscle to muscle and from person to person.

A common technique to establish the specific muscle fiber type assesses the myosin molecules heavy chain that exists in three different forms or isoforms. Assessment evaluates a fibers differential sensitivity to altered pH of the enzyme myosin ATPase (a measure of myosin phenotype). ${ }^{26,28,34,35}$ The different characteristics of this enzyme determine the rapidity of ATP hydrolysis in the myosin heavy chain region and thus the velocity of sarcomere shortening. More specifi-
cally, acid pH inactivates the activity of the specific myosin ATPase in fast-twitch fibers, but this enzyme remains fairly stable at an alkaline pH ; these fibers stain dark for this enzyme. In contrast, specific myosin ATPase activity for slowtwitch fibers remains high at an acid pH but becomes inactive in an alkaline milieu; these fibers stain light for myosin ATPase. Figure 18.15 illustrates serial cross sections of the human vastus lateralis muscle with identification of type I and type II muscle fibers and subdivisions. Table 18.2 lists different classification schemes for skeletal muscle fiber types on the basis of morphology, histochemistry and biochemistry, function, and contractility.

## Fast-Twitch Fibers (Type II)

Fast-twitch muscle fibers exhibit the following four characteristics:

1. High capability for electrochemical transmission of action potentials
2. High myosin ATPase activity
3. Rapid $\mathrm{Ca}^{2+}$ release and uptake by an efficient sarcoplasmic reticulum
4. High rate of crossbridge turnover

These four factors contribute to this fibers rapid energy generation for quick, powerful muscle actions. The fasttwitch fibers intrinsic speed of shortening and tension development ranges three to five times faster than slow-twitch fibers (see following section). Fast-twitch fibers rely on a well-developed, short-term glycolytic system for energy transfer. Fast-twitch fiber activation predominates in anaerobic-type sprint activities and other forceful muscle actions that rely almost entirely on anaerobic energy metabolism. ${ }^{16,24}$ Activation of fast-twitch fibers plays an important role in the stop-and-go or change-of-pace sports such as basketball, soccer, lacrosse,

TABLE 18.2 Classification of Human Skeletal Muscle Fiber Types

| Fiber Type | Type I Fibers | Type Ila Fibers | Type Ilx Fibers | Type IIb Fibers |
| :---: | :---: | :---: | :---: | :---: |
| Contraction time | Slow | Moderately fast | Fast | Very fast |
| Size of motor neuron | Small | Medium | Large | Very large |
| Resistance to fatigue | High | Fairly high | Intermediate | Low |
| Activity used for | Aerobic | Long-term anaerobic | Short-term anaerobic | Short-term anaerobic |
| Maximum duration of use | Hours | $<30$ minutes | $<5$ minutes | $<1$ minute |
| Force production | Low | Medium | High | Very high |
| Mitochondrial density | High | High | Medium | Low |
| Capillary density | High | Intermediate | Low | Low |
| Oxidative capacity | High | High | Intermediate | Low |
| Glycolytic capacity | Low | High | High | High |
| Major storage fuel | Triacylglycerol | Creatine phosphate, glycogen | Creatine phosphate, glycogen | Creatine phosphate, glycogen |
| Myosin-heavy chains, human genes | MYH7 ${ }^{\text {a }}$ | MYH2 | MYH1 | MYH4 |



Figure 18.15 Serial cross sections obtained by muscle biopsy of human vastus lateralis muscle ( $\mathbf{A}$ and $\mathbf{B}$ ) with identification of type I and type IIA, B, and C fiber subdivisions. The C fiber represents a former classification of a normally rare and undifferentiated subtype that may contribute to reinnervation and motor unit transformation. (C) Thick unstained section (40 $50 \mu \mathrm{~m}$ ) where all fibers appear similar. Three other panels indicate same fibers stained for myosin ATPase activity at a preincubation pH of (D) 4.3 (highly acidic), (E) 4.6 (intermediate acidity), and (F) 10.4 (alkaline).
or field hockey. These types of activities demand rapid energy that only anaerobic pathways generate. In a Practical Sense on page 373 describes a popular jumping test to infer the immediate power output from ATP and PCr. Theoretically, individuals with a predominance of fast-twitch muscle fibers should achieve relatively high scores on such a test.

Type II fibers distribute in three primary subtypes, type IIa, type IIx, and type IIb. Recent studies show that human skeletal muscle contains type I, type IIa, and type IIx fibers (previously referred to as type IIb) and a new type IIb subtype. ${ }^{41}$ Types IIa, IIx, and IIb fibers are also found in skeletal muscle of other mammals (e.g., rodents and cats) as well.

## IN A PRACTICAL SENSE

## Predicting Peak Anaerobic Power Output Using a Vertical Jump Test

Peak anaerobic power output underlies success in many sports activities. The vertical jump test is often used to predict explosive peak anaerobic power output from the intramuscular high-energy phosphates.

## VERTICAL JUMP TEST

The vertical jump test measures the highest distance jumped from a semicrouched position in the following protocol:

1. Establish standing reach height. The subject, standing with the preferred shoulder adjacent to a wall and feet flat on the floor, reaches as high as possible to touch the wall. The starting point (standing reach height) represents the distance from the wall mark (middle finger) to the floor, recorded in centimeters (cm) (Fig. A).
2. Bend the knees to about a 90 angle while moving the arms back in a winged position (Fig. B).
3. Thrust forward and upward, touching as high as possible on the wall (Fig. C).
4. At a minimum, perform three trials of the jump test, using the highest score as the vertical height. An average of the last 3 trials of 10 provides a more dependable jump height.
5. Compute vertical jump height ( cm ) as the difference between standing reach height and vertical height achieved in the jump.

## PREDICTING IMMEDIATE ANAEROBIC POWER OUTPUT

The following equation for males and females predicts peak anaerobic power output in watts ( $\mathrm{PAP}_{\mathrm{w}}$ ) from vertical jump height in cm $\left(\mathrm{V} \mathrm{J}_{\mathrm{cm}}\right)$ and body mass in kilograms $\left(\mathrm{BM}_{\mathrm{kg}}\right)$ :

$$
\mathrm{PAP}_{\mathrm{w}}=60.7\left(\mathrm{~V} \mathrm{~J}_{\mathrm{cm}}\right)+45.3\left(\mathrm{BM}_{\mathrm{kg}}\right)-2055
$$

## EXAMPLE

A 21-year-old male who weighs 78 kg records a vertical jump of 43 cm (standing reach height, 185 cm ; vertical height, 228 cm ); predict peak anaerobic power output in watts.

## COMPUTATIONS

$$
\begin{aligned}
\mathrm{PAP}_{\mathrm{w}} & \left.=60.7(\mathrm{~V})_{\mathrm{cm}}\right)+45.3\left(\mathrm{BM}_{\mathrm{kg}}\right)-2055 \\
& =60.7(43 \mathrm{~cm})+45.3(78 \mathrm{~kg})-2055 \\
& =4088.5 \mathrm{~W}
\end{aligned}
$$

## COMPARISONS

The average peak power output measured with this vertical jump protocol averages 4620.2 (SD $\pm 822.5$ ) W for males and 2993.7 ( $\mathrm{SD} \pm 542.9$ ) W for females.

## REFERENCE

Sayers S, et al. Cross-validation of three jump power equations. Med Sci Sports Exerc 1999;31:572.

(A) Starting point (standing reach height), (B) just prior to jumping, and (C) final point in determining vertical jump height.

The type IIa fiber exhibits fast shortening speed and a moderately well-developed capacity for energy transfer from both aerobic (high level of aerobic enzyme succinic dehydrogenase, or SDH) and anaerobic (high level of anaerobic enzyme phosphofructokinase, or PFK) sources. These fibers represent the fast oxidative glycolytic (FOG) fibers. The type 11b fiber possesses the greatest anaerobic potential and most rapid shortening velocity; it represents the true fast-glycolytic (FG) fiber. A type 11x fiber falls midway between its a and b counterparts in physiologic and metabolic characteristics.

## Slow-Twitch Fibers (Type I)

Slow-twitch fibers generate energy for ATP resynthesis predominantly through the aerobic system of energy transfer. Their four distinguishing characteristics include:

1. Low myosin ATPase activity
2. Slow calcium handling ability and shortening speed
3. Less well-developed glycolytic capacity than fasttwitch fibers
4. Large and numerous mitochondria

Slow-twitch fibers receive their characteristic red pigmentation from their rich mitochondria supply and accompanying iron-containing cytochromes combined with high myoglobin levels. A high concentration of mitochondrial enzymes links closely to a slow-twitch fibers enhanced aerobic metabolic machinery. These characteristics make slow-twitch fibers highly fatigue resistant and ideally suited for prolonged aerobic exercise. The fibers have been labeled SO (slowoxidative) fibers to describe their slow shortening speed and reliance on oxidative metabolism. Unlike fast-twitch fibers that fatigue readily, SO fibers (more precisely, motor units) are selectively recruited in aerobic activities. ${ }^{23}$

Muscle glycogen depletion patterns indicate that prolonged, high-intensity aerobic exercise demands almost exclusive reliance on slow-twitch muscle fibers. Even after exercising for 12 hours, the limited glycogen remaining in active muscle exists mostly in the relatively unused fast-twitch fibers. Differences in oxidative capacity between the two fiber types also determine the magnitude of blood flow through muscle, with slow-twitch fibers receiving the largest quantity. ${ }^{29}$

Most researchers classify slow-twitch fibers as type I, and fast-twitch fibers (and proposed subdivisions) as type II. Both slow and fast muscle fiber types contribute during nearmaximum aerobic and anaerobic exercise as in middledistance running or swimming or basketball, field hockey, or soccer, which combine high levels of aerobic and anaerobic energy transfer.

## INTEGRATIVE QUESTION

Present the pros and cons for muscle fiber typing of children to guide them into sports to increase their likelihood of future success.

## GENES THAT DEFINE SKELETAL MUSCLE PHENOTYPE

Skeletal muscle fiber types in adult animals (and most likely humans) regulate by several independent signaling pathways. These include pathways involved with the Ras/mitogenactivated protein kinase (MAPK), calcineurin, calcium/ calmodulin-dependent protein kinase IV, and the peroxisome proliferator $\gamma$ coactivator $1\left(\mathrm{PGC}^{1} \alpha\right)$, a coactivator that promotes mitochondrial biogenesis, mitochondrial fatty acid oxidation, and hepatic gluconeogenesis. $\mathrm{PGC}^{-1} \alpha$ also provides a direct link between external physiologic stimuli and the regulation of mitochondrial biogenesis, and is a major factor that regulates muscle fiber type determination. This pathway may be also involved in controlling blood pressure, regulating cellular cholesterol balance, and the development of obesity. The Ras/MAPK signaling pathway links motor neurons and signaling systems, coupling excitation and transcription regulation to promote nerve-dependent induction of muscle regeneration.

Mice that harbor an activated form of $\mathrm{PGC}^{-1} \alpha$ display an endurance phenotype, with a coordinated increase in
oxidative enzymes and mitochondrial biogenesis and an increased proportion of slow-twitch muscle fibers. Thus, through functional genomics a signaling network exists to control skeletal muscle fiber-type transformation and metabolic profiles that protect against insulin resistance and obesity. Other pathways also influence adult muscle characteristics. For example, physical force generated inside a muscle fiber may release the transcription factor serum response factor (SRF) from the structural muscle protein titin, leading to increased muscle growth.

## FIBER TYPE DIFFERENCES AMONG ATHLETIC GROUPS

Several observations concern muscle fiber type and the possible influence of specific training on fiber composition and metabolic capacity. Men, women, and children on average possess 45 to $55 \%$ slow-twitch fibers in their arm and leg muscles. The fast-twitch fibers probably distribute equally between type IIa and type IIb subdivisions. Although no gender differences exist in fiber distribution, large interindividual variation occurs. Generally, the trend in ones muscle fiber type distribution remains consistent among the bodys major muscle groups.

Certain patterns of muscle fiber distribution appear in comparisons among highly proficient athletes. ${ }^{42}$ For example, successful endurance athletes possess predominantly slowtwitch fibers in the major muscles activated in their sport. In contrast, fast-twitch fibers predominate for elite sprint athletes. Figure 18.16 illustrates fiber-type distribution for top Nordic competitors in different sports. Athletic groups with the highest aerobic and endurance capacities (e.g., distance runners and cross-country skiers) possess the highest percentage of slow-twitch fibers, often 90 to $95 \%$ in the legs gastrocnemius muscle. Weightlifters, ice hockey players, and sprinters have more fast-twitch fibers and relatively lower aerobic capacities. As might be expected, men and women who perform in middledistance events display approximately equal percentages of the two fiber types. The same distribution also occurs in power athletesthrowers, jumpers, and high jumpers. ${ }^{9}$

The relatively clear-cut distinctions between exercise performance and muscle fiber composition pertain mainly to elite athletes with prominence in a sport category. Even among this group, muscle fiber composition does not solely determine performance success. This seems reasonable because successful performance reflects blending of many physiologic, biochemical, neurologic, and biomechanical support systems, not simply the single factor of muscle fiber type.

Endurance athletes have relatively normal-sized muscle fibers, with a tendency toward enlargement of the slow-twitch fibers. Conversely, weightlifters and other power athletes show definite enlargement in both fiber types, particularly fast-twitch fibers, which may exceed by $45 \%$ those of endurance athletes or sedentary persons of the same age. ${ }^{43,44}$ Strength and power training induce enlargement of the fibers contractile apparatusspecifically the actin and myosin filamentsand total glycogen content. Larger muscle fibers


Figure 18.16 Muscle fiber composition (\% slow-twitch fibers, left side) and maximal oxygen consumption (right side) in athletes representing different sports. The outer white bars denote the range. (From Bergh U, et al. Maximal oxygen uptake and muscle fiber types in trained and untrained humans. Med Sci Sports 1978;10:151.)
in male athletes and a larger total muscle mass are the principal gender differences in muscle morphology. Chapter 22 discusses the potential for exercise training to alter the metabolic and fiber-type characteristics and size of skeletal muscle.

## Summary

1. Various connective tissue wrappings that encase skeletal muscle blend into and join the tendinous attachment to bone. This harness enables muscles to act on bony levers to transform chemical energy of ATP into mechanical energy of motion.
2. A skeletal muscle fiber by weight consists of $75 \%$ water, $20 \%$ protein, and the remainder is inorganic salts, enzymes, pigments, fats, and carbohydrates.
3. The muscles oxygen consumption during vigorous exercise increases up to 70 times the resting level. Immediate adjustments and longer term training adaptations that increase the size of the local vascular bed support this elevated metabolic requirement.
4. The sarcomere provides the functional unit of the muscle fiber. It contains the contractile proteins actin and myosin. An average muscle fiber contains 4500 sarcomeres and 16 billion thick (myosin) and 64 billion thin (actin) filaments.
5. Myosin projections, or crossbridges, serve as structural links between thick and thin contractile filaments. During muscle action, tropomyosin and troponin regulate the make-and-break contacts between the filaments.
6. Tropomyosin inhibits actin and myosin interaction; troponin plus $\mathrm{Ca}^{2+}$ trigger the myofibrils to interact and slide past each other.
7. The triad and T-tubule system function as a microtransportation network to spread the action potential
from the fibers outer membrane inward to deeper cell regions.
8. Muscle action takes place when $\mathrm{Ca}^{2+}$ activates actin; this causes the myosin crossbridges to attach to active sites on the actin filaments. A decease in $\mathrm{Ca}^{2+}$ concentration produces relaxation.
9. The sliding filament model proposes that a muscle shortens or lengthens because protein filaments slide past each other without altering their length. The mechanism of excitation contraction coupling links electrochemical and mechanical events to achieve muscle action.
10. Contractile and metabolic characteristics classify the two types of muscle fibers: (1) fast-twitch (FT) fibers that generate energy predominantly anaerobically for quick, powerful actions and (2) slowtwitch (ST) that shorten relatively slowly and generate energy predominantly by aerobic metabolism. An intermediate, fast oxidative glycolytic (FOG) fiber also exists.
11. Skeletal muscle fiber-type phenotype in adult animals, including humans, is regulated by several independent signaling pathways. These include the Ras/mitogen-activated protein kinase (MAPK), calcineurin, calcium/calmodulin-dependent protein kinase IV, and the peroxisome proliferator $\gamma$ coactivator $1\left(\mathrm{PGC}^{1} \alpha\right)$.
12. Most likely, genetic factors explain the variation in muscle fiber types, yet specific exercise training may produce some modification.

References are available online at http://thepoint.lww.com/mkk7e.

## CHAPTER 19



## Neural Control of Human Movement

## CHAPTER OBJECTIVES

- Draw the major structural components of the brain, including the four lobes of the cerebral cortex
> Discuss specific pyramidal and extrapyramidal tract functions
- Diagram the anterior motor neuron and discuss its role in human movement
- Draw and label the basic components of a reflex arc
> Define the terms (1) motor unit, (2) neuromuscular junction, and (3) autonomic nervous system
- Summarize the events in motor unit excitation prior to muscle action
> Outline motor unit facilitation and inhibition and the contribution of each to exercise performance and responsiveness to resistance training
> Discuss variations in twitch characteristics, resistance to fatigue, and tension development in the different motor unit categories
> Describe mechanisms that adjust force of muscle action along the continuum from slight to maximum
- Define fatigue and discuss factors that act and interact to induce neuromuscular fatigue
> List and describe functions of the proprioceptors within joints, muscles, and tendons

The effective application of force during complex learned movements (e.g., tennis serve, shot put, golf swing) depends on a series of coordinated neuromuscular patterns, not just on muscle strength. The neural circuitry in the brain, spinal cord, and periphery functions somewhat similar to a sophisticated computer network. In response to changing internal and external stimuli, hundreds of millions of bits of sensory input automatically synchronize for near-instantaneous processing by central neural control mechanisms. The input becomes properly organized, routed, and transmitted with extreme efficiency to the effector organs, the skeletal muscles. ${ }^{27}$

## NEUROMOTOR SYSTEM ORGANIZATION

The human nervous system consists of two major parts:

1. Central nervous system (CNS) consisting of the brain and spinal cord
2. Peripheral nervous system (PNS) consisting of nerves that transmit information to and from the CNS

Figure 19.1 presents an overview of these two subdivisions.

## Central Nervous SystemThe Brain

Over time the human brain has remained remarkably complex, but with selective growth of different anatomic areas. From a comparative perspective, the size of the human brain exceeds that of most (but not all) mammals. Evolution of the cortex, particularly the frontal and temporal lobes, coincides with unique human functions like spoken and written language, reasoning, and abstract thinking. Such differentiation frames the hypothesis that larger, more complex brains allow greater neural circuitry within the cortex and hence increased intellectual and higher center functioning.

For decades, conventional wisdom maintained that the number of brain cells was fixed at birth, unlike the cells of other organ systems that continually renew themselves throughout life. Neurobiologists now believe that brain cells, spinal neurons, and neural circuits are created throughout life, with elimination of unneeded or redundant synapses in developing neural tissues. From birth through late adolescence, the brain probably adds billions of new cells, literally constructing new circuits from these newly formed cells. ${ }^{14}$ After adolescence, the plasticity of neuronal addition and formation of new circuits slows but does not stop, even into old age. Regular physical activity appears to contribute to the development and maintenance of optimal neural circuitry in middle and older age.

Figure 19.2 categorizes the brain into six main areas: medulla oblongata, pons, midbrain, cerebellum, diencephalon, and telencephalon. Figure 19.2C depicts four lobes of the cerebral cortex and associated sensory areas. As a frame of reference, the body has roughly 10 million sensory (afferent) neurons, 50 billion central neurons, and 500,000 motor (efferent) neurons. This represents a ratio of about 20 to 1 between the sensory and motor circuits.

## Brainstem

The medulla, pons, and midbrain compose the brainstem. The medulla, located immediately above the spinal cord, extends into the pons and serves as a bridge between the two hemispheres of the cerebellum. The midbrain, only 1.5 cm long, attaches to the cerebellum and forms a connection between the pons and cerebral hemispheres. The midbrain contains parts of the extrapyramidal motor system, specifically the red nucleus and substantia. The reticular formation integrates various incoming and outgoing signals that flow through it. These signals originate from the stretching of sensors in joints and muscles, from pain receptors in the skin, and as visual signals from the eye and auditory impulses from the ear. Once activated, the reticular system produces either inhibitory or facilitory effects on other neurons. Twelve pairs of cranial nerves innervate predominantly the head region. Each cranial nerve has a name and associated number (originally derived by Galen about 1800 years ago).

## Cerebellum

The cerebellum consists of two peach-sized mounds of folded tissue with lateral hemispheres and a central vermis. It functions by means of intricate feedback circuits to monitor and coordinate other areas of the brain and spinal cord involved in motor control. The cerebellum receives motor output signals from the central command in the cortex. This specialized brain tissue also obtains sensory information from peripheral receptors in muscles, tendons, joints, and skin and from visual, auditory, and vestibular end organs. The cerebellum functions as the major comparing, evaluating, and integrating center for postural adjustments, locomotion, maintenance of equilibrium, perceptions of speed of body movement, and other diverse reflex-related movement functions. Movement tasks first learned by trial and error, like riding a bicycle or swinging a golf club, remain coded as coordinated patterns in the cerebellar memory banks. In essence, this motor control center fine-tunes all forms of muscular activity. ${ }^{29}$

## Diencephalon

The diencephalon, located immediately above the midbrain, forms part of the cerebral hemispheres. The thalamus, hypothalamus, epithalamus, and subthalamus compose the major structures of the diencephalon. The hypothalamus, situated below the thalamus, regulates metabolic rate and body temperature. The hypothalamus also influences activity of the autonomic nervous system (see p. 382); it receives regulatory input from the thalamus and limbic brain system and responds to the effects of diverse hormones (see Chapter 20). Changes in arterial blood pressure and blood gas tensions influence hypothalamic activity via peripheral receptors located in the aortic arch and carotid arteries.


Figure 19.1 The two divisions of the human nervous system. The central nervous system (CNS) contains the brain (including retinas), spinal cord, and integrating and control centers; the cranial nerves and spinal nerves compose the peripheral nervous system (PNS). The PNS further subdivides into the afferent (sensory) and efferent (motor) divisions. The efferent division consists of the somatic nervous system and autonomic nervous system (sympathetic and parasympathetic divisions).


Figure 19.2 A. Side (medial) view of the brain and brainstem. B. Superior view of the brain. C. Four lobes of the cerebral cortex.

## Telencephalon

The telencephalon contains the two hemispheres of the cerebral cortex, including the corpus striatum and medulla. The cerebral cortex makes up approximately $40 \%$ of the total brain weight. It divides into four lobes: frontal, temporal, parietal, and occipital. Neurons in the cortex provide specialized sensory and motor functions. Beneath each cerebral hemisphere and in close association with the thalamus lie the basal ganglia, which play an important role in the control of motor movements.

## Limbic System

In 1878 , French surgeon, neurologist, and anthropologist Paul Pierre Broca (1824 1880) described a group of areas on the medial surface of the cerebrum that were distinctly different from the surrounding cortex. Using the Latin word for border (limbus), Broca named the area the limbic lobe because its structures formed a ring or border around the brainstem and corpus callosum on the medial surface of the temporal lobe. ${ }^{3}$ Broca also discovered the speech center now known as Brocas area, or the third circumvolution of the frontal lobe. Broca should be credited as the founder of modern brain surgery.

## Central Nervous SystemThe Spinal Cord

Figure 19.3 illustrates the spinal cord, about 45 cm in length and 1 cm in diameter, encased by 33 vertebrae ( 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal). The bony vertebral column encases and protects the spinal cord, which attaches to the brainstem. The spinal cord provides the major conduit for the two-way transmission of information from the skin, joints, and muscles to the brain. It provides for communication throughout the body via spinal nerves of the PNS (see p. 382). These nerves exit the cord through small openings or notches between the vertebrae. Each spinal nerve connects to the spinal cord by the dorsal root and ventral root branches. Table 19.1 lists common names that describe the collections of spinal cord neurons and axons.

When viewed in cross section, the spinal cord shows an H-shaped core of gray matter (Fig. 19.4). The ventral (anterior) and dorsal (posterior) horns describe the limbs of this core. The spinal cord core contains principally three types of neurons: motor neurons, sensory neurons, and interneurons. The motor neurons (efferent) run through the ventral horn to supply the extrafusal and intrafusal skeletal muscle fibers (see p. 393). Sensory (afferent) nerve fibers enter the spinal cord from the periphery by way of the dorsal horn. The white matter, containing the ascending and descending nerve tracts, surrounds the gray matter within the cord.

## Ascending Nerve Tracts

Ascending nerve tracts in the spinal cord forward sensory information from peripheral receptors to the brain for


Figure 19.3 Human central nervous system anatomy. A. Spinal cord showing the peripheral nerves. B. Ventral view of spinal cord section illustrates dorsal and ventral root neural pathways and nerve impulse direction. C. Cross section through one cervical vertebra. D. Primary spinal cord structures. E. Enlarged view of the junction of three thoracic vertebral bodies.

| TABLE 19.1 | mmon Names Describing Neurons and Axons of the Spinal Cord |
| :---: | :---: |
| Name | Description/Example |
| Neurons |  |
| Gray matter | Generic term for a collection of neuronal cell bodies in the CNS (neurons appear gray in a freshly dissected brain) |
| Cortex | Collection of neurons forming a thin sheet, usually at the brains surface; example: cerebral cortex, the sheet of neurons found just under the surface of the cerebrum |
| Nucleus | Distinguishable mass of neurons, usually deep in the brain (not to be confused with the nucleus of a cell); example: lateral geniculate nucleus, a cell group in the brainstem relaying information from the eye to the cerebral cortex |
| Substantia | Related neurons deep within the brain, but with less distinct borders than those of nuclei; example: substantia nigra, a brainstem cell group involved in voluntary movement control |
| Locus (pluralloci) | Small, well-defined group of cells; example: locus coeruleus, a brainstem group of cells involved in control of wakefulness and behavioral arousal |
| Ganglion (pluralganglia) | From the Greek term for knot; collection of neurons in the peripheral nervous system; example: dorsal root ganglia that contain the cell bodies of sensory axons entering the spinal cord in the dorsal roots; only one cell grouping, the basal ganglia, in the CNS goes by this name; the basal ganglia that lie deep within the cerebrum control movement |
| Axons |  |
| Nerve | A bundle of axons in the peripheral nervous system; the optic nerve is the only collection of CNS axons termed nerve |
| White matter | Generic term for a collection of CNS axons (neurons appear white in a freshly dissected brain) |
| Tract | Collection of CNS axons having a common site of origin and a common destination; example: corticospinal tract that originates in the cerebral cortex and ends in the spinal cord |
| Bundle | Collection of axons running together but not necessarily having the same origin and destination; example: medial forebrain bundle that connects the brainstem with the cerebral cortex |
| Capsule | Collection of axons that connect the cerebrum with the brainstem; example: internal capsule that connects the brainstem with the cerebral cortex |
| Commissure | Any collection of axons that connect one side of the brain to the other side |
| Lemniscus | A tract that meanders through the brain in ribbonlike fashion; example: medial lemniscus that brings tactile information from the spinal cord through the brainstem |

From Bear MF, et al. Neuroscience: exploring the brain. 3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2006.
processing. Three neurons typically form the sensory pathway. The dorsal root ganglion contains the cell body of the first neuron whose axon relays information into the spinal cord. The cell body of the second neuron lies within the spinal cord itself; its axon passes up the cord to the thalamus,


Figure 19.4 Descending spinal cord tracts from the brain. (From Bear MF, et al. Neuroscience: exploring the brain.3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2006.)
which contains the third neurons cell body. The axon of the third neuron passes up to the central command center in the cerebral cortex.

Sensory Receptors. Peripheral sensory nerve endings serve as specialized receptors to detect conscious and subconscious sensory information. The conscious receptors show sensitivity to body position (kinesthesia and proprioception), temperature, and sensations of light, sound, smell, taste, touch, and pain. Receptors also monitor subconscious changes in the bodys internal environment; these include chemoreceptors that respond to changes in blood gas tension $\left(\mathrm{PO}_{2}, \mathrm{PCO}_{2}\right)$ and pH and baroreceptors that react rapidly to even small changes in arterial blood pressure. The term mechanoreceptors generally refers to the sensory receptors sensitive to mechanical stimuli of touch, pressure, stretch, and motion.

## Descending Nerve Tracts

Axons from the brain move downward through the spinal cord along two major pathways displayed in Figure 19.4. The
pyramidal tract (lateral tract) activates the skeletal musculature in voluntary movement under direct cortical control. The other pathway, the extrapyramidal tract (ventromedial tract), controls posture and muscle tone via the brainstem.

Pyramidal (Lateral) Tract. Neurons in the pyramidal tract (including the corticospinal and rubrospinal tracts) transmit impulses downward through the spinal cord. By means of direct routes and interconnecting neurons in the cord, these nerves eventually excite the alpha ( $\alpha$ ) motor neurons that control and modulate the fine and gross properties of skeletal muscles during all purposeful movements. The corticospinal tract, the longest and one of the largest CNS tracts, has two thirds of its axons originating from the brains frontal lobe, collectively called the motor cortex.

Extrapyramidal (Ventromedial) Tract. The extrapyramidal neurons (reticulospinal, vestibulospinal, and tectospinal tracts) originate in the brainstem and connect at all levels of the spinal cord. They control posture and provide a continual background level of neuromuscular tone.

## Reticular Formation

The reticular formation provides an extensive and intricate neural network through the core of the brainstem that integrates the spinal cord, cerebral cortex, basal ganglia, and cerebellum. It receives a continuous flow of sensory data. Once activated, it either inhibits or facilitates other neurons. For example, the reticular formation helps to control posture by regulating the sensitivity of neurons to the antigravity muscles that maintain upright posture. Excitation of peripheral sensory neurons arouses the reticular nerve cells to excite the cerebral cortex. This initiates transmission of signals back to the reticular system to maintain appropriate cortical arousal and wakefulness. The reticular formation also exerts a powerful influence on cardiovascular and pulmonary regulation.

## Peripheral Nervous System

The peripheral nervous system contains 31 pairs of spinal nerves and 12 pairs of cranial nerves. Figure 19.5 shows the distribution of the 12 pairs of cranial nerves numbered I through XII. Cranial nerves I and II serve visual and olfactory functions and are part of the CNS. Cranial nerves emerge through foramina, or fissures, in the skull (cranium). Cranial nerves, as do their spinal counterparts, contain fibers that transmit sensory and/or motor information. Their neurons innervate muscles or glands or transmit impulses from sensory areas into the brain. The spinal nerves consist of 8 pairs of cervical nerves, 12 pairs of thoracic nerves, 5 pairs of lumbar nerves, 5 pairs of sacral nerves, and 1 pair of coccygeal nerves. A specific letter and number identifies these nerves (e.g., C-1, first nerve from the cervical region; T-4, fourth nerve in thoracic region). Careful research has traced the exact location of the
spinal nerves by mapping the tissues they innervate. This is fortuitous because an injury to a specific area of the spinal cord produces predictable neurologic damage.

The peripheral nervous system includes afferent neurons that relay sensory information from receptors in the periphery toward the CNS and efferent neurons that transmit information away from the brain to peripheral tissues. Somatic and autonomic nerves are the two types of efferent neurons. Somatic nerve fibers (also called motor neurons or motoneurons) innervate skeletal muscle. Their firing above a threshold level always produces an excitatory response to activate muscle. The autonomic nerves (also called visceral, involuntary, or vegetative nerves) activate cardiac muscle, sweat and salivary glands, some endocrine glands, and smooth muscle cells (also called involuntary muscle) in the intestines and walls of blood vessels. Autonomic activity produces either an excitatory or inhibitory effect depending on the specific neurons activated.

Whereas tissues of the heart and viscera display considerable autonomic excitability, conscious control also affects these tissues. For example, individuals who practice yoga or meditation control their heart rate and blood flow on command. Such conscious control of the autonomic system has some application as an alternative treatment in medicine (e.g., gastrointestinal disturbances, hypertension) and to enhance sports performance (e.g., lower heart rate, steadiness). Competitors in archery and biathlon control cardiovascular activity and respiratory movements to temporarily halt the normal breathing cycle and slow heart rate during the crucial steadiness phase of the performance (i.e., immediately prior to releasing the bowstring or firing the rifle).

## Sympathetic and Parasympathetic <br> Nervous Systems

The autonomic nervous system subdivides into sympathetic and parasympathetic components. Based on anatomic and physiologic differences, these neurons operate in parallel but use structurally distinct pathways and differ in their transmitter systems. Figure 16.5 (p. 331) shows that axons of the sympathetic division emerge only from the middle third of the spinal cord (thoracic and lumbar segments); in contrast, preganglionic axons of the parasympathetic division emerge only from the brainstem and lowest (sacral) spinal cord segments. The two systems complement each other anatomically.

Sympathetic fiber distribution, while displaying some overlap with parasympathetic fibers, supplies the heart, smooth muscle, sweat glands, and viscera. Parasympathetic nervous system fibers leave the brainstem and sacral segments of the spinal cord to supply the thorax, abdomen, and pelvic regions.

Regions of the medulla, pons, and diencephalon control the autonomic nervous system. Fibers that originate in the medullary region of the lower brainstem control blood pressure, heart rate, and pulmonary ventilation, whereas nerve fibers of upper hypothalamic origin regulate body temperature.


Figure 19.5 Distribution of the 12 cranial nerves (CN). (From Moore KL, Dalley AF II, eds. Clinically oriented anatomy. 6th ed. Baltimore: Lippincott Williams \& Wilkins, 2009.)


Figure 19.6 Reflex arc showing afferent and efferent neurons plus an interneuron in a spinal cord segment. The darker shaded or gray matter contains the neuron cell bodies; longitudinal columns of nerve fibers make up the white matter. Stimulation of a single $\alpha$-motor neuron activates up to 3000 muscle fibers. The motor neuron and the fibers it innervates collectively constitute the motor unit. The figure shows only one side of the spinal nerve complex.

## The Reflex Arc

Figure 19.6 diagrams the neural arrangement for a typical reflex arc in one of the 31 spinal cord segments. Afferent neurons that enter the spinal cord through the dorsal (sensory)
root transmit sensory input from peripheral receptors. These neurons interconnect (synapse) in the cord through interneurons that relay information to different cord levels. The impulse then passes over the motor root pathway via anterior motor neurons to the effector organthe muscles.

An example of a reflex is when one suddenly touches a hot object. Stimulation of pain receptors in the fingers transmits sensory information over afferent fibers to the spinal cord. This activates efferent motor fibers to elicit an appropriate muscular response (removing the hand rapidly). Concurrently, the signal transmits through interneuron activity up the cord to sensory areas in the brain, the area that actually feels the pain. These various levels of operation for sensory input, processing, and motor output, including the reflex action just described, cause removal of the hand from the hot object before the perception of pain. Reflex actions in the spinal cord and other subconscious areas of the CNS control many muscle functions. Literally hundreds of hours of practicing a particular motor task grooves the neuromuscular movements to become automatic, no longer requiring conscious control. Unfortunately, improper practice also can automate a task to produce less than optimal neuromuscular actions. Most individuals who practice the golf swing, for example, do so by reinforcing poor habits. It starts with the grip and the first 6 inches of the takeaway in the backswing. Setting up with an improper grip, followed by a rapid cocking of the wrists at the start of the backswing, fuels a recipe for disaster (meaning that continual poor practice reinforces nonoptimal mechanics). Instead of hitting one ball after another, hours on end, the aspiring golfer should practice correct swing mechanics. The adage practice makes perfect should be amended to perfect practice makes perfect performance.

## NERVE SUPPLY TO MUSCLE

One nerve or its terminal branches innervate at least one of the bodys approximately 250 million muscle fibers. The typical individual possesses only about 420,000 motor neurons; thus, a single nerve usually supplies many individual muscle fibers. The number of muscle fibers per motor neuron generally relates to a muscles particular movement function. Delicate and precise work of the eye muscles, for example, requires that a neuron control fewer than 10 muscle fibers. For less complex movements of the large muscle groups, a motor neuron may innervate as many as 2000 or 3000 fibers. For muscular activity, the spinal cord is the major processing and distribution center for motor control. The next sections examine how information processed in the CNS activates the muscles to trigger an appropriate motor response.

## Motor Unit Anatomy

The motor unit makes up the functional unit of movement; this anatomic unit consists of the anterior motor neuron and the specific muscle fibers it innervates. The individual and combined actions of motor units produce specific muscle actions. Each muscle fiber generally receives input from only one neuron, yet a motor neuron may innervate many muscle fibers because the terminal end of an axon forms numerous branches. Motor neuron pool describes the collection of $\alpha$-motor neurons that innervate a single muscle (e.g., triceps


Figure 19.7 Motor unit and motor neuron pool. A. Motor unit represents an $\alpha$-motor neuron and the fibers it innervates. B. Motor neuron pool represents all the $\alpha$-motor neurons that innervate one muscle.
or biceps) (Fig. 19.7). Different motor points exist within the muscle to allow neural stimulation throughout the muscles length. ${ }^{26}$ Some motor units contain up to 1000 or more muscle fibers, whereas motor units of the larynx, fingers, or eyeball contain relatively few. For example, the first dorsal interosseous muscle of the finger contains 120 motor units that control 41,000 fibers; the medial gastrocnemius (calf) muscle contains 580 motor units and 1,030,000 muscle fibers. The average ratio of muscle fibers to motor unit is 340 for the finger muscle and about 1800 for the gastrocnemius muscle. Individual differences in muscle fiber motor unit ratios probably contribute significantly to variation in sport skill performance.

## The Anterior Motor Neuron

The anterior motor neuron illustrated in Figure 19.8 consists of a cell body, axon, and dendrites. Its unique design allows transmission of an electrochemical impulse from the spinal cord to the muscle. The cell body houses the neurons control centerthe structures involved in replication and transmission


Figure 19.8 The anterior ( $\alpha$ ) motor neuron consists of a cell body, axon, and dendrites. Top inset shows a nerve trunk containing numerous individual nerve fibers, including a bare axon. Bottom inset shows a node of Ranvier on the bare axon, which permits impulses to jump from one node to another as the electrical current travels toward the terminal branches at the motor endplate.
of the genetic code. The spinal cords gray matter contains the cell body of the motor neuron. The axon extends from the cord to deliver the impulse to the muscle; dendrites consist of short neural branches that receive impulses through numerous connections and conduct them toward the cell body. Nerve cells conduct impulses in one direction onlydewn the axon, away from the original stimulation point.

The myelin sheath, a lipoprotein membrane that wraps around the axon over most of its length, encases larger nerve fibers. A large part of this sheath acts as an electrical insulator that envelops the axon akin to the plastic coating around a copper electrical wire. A specialized cell known as a

Schwann cell covers the bare axon and then spirals around it, sometimes up to 100 times in the biggest fibers. A thinner outermost membrane, the neurilemma, covers the myelin sheath. The nodes of Ranvier (named for Paris physician and histologist Louis Antoine Ranvier [1835 1922], who also discovered the myelin sheath) interrupt the Schwann cells and myelin every 1 or 2 mm along the axons length. Whereas myelin insulates the axon to the flow of ions, the nodes of Ranvier permit depolarization of the axon. This alternating sequence of myelin sheath and node of Ranvier at about 1-mm intervals allows impulses to jump from node to node (saltatory conduction) as the electrical current travels toward
the terminal branches at the motor endplate. This type of conduction causes faster transmission velocities in myelinated fibers compared to unmyelinated fibers. Conduction speed in a nerve fiber increases in direct proportion to a fibers diameter and thickness of its myelin sheath. Large, myelinated neurons conduct impulses at speeds that exceed $100 \mathrm{~m} \cdot \mathrm{~s}^{-1}$ (224 mph).

Four different nerve fiber groups exist based on size (and thus transmission velocity):

2. A-beta $\left(A-\beta\left[612 \mu \mathrm{~m} ; 3575 \mathrm{~m} \cdot \mathrm{~s}^{-1}\right]\right)$
3. A-delta (A- $\delta\left[15 \mu \mathrm{~m} ; 535 \mathrm{~m} \cdot \mathrm{~s}^{-1}\right]$ )
4. C-nerve fibers ( $0.2 \quad 1.5 \mu \mathrm{~m} ; 0.52 .0 \mathrm{~m} \cdot \mathrm{~s}^{-1}$ )

Myelin insulation covers the A- $\alpha$, A- $\beta$, and A- $\delta$ nerve fibers, while C nerve fibers remain unmyelinated. The thickness of a nerve fiber dictates the speed of neural transmission within the fiberthe thickest A- $\alpha$ fibers have the fastest transmission speeds, while the smallest $C$ fibers have the slowest transmission speed. These relatively tiny fibers relay information related to pain, temperature, and itch. To give some perspective about the speed of transmission, impulses in C nerve fibers travel about 2.2 mph , slower than most people walk. In contrast, the A- $\delta$ fibers conduct action potentials at the speed of the winning $100-\mathrm{m}$ Olympic dash, while the A- $\beta$ fibers that relay information related to touch travel at speeds close to that of most propeller-driver aircraft. As discussed in the section on proprioception, the $\gamma$-efferent fibers connect with special stretch sensors in skeletal muscle that detect minute changes in muscle fiber length.

All muscle action ultimately depends on three primary sources of input to $\alpha$-motor neurons (motor units):

1. Dorsal root ganglion cells with axons that innervate specialized muscle spindle sensory units embedded within the muscle
2. Motor neurons in the brain, primarily in the cerebral cortexs precentral gyrus
3. Excitatory and inhibitory spinal cord interneurons, which make up the largest input

Neuromuscular Junction (Motor Endplate). The neuromuscular junction (NMJ) or motor endplate represents the interface between the end of a myelinated motor neuron and muscle fiber (Fig. 19.9). It transmits the nerve impulse to initiate muscle action. Each skeletal muscle fiber usually contains one NMJ.

Five common features describe the NMJ. ${ }^{5}$

1. Schwann cells are present.
2. Terminal section of the neuron contains the neurotransmitter substance acetylcholine (ACh).
3. Basement membrane lines the synaptic space.
4. Membrane across from the synaptic space (the postsynaptic membrane) contains ACh receptors.
5. Connector microtubules at the postsynaptic membrane transmit the electrical signal deep within the muscle fiber.

The terminal portion of the axon below the myelin sheath forms several smaller axon branches whose endings become the presynaptic terminals. This region possesses approximately 50 to 70 ACh -containing vesicles per square micrometer. They lie close to (but do not come in contact with) the muscle fibers sarcolemma. The invaginated region of the postsynaptic membrane (also called the synaptic gutter) has numerous infoldings that increase the membranes surface area. The synaptic cleft between the synaptic gutter and the presynaptic terminal of the axon serves as the region for neural impulse transmission between nerve and muscle fiber.

Excitation. Excitation normally occurs only at the NMJ. When an impulse arrives at the NMJ, ACh releases from saclike vesicles in the terminal axons into the synaptic cleft. ACh, which changes a basically electrical neural impulse into a chemical stimulus, then combines with a transmitter receptor complex in the postsynaptic membrane. The resulting change in electrical properties of the postsynaptic membrane elicits an endplate potential that spreads from the motor endplate to the extrajunctional sarcolemma of muscle. This causes an action potential or wave of depolarization to travel the length of the muscle fiber, enter the T-tubule system, and spread to the inner structures of the muscle fiber to prime the contractile machinery for excitation.

The enzyme cholinesterase (concentrated at the borders of the junctional folds at the synaptic cleft) degrades ACh within 5 ms of its release from the synaptic vesicles. ACh hydrolysis by cholinesterase allows the postsynaptic membrane to repolarize rapidly. The axon resynthesizes the end products of cholinesterase action (acetic acid and choline) to ACh so the entire process can begin again when another neural impulse arrives.

Facilitation. ACh release from synaptic vesicles excites the postsynaptic membrane of its connecting neuron. This changes membrane permeability so sodium ions can diffuse into the stimulated neuron. An action potential generates if the change in transmembrane microvoltage (influx of extracellular sodium and/or efflux of intracellular potassium) reaches the threshold for excitation. The term excitatory postsynaptic potential (EPSP) describes this change in membrane potential at the junction between two neurons (Fig. 19.10A). The arrival of a subthreshold EPSP does not cause the neuron to discharge. Instead, the flow of positive charges into the cell increases to lower its resting membrane potential (usually an electrical potential of 65 mV between outside and inside the cell), temporarily increasing its tendency to fire. The neuron fires when many subthreshold excitatory impulses arrive in rapid succession and the resting membrane potential lowers to about 50 mV . Temporal summation describes this condition of repeated subthreshold stimulation. Simultaneous stimulation of surrounding presynaptic terminals of the same neuron produces spatial summation (and subsequent firing of the muscle fiber). This can induce an action potential from the summing of each individual effect.


Figure 19.9 Microanatomy of the neuromuscular junction, including details of the presynaptic and postsynaptic contact area between the motor neuron and the muscle fiber it innervates. Inset table shows representative values for ionic concentrations across the motor neuron membrane.

## integrative question

Describe neuromuscular factors that help to explain performance differences among individuals who devote equal time practicing the volleyball spike.

The phenomenon of neural facilitation (disinhibition) affects neurons within the CNS rather than electrochemical events at the NMJ because the NMJ does not release inhibitory neurotransmitters. Three factors produce neuronal facilitation:

1. Decreased sensitivity of the motor neuron to inhibitory neurotransmitters
2. Reduced quantity of inhibitory neurotransmitter substance transported to the motor neuron
3. Combined effect of both mechanisms

Neural facilitation exerts an important influence under special movement conditions. In all-out strength and power activities, disinhibiting and maximally activating all motor neurons (synchronously) required for a movement becomes crucial to topflight performance. ${ }^{14,16,24}$ Enhanced facilitation (disinhibition) leads to full activation of muscle groups during all-out effort and largely accounts for the rapid and highly specific strength increases during the early stages of resistance training. ${ }^{9,10,25,28}$ Chapter 22 discusses the potential for augmenting maximal strength performance through CNS facilitation with intense concentration or psyching.

Inhibition. Some presynaptic terminals produce inhibitory impulses. The inhibitory transmitter substance increases the postsynaptic membranes permeability to potassium and chloride ion efflux, thus increasing the cells


Figure 19.10 A. Generation of an excitatory postsynaptic potential (EPSP). An impulse arriving in the presynaptic terminal (top inset) causes neurotransmitter release. The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. The membrane becomes hyperpolarized when $\mathrm{Na}^{+}$enters the postsynaptic cell through the open channels. The EPSP represents the resulting microvoltage change in membrane potential (Vm) recorded by a microelectrode in the cell. B. Generation of an inhibitory postsynaptic potential (IPSP). An impulse arriving in the presynaptic terminal (top inset) causes neurotransmitter release. The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. The membrane becomes hyperpolarized if $\mathrm{Cl}^{-}$enters the postsynaptic cell through the open channels. The IPSP represents the resulting change in Vm recorded by a microelectrode in the cell. (From Bear MF, et al. Neuroscience: exploring the brain. 3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2006.)
resting membrane potential to create an inhibitory postsynaptic potential (IPSP; Fig. 19.10B). The IPSP hyperpolarizes the neuron, making it more difficult to fire. A large IPSP prevents initiation of an action potential when a motor neuron receives both excitatory and inhibitory stimulation. For example, one usually can override (inhibit) the reflex to pull the hand away when removing a splinter, and so steady the hand to facilitate this unpleasant but necessary task.

The precise neurochemical that provokes an IPSP remains unknown, although $\gamma$-aminobutyric acid (GABA) and the amino acid glycine exert inhibitory effects. Neural inhibition has protective functions and reduces the input of unwanted stimuli to produce a smooth, purposeful response.

## INTEGRATIVE QUESTION

Explain how drugs that mimic neurotransmitters can affect physiologic response and exercise performance.

## MOTOR UNIT FUNCTIONAL CHARACTERISTICS

A motor unit contains only one specific muscle fiber type (type I or type II) or a subdivision of the type II fiber with the same metabolic profile. Table 19.2 classifies motor units based on the following three physiologic and mechanical properties of the muscle fibers they innervate:

1. Twitch characteristics
2. Tension characteristics
3. Fatigability

## Twitch Characteristics

Early experiments in motor unit physiology revealed that motor units developed high, low, or intermediate tension in response to a single electrical stimulus. Additionally, motor units with low force capacity exhibited a slow shortening time
(and time to peak force) but remained fatigue resistant, whereas units with higher force capacity shortened rapidly but fatigued earlier. Figure 19.11 illustrates the major characteristics for the three common motor unit categories:

1. Fast twitch, high force, and fast fatigue (type IIx)
2. Fast twitch, moderate force, and fatigue resistant (type IIa)
3. Slow twitch, low force, and fatigue resistant (type I)

Relatively large motor neurons with fast conduction velocities innervate the two major subdivisions of fast-twitch muscle fibers. These motor units generally contain between 300 and 500 muscle fibers. The fast-fatigable (FFtype IIx) and fast fatigue-resistant (FRtype IIa) units reach greater peak tension and develop it faster than slow-twitch (Stype I) motor units that receive innervation from smaller motor neurons with slow conduction velocities. The slower contracting units exhibit more fatigue resistance than the fast-twitch units. Specific exercise training modifies the unique metabolic characteristics of each specific muscle fiber type. With prolonged aerobic training, fast-twitch muscle fibers become almost as fatigue resistant as slow-twitch counterparts (see Chapter 22).

Motor neurons themselves have a trophic or stimulating effect on the muscle fibers they innervate in a way that modulates the fibers properties and adaptive response to stimuli. ${ }^{8}$ Surgically innervating fast-twitch muscle fibers with the neuron from a slow-twitch motor unit eventually alters the twitch characteristics of the fast-contracting fibers. Furthermore, application of long-term, low-frequency stimulation to intact fast-twitch motor units induces conversion of the muscle fibers to the slow-twitch type. ${ }^{14,22}$ This neurotrophic effect suggests that the myoneural junction takes on much greater significance than just serving as the site of muscle fiber depolarization. It indicates a remarkable plasticity of skeletal muscle that may indeed be altered through long-term use.

## Tension Characteristics

A stimulus strong enough to trigger an action potential in the motor neuron activates all of the accompanying muscle fibers

TABLE 19.2 Characteristics and Correspondence Between Motor Units and Muscle Fiber Types

|  | Force <br> Production | Contraction <br> Speed | Fatigue <br> Resistance | Sag $^{\boldsymbol{a}}$ | Muscle Fiber Type in <br> the Motor Unit |
| :--- | :---: | :--- | :---: | :--- | :---: |
| Motor Unit Designation | High | Fast | Low | Yes | Fast glycolytic (FG) |
| Fast fatigable (FFtype IIx) | Moderate | Fast | Moderate | Yes | Fast oxidative glycolytic (FOG) |
| Fastfatigue-resistant (FRtype IIa) | Low | Slow | High | No | Slow oxidative (SO) |
| Slow (Stype I) |  |  |  |  |  |

Modified from Lieber RL. Skeletal muscle structure, function, \& plasticity: the physiologic basis of rehabilitation. 3rd ed. Baltimore: Lippincott Williams \& Wilkins, 2009.
${ }^{a}$ Under repetitive stimuli, some motor units respond smoothly with a systematic increase in tension, while others first increase tension and then decrease or sag in response to the same tetanic stimulus. These sag characteristics can classify the different motor units. Only the slow motor units do not exhibit sag. This probably relates more to their diminished force-generating capabilities than fatigue characteristics.


Figure 19.11 Speed, force, and fatigue characteristics of motor units. Phasic motor neurons fire rapidly with short bursts; tonic motor neurons fire slowly but continuously.
in the motor unit to contract synchronously. A motor unit does not exert a force gradationeither the impulse elicits an action or it does not. After the neuron fires and the impulse reaches the NMJ, all fibers of the motor unit react simultaneously. This action embodies the principle of all or none that relates to the normal function of skeletal muscle.

## Gradation of Force

The force of muscle action varies from slight to maximal via two mechanisms:

1. Increased number of motor units recruited
2. Increased frequency of motor unit discharge

A muscle generates considerable force when activated by all of its motor units. Repetitive stimuli that reach a muscle before it relaxes also increase the total tension. Blending recruitment of motor units and modification of their firing rate permits optimal patterns of neural discharge that allow a wide variety of graded muscle actions. These range from the delicate touch of the eye surgeon to the maximal effort in throwing a baseball from deep center field on a straight line to throw out a runner charging home plate.

Control of Motor Function and Motor Unit Activity. Low-force muscle actions activate only a few motor units; a
higher force requirement progressively enlists more motor units. Motor unit recruitment describes adding motor units to increase muscle force. As muscle force requirements increase, motor neurons are recruited with progressively larger axons. This exemplifies the size principlean anatomic basis for the orderly recruitment of specific motor units to produce a smooth muscle action.

All of the motor units in a muscle do not fire at the same time (FIg. 19.12). If they did, it would be virtually impossible to control muscle force output. Consider the tremendous gradation of forces and speeds that muscles generate. When lifting a barbell, for example, specific muscles act to move the limb at a particular speed under a set rate of tension development. One can lift a relatively light weight at a number of speeds. But as weight increases, the speed options decrease accordingly. When lifting a pencil, one generates just enough force to lift the pencil regardless of how fast or slowly the arm moves. From the standpoint of neural control, the selective recruitment and firing pattern of the fast-twitch and slowtwitch motor units that control shoulder, arm, hand, and finger movements (and perhaps other stabilizing regions) provide the mechanism to produce the desired coordinated response.

In accordance with the size principle, slow-twitch motor units with lower thresholds for activation are selectively recruited during light to moderate effort. Activation of


## TType IIx $\square$ Type Ila $\square$ Type I

Figure 19.12 Recruitment of slow-twitch (type I) and fasttwitch (type Ila and b) muscle fibers (motor units) in relation to exercise intensity. More intense exercise progressively recruits more fast-twitch fibers.
slow-twitch units occurs during sustained jogging or cycling or slow swimming or slowly lifting a relatively light weight. More rapid, powerful movements progressively activate fast-twitch fatigue-resistant (type IIa) units up through the fast-twitch fatigable (type IIx) units at peak force. As a runner or cyclist reaches a hill during a distance race, some fasttwitch units become activated to maintain a fairly constant pace over varying terrain. Large single muscles with broad origins and/or insertions (like the deltoid), contain smaller, independently controlled muscles within muscles that activate depending on the segments line of action and direction of the intended motion. Such an arrangement allows CNS flexibility to fine-tune skeletal muscle activity to meet the demands of the imposed motor task. ${ }^{30}$

The differential control of motor unit firing patterns represents a major factor that distinguishes skilled from unskilled performances and specific athletic groups. ${ }^{6}$ Weightlifters generally exhibit a synchronous pattern of motor unit firing (i.e., many motor units recruited simultaneously during a lift), whereas the firing pattern of endurance athletes is more asynchronous (i.e., some motor units fire while others recover). The synchronous firing of fast-twitch motor units allows the weightlifter to generate force quickly for the desired lift. In contrast, for the endurance athlete, the asynchronous firing of predominantly slow-twitch, fatigue-resistant units serves as a built-in recuperative period so performance can continue with minimal fatigue. This occurs because motor units share the burden of multiple movements and intensities during exercise.

## INTEGRATIVE QUESTION

Explain how knowledge of neuromuscular exercise physiology can help to enhance an athletes (1) strength and power and (2) sports skill performance.

## Neuromuscular Fatigue

Fatigue represents the decline in muscle tension or force capacity with repeated stimulation or during a given time period. This definition also encompasses perceptual alterations of increased difficulty to achieve a desired submaximal or maximal exercise outcome. Many complex factors produce motor unit fatigue, each relating to specific exercise demands that produce it. ${ }^{1,13,15,17,18}$

Voluntary muscle actions exhibit four main components listed in the following order of nervous system hierarchy:

1. Central nervous system
2. Peripheral nervous system
3. Neuromuscular junction
4. Muscle fiber

Fatigue occurs from interrupting the chain of events between the CNS and muscle fiber, regardless of the reason. Four examples include:

1. Exercise-induced alterations in levels of CNS neurotransmitters serotonin, 5-hydroxytryptamine (5-HT), dopamine, and ACh in various brain regions, along with the neuromodulators ammonia and cytokines secreted by immune cells alter ones psychic or perceptual state to disrupt ability to exercise. ${ }^{4,19}$
2. Reduced glycogen content of the active muscle fibers relates to fatigue during prolonged intense exercise. ${ }^{2,7}$ This nutrient fatigue occurs even with sufficient oxygen available to generate energy through aerobic pathways. Depletion of phosphocreatine ( PCr ) and a decline in total adenine nucleotide pool (ATP + ADP + AMP) also accompanies the fatigue state in prolonged submaximal exercise. ${ }^{2}$
3. Oxygen lack and increased level of blood and muscle lactate relate to muscle fatigue in short-term, maximal exercise. The dramatic increase in $\left[\mathrm{H}^{+}\right]$in the active muscle dramatically disrupts the intracellular environment. ${ }^{12,23}$ Alterations in contractile function in anaerobic exercise also relate to five factors: (1) PCr depletion, (2) changes in myosin ATPase, (3) impaired glycolytic energy transfer capacity from reduced activity of the key enzymes phosphorylase and phosphofructokinase, (4) disturbance in the T-tubule system for transmitting the impulse throughout the cell, (5) and ionic imbalances. ${ }^{11}$ Downregulation in muscle $\mathrm{Na}^{+}, \mathrm{K}^{+}$, and $\mathrm{Ca}^{2+}$ release, distribution, and uptake alters the myofilament activity and impairs muscular
performance, ${ }^{16}$ even though nerve impulses continue to bombard the muscle fiber.
4. Fatigue occurs at the NMJ when an action potential fails to cross from the motor neuron to the muscle fiber. The precise mechanism for this aspect of neural fatigue remains unknown.

As muscle function changes (often declines) during prolonged submaximal exercise, additional motor-unit recruitment maintains the crucial force output necessary to maintain a relatively constant level of performance. During all-out exercise that presumably activates all motor units, a decrease in neural activity (as measured by the electromyogram or EMG) accompanies fatigue. Reduced neural activity supports the contention that failure in neural or myoneural transmission produces fatigue in maximal effort.

## INTEGRATIVE QUESTION

From a neuromuscular perspective, discuss the validity of the adage Perfect practice makes for perfect performance.

## RECEPTORS IN MUSCLES, JOINTS, AND TENDONS: THE PROPRIOCEPTORS

Muscles and tendons contain specialized sensory receptors sensitive to stretch, tension, and pressure. These end organs, known as proprioceptors, almost instantaneously relay information about muscular dynamics and limb movement to conscious and subconscious portions of the CNS. Proprioception allows continual monitoring of the progress of any sequence of movements and serves to modify subsequent motor behavior. ${ }^{20}$

## Muscle Spindles

The muscle spindles provide mechano-sensory information about changes in muscle fiber length and tension. They primarily respond to any stretch of a muscle. Through reflex response, they initiate a stronger muscle action to counteract this stretch.

## Structural Organization

Figure 19.13 shows a fusiform muscle spindle aligned in parallel to regular muscle fibers or extrafusal fibers. When the muscle stretches, the spindles also stretch. The number of

## FOCUS ON RESEARCH

## Muscular Fatigue: A Complex Phenomenon

Merton PA. Voluntary strength and fatigue. J Physiol (Lond) 1954;123:553.

- Since the turn of the 20th century, scientists have attempted to explain why repeated maximal muscular activity produced decreased tension output or fatigue in muscle. The debate over the site of fatigue focuses on the existence of either a central or peripheral mechanism. Central mechanism refers to a location proximal to the motor neuron (i.e., mainly the brain); a peripheral mechanism involves the motor units (i.e., anterior motor neurons, motor endplates, and muscle fibers). Merton reasoned that he could distinguish central and peripheral mechanisms by inducing fatigue in a muscle group with maximal voluntary contractions (MVCs) and then stimulating the motor unit electrically. Extra localized electrical stimulations failure to increase force production (i.e., no change in fatigue pattern) would indicate a purely peripheral fatigue site. In contrast, an increase in muscle tension (i.e., pattern of fatigue decreased) with electrical stimulation would support a central site hypothesis for muscular fatigue.

Merton experimented mainly on himself with an apparatus modified from one used to measure force
recordings of excised muscle from animals (left figure) that measured muscle tension output of the isolated adductor pollicis that produces thumb adduction. The upper arm remained fixed in a flexed position with the hand rotated outward and stabilized in a grasping position. The arm and hand rested in a splint-type device that allowed only thumb abduction/adduction movement. This hand and arm position enabled isolation and recording of muscle tension by either voluntary muscle action or electrical stimulation via the ulnar nerve.

Subjects performed maximal isometric actions to fatigue. Merton then delivered a series of single twitches evoked by stimulation of the ulnar nerve at approximately 12 -second intervals preceding and following fatigue. The top tracing in the right figure below shows the fatigue curve for the muscles during the sustained isometric MVC. Tension declined linearly over time, reaching onehalf its initial value in 1 minute. The lower tracing shows the corresponding action potentials in response to repeated nerve stimulation. Stimulating the motor nerve electrically did not alter the fatigue pattern. Merton reasoned that some part of the peripheral apparatus directly affected fatigue during MVC. Nerve stimulation did not diminish

spindles within a quantity of muscle varies depending on the muscle group. On a relative basis, muscles involved in complex movements contain more spindles per gram of muscle than muscles that perform gross movement patterns. The spindle, covered by a sheath of connective tissue, contains two specialized types of muscle fiber called intrafusal fibers. One type of intrafusal fiber, the fairly large nuclear bag fiber, contains numerous nuclei packed centrally through its diameter. Each spindle usually contains two nuclear bag fibers. The other type of intrafusal fiber, the nuclear chain fiber, contains many nuclei along its length. These fibers attach to the surface of the longer nuclear bag fibers. Each spindle usually contains four to five chain fibers. The ends of the intrafusal fibers contain actin and myosin filaments and exhibit shortening capability.

Two sensory afferent fibers and one motor efferent fiber innervate the spindles. A primary afferent nerve fiber, the annulospiral nerve fiber (composed of a set of rings in
spiral configuration), entwines about the mid-region of the bag fiber. This fiber responds directly to the stretch of the spindle; its firing frequency or discharge rate increases in proportion to the stretch. A second group of smaller sensory nerve fibers, the flower-spray endings, makes connections mainly on the chain fibers but also attaches to the bag fibers. These endings show less sensitivity to stretch than annulospiral fibers. Activation of the annulospiral and flowerspray sensors relays impulses through the dorsal root into the cord to produce reflex activation of the motor neurons to the stretched muscle. This causes the muscle to act more forcefully and shorten, which reduces the stretch stimulus from the spindles.

The third type of spindle nerve fiber, the thin $\boldsymbol{\gamma}$-efferent fiber that innervates the contractile, striated ends of the intrafusal fibers, serves a motor function. Higher centers in the brain activate these fibers to maintain optimal sensitivity of the spindle at all muscle lengths. Regardless of the muscles


Figure 19.13 Structural organization of the muscle spindle with an enlarged view of the equatorial region of the spindle.
overall length, $\gamma$-efferent stimulation activates the intrafusal fibers to regulate their length and sensitivity. This mechanism prepares the spindle for other lengthening actions, even when the muscle remains shortened. Adjustments in $\gamma$-efferent activation allow the spindle to continuously monitor the length of the muscles that contain them.

## The Stretch Reflex

The muscle spindle detects, responds to, and modulates changes in the length of the extrafusal muscle fibers. This provides an important regulatory function for movement and maintenance of posture. Postural muscles continuously receive neural input to sustain their readiness to respond to conscious (voluntary) movements. These muscles require continual subconscious activity to adjust to the pull of gravity in upright posture. Without this monitoring and feedback mechanism, the body would literally collapse into a heap from the absence of tension in neck muscles, spinal muscles, hip flexors, abdominal muscles, and large leg musculature. To this end, the stretch reflex provides a fundamental controlling mechanism.

Three main components make up the stretch reflex:

1. Muscle spindle that responds to stretch
2. Afferent nerve fiber that carries the sensory impulse from the spindle to the spinal cord
3. Efferent spinal cord motor neuron that activates the stretched muscle fibers

Figure 19.14 illustrates the patellar tendon stretch reflex (knee-jerk reflex), the simplest autonomic reflex arc that
involves only one synapse (monosynaptic). The spindles lie parallel to the extrafusal fibers so they stretch when these fibers elongate as the hammer strikes the patellar tendon. The spindles sensory receptors fire when its intrafusal fibers stretch. This directs impulses through the dorsal root into the spinal cord to directly activate the anterior motor neurons. The gray matter contains neuron cell bodies; the white matter carries longitudinal columns of nerve fibers. Stimulation of a single $\alpha$-motor neuron affects up to 3000 muscle fibers. The reflex also activates interneurons within the cord to facilitate the appropriate motor response. For example, excitatory impulses activate synergistic muscles that support the desired movement, while inhibitory impulses flow to motor units that normally counter the movement. In this way, the stretch reflex acts as a self-regulating, compensating mechanism. This salient feature allows the muscle to adjust automatically to differences in load (and length) without requiring immediate information processing through higher CNS centers.

## Golgi Tendon Organs

In contrast to the muscle spindles that lie parallel to the extrafusal muscle fibers, the Golgi tendon organs (first identified in 1898 by Italian physician Camillo Golgi (1843 1926) and named in honor of him) connect to up to 25 extrafusal fibers near the tendons junction to the muscle. These finetuned sensory receptors detect differences in the tension generated by active muscle rather than muscle length. Figure 19.15 shows that the Golgi tendon organs respond as


Figure 19.14 The patella tendon stretch reflex (shows only one side of the spinal nerve complex).
a feedback monitor to discharge impulses under either of two conditions:

1. Tension created in the muscle when it shortens
2. Tension when the muscle stretches passively

When stimulated by excessive tension, the Golgi receptors transmit signals to the spinal cord to elicit reflex inhibition of the muscles they supply. This occurs from the overriding influence of the inhibitory spinal interneuron on the motor neurons supplying the muscle. Consider Golgi tendon organs as a protective sensory mechanism much like a governor mechanism that sets the speed limit for motorized go-carts. Excessive change in muscle tension increases the Golgi sensors discharge to depress motor neuron activity and reduces force output. Golgi receptors remain relatively inactive and exert little influence if muscle action produces little tension. Ultimately, the Golgi tendon organs protect the
muscle and surrounding connective tissue harness from injury from sudden or excessive load.

## Pacinian Corpuscles

Pacinian corpuscles are small, ellipsoidal bodies located close to the Golgi tendon organs and embedded in a single, unmyelinated nerve fiber. These sensitive sensory receptors respond to quick movement and deep pressure. Deformation or compression of the onionlike capsule by a mechanical stimulus transmits pressure to the sensory nerve ending within its core to change the electric potential of the sensory nerve ending. If this generator potential achieves sufficient magnitude, a sensory signal propagates down the myelinated axon that leaves the corpuscle and enters the spinal cord.

Pacinian corpuscles act as fast-adapting mechanical sensors. They discharge a few impulses at the onset of a steady

## IN A PRACTICAL SENSE

## How to Determine Upper-Arm Muscle and Fat

Girth measurements include bone surrounded by a mass of muscle tissue ringed by a layer of subcutaneous fat (Fig. A). Muscle represents the largest component of girth (except in obese and elderly persons), so girth indicates ones relative muscularity. The procedure for estimating limb muscle area assumes similarity between a limb and a cylinder, with subcutaneous fat evenly distributed around the cylinder (Fig. A).

## MEASUREMENTS

Determine the following:

1. Upper-arm girth (relaxed triceps; $\mathrm{G}_{\text {arm }}$ ): Measure with arm extended relaxed at the side (or parallel to the ground in an abducted position). Measure girth (cm) midway between the acromial and olecranon process (Fig. B).
2. Triceps skinfold ( $\mathrm{St}_{\text {trif }}$ ): Measure in decimeters ( $\mathrm{dm} ; \mathrm{mm} \div 10$ ) on the back of the arm over the triceps muscle as a vertical fold at the same level as the relaxed arm girth (Fig. C).
3. Arm muscle area, $\mathrm{cm}^{2}$

$$
=\left[\mathrm{G}_{\text {arm }}-\left(\pi \mathrm{Sf}_{\mathrm{tri}}\right)\right] \div 4 \pi
$$

$$
=(30.0 \mathrm{~cm})-(\pi 2.5 \mathrm{dm})^{2} \div 4 \pi
$$

$=488.4 \div 12.566$
$=38.9 \mathrm{~cm}^{2}$
3. Arm area (A), $\mathrm{cm}^{2}$

$$
=\left(\mathrm{G}_{\mathrm{arm}}\right)^{2} \div 4 \pi
$$

$=(30.0 \mathrm{~cm})^{2} \div 4 \pi$
$=900 \div 12.566$
$=71.6 \mathrm{~cm}^{2}$
4. Arm fat area, $\mathrm{cm}^{2}$
$=$ arm area - arm muscle area
$=71.6 \mathrm{~cm}^{2}-38.9 \mathrm{~cm}^{2}$
$=32.7 \mathrm{~cm}^{2}$
5. Arm fat index, \% fat area

$$
=(\text { arm fat area } \div \text { arm area }) \times 100
$$

$=\left(32.7 \mathrm{~cm}^{2} \div 71.6\right) \times 100$
$=45.7 \%$

## EXAMPLE

Data: Upper-arm girth $\left(\mathrm{G}_{\mathrm{arm}}\right)$ in $\mathrm{cm}=30.0 ; \mathrm{Sf}_{\mathrm{tri}}=2.5 \mathrm{dm}(25 \mathrm{~mm})$.

## COMPUTATIONS

1. Arm muscle girth, cm
$=\mathrm{G}_{\text {arm }}-\left(\pi \mathrm{Sf}_{\text {tri }}\right)$
$=30.0 \mathrm{~cm}-(\pi 2.5 \mathrm{dm})$
$=30.0-7.854$
$=22.1 \mathrm{~cm}$

(A) Upper-arm composition and area


CTriceps skinfold, mm


Figure 19.15 Golgi tendon organ, named for the Italian anatomist and Nobel laureate Camillo Golgi who first described these proprioceptors in the late 1800s. Excessive tension or stretch on a muscle activates the Golgi receptors to initiate a reflex inhibition of the muscles they supply. The Golgi tendon organ functions as a protective sensory mechanism to detect and subsequently inhibits undue strain within the muscle tendon structure.
stimulus and then remain electrically silent or they discharge a second volley of impulses when the stimulus ceases. They detect changes in movement or pressure rather than the magnitude of movement or the quantity of pressure applied.

## Summary

1. Neural control mechanisms located in the central nervous system (CNS) regulate human movement.
2. Skeletal muscles respond to internal and external stimuli where bits of sensory input automatically are coded, routed, organized, and transmitted to the effector organthe skeletal muscles.
3. Tracts of neural tissue descend from the brain to influence spinal cord neurons. Neurons in the extrapyramidal tract control posture and provide a continual background level of neuromuscular tone; the pyramidal tract neurons stimulate discrete muscular movements.
4. The cerebellum fine-tunes muscle activity through its function as the major comparing, evaluating, and integrating center.
5. The spinal cord and other subconscious areas of the CNS control many muscle functions. The reflex arc provides the basic mechanism to process automatic muscle actions.
6. The motor unit makes up the functional unit of movement. The number of muscle fibers in a motor unit depends on a muscles movement function. Intricate movement patterns require a small fiber-to-neuron ratio; a single neuron can innervate 1000 muscle fibers for gross movements.
7. The anterior motor neuron (cell body, axon, and dendrites) transmits electrochemical nerve impulses from the spinal cord to the muscle. The dendrites receive impulses and conduct them toward the cell body; the axon transmits the impulse one way down the axon to the muscle.
8. The neuromuscular junction (NMJ) establishes the interface between motor neuron and muscle fiber. Acetylcholine (ACh) release at the NMJ provides the chemical stimulus that activates the muscle fiber.
9. Stimulation of a muscle fiber progresses in the following six-step sequence: (1) action potential
propagates down the motor neurons axon; (2) calcium channels open at the end of the nerve terminal; (3) calcium moves into the nerve terminal;
(4) ACh primes for release; (5) ACh traverses the synapse and binds to ACh receptors on the postsynaptic membrane at the sarcolemma; and (6) endplate potential generates and a depolarization wave spreads throughout the T-tubular network.
10. Excitatory and inhibitory impulses continually bombard the synaptic junctions between neurons. These impulses alter a neurons threshold for excitation by increasing or decreasing its tendency to fire.
11. During all-out power exercise, a high degree of neural facilitation (disinhibition) proves beneficial because it maximally activates a muscles motor units.
12. Motor units classify into three types depending on speed of muscle action, force generated, and fatigability: (1) fast twitch, high force, fast fatigue; (2) fast twitch, moderate force, fatigue resistant; and (3) slow twitch, low force, fatigue resistant.
13. Muscle force gradation progresses through the interaction of factors that regulate the number and type of motor units recruited and their discharge frequency. Low-intensity exercise recruits slowtwitch motor units, followed by fast-twitch unit activation when requiring more-powerful forces.
14. Alterations in motor unit recruitment and firing pattern help to explain the rapid strength improvement during the early stages of resistance training.
15. Sensitive sensory receptors in muscles, tendons, and joints relay information about muscle dynamics and limb movement to specific portions of the CNS to provide important sensory feedback during physical activity.
16. Golgi sensory receptors are sensitive to quick movement and deep pressure. Pacinian corpuscles detect changes in movement or pressure.

References are available online at http://thepoint.lww.com/mkk7e.

## CHAPTER 20



## The Endocrine System: Organization and Acute and Chronic Responses to Exercise

## CHAPTER OBJECTIVES

- Draw the locations of the bodys major endocrine glands
- List the sequence of events to show how hormones affect specific target cell functions
> Outline the role of the intracellular messenger cyclic $3^{\prime}, 5^{\prime}$-adenosine monophosphate (cyclic AMP)
- Explain how hormones affect enzyme activity and enzyme-mediated membrane transport
> Describe the influence of hormonal, humoral, and neural stimulation on endocrine gland activity
- List the anterior and posterior pituitary gland hormones, their functions, and how acute and chronic physical activity affect their release
> List the thyroid gland hormones, their functions, and how acute and chronic physical activity affect their release
- List the adrenal medulla and adrenal cortex hormones, their functions, and how acute and chronic physical activity affect their release
$>$ List hormones of the $\alpha$ - and $\beta$-cells of the pancreas, their functions, and how acute and chronic physical activity affect their release
- Define type 1 and type 2 diabetes and the symptoms and effects of each disorder
- Describe three test options for diagnosing diabetes mellitus
- List the fasting blood glucose classification categories for type 2 diabetes
> List risk factors for type 2 diabetes and benefits of regular physical activity to prevent and treat this disease
> Outline how exercise training affects endocrine function
- Describe the effect of resistance training on testosterone and growth hormone release
> Characterize the functions of opioid peptides, their response to physical activity, and possible role in the exercise high
> Outline interactions among short-term, moderate, and exhaustive exercise, exercise training, susceptibility to illness, and immune function

The endocrine system integrates and regulates bodily functions to stabilize the internal environment. Hormones produced by endocrine glands affect all aspects of human function; they activate enzyme systems, alter cell membrane permeability, trigger muscular contraction and relaxation, stimulate protein and fat synthesis, initiate cellular secretion, and determine how the body responds to physical and psychologic stress. The following sections provide a general overview of the endocrine system, its functions during rest and physical activity, and responses to acute exercise and training.

## ENDOCRINE SYSTEM OVERVIEW

Relatively small compared with other body organs, the combined weight of the endocrine organs averages 0.5 kg . Figure 20.1 shows the location of the major endocrine organs-the pituitary, thyroid, parathyroid, adrenal, pineal, and thymus glands. Several other organs contain discrete areas of endocrine tissue that also produce hormones. These include the pancreas, gonads (ovaries and testes), hypothalamus, and adipose (fat) tissues. The hypothalamus also serves as a major organ of the nervous system; thus it functions as a neuroendocrine organ. Pockets of hormone-producing cells also form in the walls of the small intestine, stomach, kidneys, and myocytes in the heart s atria, although these organs exert little influence on hormone production per se.

## ENDOCRINE SYSTEM ORGANIZATION

The endocrine system (the term endocrine means hormone secreting ) consists of a host organ (gland), minute quantities of chemical messengers (hormones), and a target or receptor organ. Glands classify as either endocrine or exocrine. Some glands serve both functions.

Endocrine glands possess no ducts (referred to as ductless glands) and secrete substances directly into extracellular spaces around the gland. Figure 20.2 shows that these hormones then diffuse into blood for transport throughout the body to fulfill their intercellular communication functions. Exocrine glands, in contrast, contain secretory ducts that carry substances directly to a specific compartment or surface. Examples of exocrine glands include sweat glands and
glands of the upper digestive tract. The nervous system controls almost all exocrine glands.

## Types of Hormones

Hormones, chemical substances synthesized by specific host glands, enter the bloodstream for transport throughout the body. Hormones generally fit into one of two categories: steroid-derived hormones and amine and polypeptide hormones synthesized from amino acids. In contrast to steroid hormones, amine and peptide hormones are soluble in blood plasma. This allows easy uptake at target sites. The term halflife describes the time required to reduce a hormone s blood concentration by one-half. For example, the half-life of epinephrine is slightly less than 3 minutes. Most orally consumed anabolic hormones such as testosterone have a half-life of approximately 3.5 hours. A hormone s half-life gives a good indication of how long its effect persists. Table 20.1 compares the storage, synthesis, release mechanism, transport medium, receptor location and receptor-ligand binding, and target organ response of the peptide, steroid, and amine hormones.

Table 20.2 lists eight different hormones produced by organs other than the major endocrine glands. Of these, prostaglandins constitute a third chemical class of hormones; they represent biologically active lipids in the plasma membrane of nearly all cells. Erythropoietin, a glycoprotein, stimulates the bone marrow s production of red blood cells.

Most hormones circulate in the blood as messengers that affect tissues a distance from the specific gland. Other hormones (e.g., prostaglandins and the gastrointestinal hormone gastrin) exert local effects in their region of synthesis.

## Hormone Target Cell Specificity

Hormones alter cellular reactions of specific target cells in four ways:

1. Modify the rate of intracellular protein synthesis by stimulating nuclear DNA
2. Change rate of enzyme activity
3. Alter plasma membrane transport via a secondmessenger system
4. Induce secretory activity


Figure 20.1 Location of the hormone-producing endocrine organs.

A target cell s response to a hormone depends largely on the presence of specific protein receptors that bind the hormone in a complementary way. Target cell receptors occur either on the plasma membrane (up to 10,000 receptors per cell) or in the cell s interior switch as occurs for fat-soluble steroid hormones that pass through the plasma
membrane. Hormone receptors exist in specific local areas or more diffusely throughout the body. For example, adrenal cortex cells contain receptors for adrenocorticotropic hormone (ACTH). In contrast, all cells contain receptors for thyroxine, the principal hormone that stimulates cellular metabolism.


Figure 20.2 Hormones secreted from endocrine glands travel in the bloodstream to exert influence on body tissues.

## Hormone Receptor Binding

Hormone receptor binding is the first step in initiating hormone action. The extent of a target cell s activation by a hormone depends on three factors:

1. Hormone concentration in the blood
2. Number of target cell receptors for the hormone
3. Sensitivity or strength of the union between hormone and receptor

Consider cell hormone receptors as dynamic structures that continually adjust to physiologic demands. Upregulation describes the state whereby target cells form more receptors in response to increasing hormone levels (to increase the hormone $s$ effect). In contrast, prolonged exposure to high hormone concentrations desensitizes target cells to blunt hormonal stimulation. Such downregulation also involves a loss of receptors to prevent target cells from overresponding to chronically high hormone levels (to decrease the hormone s effect).

Cyclic AMP: The Intracellular Messenger. The binding of a hormone with its specific receptor in the plasma
membrane alters the target cell s permeability to a particular chemical (e.g., insulin s effect on cellular glucose uptake) or modifies the target cell s ability to manufacture intracellular substances, primarily proteins. Such actions ultimately affect cellular function. Figure 20.3 shows that for the nonsteroid hormones epinephrine and glucagon, the binding hormone acts as first messenger to react with the enzyme adenylate cyclase in the plasma membrane. This forms the compound cyclic $3^{\prime} 5^{\prime}$-adenosine monophosphate (cyclic AMP) from an original ATP molecule. Cyclic AMP then acts as a ubiquitous second messenger to activate a specific protein kinase, which then activates a target enzyme to alter cellular function.

The sequence of reactions set into motion by cyclic AMP depends on three factors:

1. Type of target cell
2. Specific enzymes contained in the target cell
3. Specific hormone that acts as first messenger

In thyroid cells, for example, cyclic AMP promotes thyroxine synthesis from the binding of thyroid-stimulating hormone. In bone and muscle, cyclic AMP produced via growth-hormone binding activates anabolic reactions to synthesize amino acids into tissue proteins.

## Hormone Effects on Enzymes

Major hormone actions include altering enzyme activity and enzyme-mediated membrane transport. A hormone increases enzyme activity in one of three ways:

1. Stimulates enzyme production
2. Combines with the enzyme to alter its shape and ability to act (a chemical process known as allosteric modulation), which increases or decreases the enzyme s catalytic effectiveness
3. Activates inactive enzyme forms, thus increasing the total amount of active enzyme
In addition to altering enzyme activity, hormones either facilitate or inhibit uptake of substances by cells. Insulin, for example, facilitates glucose transport into the cell by combining with extracellular glucose and a glucose carrier within the plasma membrane. In contrast, epinephrine inhibits insulin release, thus slowing cellular glucose uptake.

Hormone action can exert potent (although often indirect) secondary effects. For instance, insulin release increases glucose uptake by muscle fibers (primary effect), which in turn increases muscle glycogen synthesis (secondary effect). This effect of insulin on glucose uptake (and glycogen synthesis) maintains fuel homeostasis during exercise. In insulin-deficient individuals, depressed glucose metabolism impairs exercise performance. Inadequate cellular glucose uptake from chronic insulin deficiency abnormally increases blood glucose concentrations. In the extreme, glucose spills into the urine. We discuss the conditions of insulin insufficiency and/or insulin resistance in more detail on pp. 421429.

## TABLE 20.1 Storage, Synthesis, Release Mechanism, Transport Medium, Receptor Location and Receptor-Ligand Binding, and Target Organ Response of the Peptide, Steroid, and Amine Hormones

|  | Peptide Hormones | Steroid Hormones | Amine Hormones |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  |  | Catecholamines | Thyroid Hormones |
| Examples | Insulin, glucagon, leptin, IGF-1 | Androgens, DHEA, cortisol | Epinephrine, norepinephrine | Thyroxine ( $\mathrm{T}_{4}$ ) |
| Synthesis and storage | Made in advance; stored in secretory vesicles | Synthesized on demand from precursors | Made in advance; stored in secretory vesicles | Made in advance; precursor stored in secretory vesicles |
| Release from parent cell | Exocytosis ${ }^{\text {a }}$ | Simple diffusion | Exocytosis | Simple diffusion |
| Transport medium | Dissolved in plasma | Bound to carrier proteins | Dissolved in plasma | Bound to carrier proteins |
| Lifespan (half-life ${ }^{\text {b }}$ ) | Short | Long | Short | Long |
| Receptor location | On cell membrane | Cytoplasm of nucleus; some have membrane receptors | On cell membrane | Nucleus |
| Response to receptor-ligand binding ${ }^{c}$ | Activation of second messenger system; may activate genes | Activate genes for transcription and translation; may have nongenomic actions | Activation of second messenger system | Activate genes for transcription and translation |
| General target response | Modification of existing proteins and induction of new protein synthesis | Induction of new protein synthesis | Modification of existing proteins | Induction of new protein synthesis |
| ${ }^{a}$ Process in which intracellular vesicles fuse with the cell membrane and release their contents into the extracellular fluid. <br> ${ }^{b}$ Amount of time required to reduce hormone concentration by one-half. <br> ${ }^{c}$ A ligand (the molecule that binds to a receptor) binds to a membrane protein, which triggers endocytosis (process of how a cell brings molecules into the cytoplasm in vesicles formed from the cell membrane). |  |  |  |  |

## Factors That Determine Hormone Levels

Hormone secretion rarely occurs at a constant rate. As with nervous system activity, hormone secretion usually adjusts rapidly to meet the demands of changing bodily conditions. For this reason, all protein hormones secrete in a pulsatile manner (see next section). Four factors determine plasma concentration of a particular hormone:

1. Quantity synthesized in the host gland
2. Rate of either catabolism or secretion into the blood
3. Quantity of transport proteins present (for some hormones)
4. Plasma volume changes

Hormone secretion rate depends on the magnitude of chemical stimulatory or inhibitory input from more than one


Figure 20.3 Action of nonsteroid hormones. Circulating hormone (first messenger) binds to a specific receptor in the cells plasma membrane to trigger production of cyclic AMP from ATP catalyzed by adenylate cyclase. Cyclic AMP then acts as second messenger to activate a protein kinase within the cell. This in turn activates a target enzyme to elicit the cellular response.

TABLE 20.2 Hormones Produced by Organs Other than the Major Endocrine Organs

| Hormone | Composition | Source and <br> Stimulus for Secretion | Target and Outcome |
| :--- | :--- | :--- | :--- |

${ }^{a}$ The kidneys release an enzyme that modifies a circulating blood protein to produce erythropoietin.
source. Insulin secretion from the pancreas, for example, responds directly to plasma changes in glucose and amino acids, norepinephrine (from sympathetic neurons) and circulating epinephrine, and acetylcholine released from parasympathetic neurons. Each of these chemical messengers supplies inhibitory or excitatory input that determines whether insulin secretion increases or decreases. Over an extended time (different for each hormone), hormone synthesis tends to equal hormone release. For a relatively short time, however, hormone release can exceed its synthesis. The term secreted amount describes the plasma concentration of a hormone. In reality, this represents the sum of hormone synthesis and release by the host gland, in addition to its uptake by receptor tissues and removal by liver and kidneys.

Hormone concentration depends on its rate of secretion into the blood and/or the rate of its metabolism (i.e., it becomes
inactive). Hormone inactivation takes place at or near receptors or in the liver or kidneys. Because blood flow to splanchnic and renal areas decreases during physical activity (blood distributes to active muscle), hormone inactivation rate decreases and plasma hormone concentration rises.

Changes in plasma volume also alter hormone concentrations, independent of the host organ s secretion rate. For example, decreased plasma volume during prolonged exercise concurrently increases plasma hormone concentration, even without an absolute change in hormone amount.

Figure 20.4 shows that three factors-hormonal, humoral, and neural-stimulate endocrine gland activity.

1. Hormonal stimulation: Hormones influence secretion of other hormones. For example, release-inhibiting hormones produced by the hypothalamus regulate


Figure 20.4 Endocrine gland stimulation. A. Hormonal. Adrenocorticotropic hormone (ACTH) stimulates release of glucocorticoid hormones by the adrenal cortex. B. Humoral. High blood glucose concentrations trigger insulin release, causing rapid cellular glucose uptake. The subsequent decrease in blood glucose removes the stimulus for insulin release. C. Neural. Sympathetic nervous system fibers trigger catecholamine release to blood. (From Marieb E, Hoehn K. Human anatomy and physiology. 7th edition, Redwood City, CA: Benjamin/Cummings, 2007)
the secretion of most anterior pituitary hormones. Anterior pituitary hormones, in turn, stimulate other endocrine organs to release their hormones into the bloodstream. The increased blood levels of a hormone produced by the final target gland provide feedback to inhibit release of anterior pituitary hormones and ultimately their own release.
2. Humoral stimulation: Changing levels of ions and nutrients in blood, bile, and other body fluids stimulate hormone release. The term humoral stimuli describes these chemicals to distinguish them from hormonal stimuli, which also are fluid-borne chemicals. For example, an increase in blood sugar concentration (the humoral agent) prompts the pancreas to release insulin. Insulin promotes glucose entry into cells, causing blood sugar levels to decline, ending the humoral stimulus for insulin release.
3. Neural stimulation: Neural activity affects hormone release. For example, sympathetic neural activation of the adrenal medulla during stress releases epinephrine and norepinephrine. The nervous system can override normal endocrine control to maintain homeostasis. Insulin action normally maintains blood sugar levels between 80 and 120 mg per 100 mL ( 1 dL ) of blood. During exercise, activation of the hypothalamus and sympathetic nervous system blunts insulin release to attenuate a further decline in blood sugar and ensure sufficient carbohydrate to fuel neural tissue and active muscle.

## Patterns of Hormone Release

Most hormones respond to peripheral stimuli on an as-needed basis. Others release at regular intervals during
a 24 -hour cycle referred to as a diurnal pattern, or cycle, of secretion. Some secretory cycles span several weeks while others follow daily cycles. Cycling patterns are not confined to one category of hormones. Pulsatile hormone release patterns reveal information not available from a single blood sample that fails to show potentially significant variation in hormone levels during a daily cycle. Patterns of release and/or amplitude and frequency of discharge provide more meaningful information regarding hormone dynamics than simply examining mean concentration at any single time.
integrative question
Explain the meaning of the following statement: Hormones act as silent messengers to integrate the body as a unit.

## RESTING AND EXERCISE-INDUCED ENDOCRINE SECRETIONS

Table 20.3 lists the different endocrine host organs and nonglandular endocrine tissues, specific hormones secreted, hormone targets, and main effects. The following sections review these hormones, with special emphasis on their immediate response to exercise and adaptations to physical training.

## Anterior Pituitary Hormones

Figure 20.5 illustrates the pituitary gland (also called the hypophysis), its secretions, and various target glands and their hormone secretions. Located beneath the base of the brain, the pituitary secretes at least six specialized polypeptide hormones. Because of its widespread influence, the anterior pituitary gland was often called the master gland. Researchers now know that the hypothalamus controls anterior pituitary activity; thus, the hypothalamus should truly claim that distinction. Each of the primary pituitary hormones has its own hypothalamic releasing hormone called a releasing factor. Neural input to the hypothalamus from anxiety, stress, and physical activity controls output of these releasing factors. In addition to the hormones displayed in Figure 20.5, the pituitary secretes proopiomelanocortin (POMC), a large precursor molecule of other active molecules. POMC provides the source of a number of neurotransmitters and hormones including ACTH, melanocortin peptides, and some of the naturally produced opiates such as $\beta$-endorphin (see p. 439). These hormones exert a remarkable range of influence, including effects on pigmentation, adrenocortical function, food intake and fat storage, and nervous and immune system functions.

## Growth Hormone

Growth hormone releasing factor from the hypothalamus influences resting growth hormone (GH) secretion by directly stimulating the anterior pituitary gland. GH (also called somatotropin) represents a family of related polypeptides (derived from one gene) that exert widespread physiologic activity because they promote cell division and cellular proliferation throughout the body. In adults, GH facilitates protein synthesis in three ways:

1. Increasing amino acid transport through the plasma membrane
2. Stimulating RNA formation
3. Activating cellular ribosomes that increase protein synthesis

GH also slows carbohydrate breakdown and initiates subsequent mobilization and use of fat as an energy source.

Growth Hormone, Physical Activity, and Tissue Synthesis. Increased physical activity of relatively short duration stimulates a sharp rise in GH pulse amplitude and the amount of hormone secreted per pulse. ${ }^{12,77,169}$ Perhaps more importantly, physical activity stimulates release of GH isoforms with extended half-lives, thereby extending GH s action on target tissues. ${ }^{122}$ Augmented GH release benefits muscle, bone, and connective tissue growth and remodeling. It also optimizes the fuel mixture during physical activity, principally decreasing tissue glucose uptake, increasing free fatty acid mobilization, and enhancing liver gluconeogenesis. The net metabolic effect of increased exercise-induced GH production preserves plasma glucose concentration for central nervous system and muscle functions. Many of the growth-promoting effects of GH result from actions of intermediary chemical messengers on different target tissues, rather than a direct effect of GH itself. These peptide messengers, produced in the liver, are termed somatomedins, or insulin-like growth factors (IGF-1 and IGF-II; see next section) because of their structural similarity to insulin. These factors exert potent peripheral effects on motor units and other tissues.

How physical activity stimulates GH release to augment protein synthesis (and subsequent muscle hypertrophy), cartilage formation, skeletal growth, and cell proliferation remains unclear, although the total integrated growth hormone concentration increases with physical activity duration in men and women. ${ }^{170}$ Concurrent measurements of circulating lactate, alanine, and pyruvate; blood glucose; and body temperature reveal no association with GH secretory patterns during exercise. ${ }^{78}$ One hypothesis suggests that exercise directly stimulates GH release (or release of somatomedins from the liver or kidneys), which in turn stimulates anabolic processes. Exercise also may indirectly affect GH by stimulating cholinergic pathways to trigger GH release. Moreover, it is known that physical activity stimulates endogenous opiate production that facilitates GH release by inhibiting the liver s production of somatostatin, a hormone that blunts GH release. ${ }^{166}$

TABLE 20.3 Endocrine Organs and Their Secretions, Targets, and Main Effects

| Location | Gland or Cells | Chemical Type | Hormone | Target | Main Effect |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Adipose tissue | Cells | Peptide | Leptin; adiponectin (resistin) | Hypothalamus, other tissues | Food intake, metabolism, reproduction |
| Adrenal cortex | Gland | Steroid | Mineralocorticoids (aldosterone) | Kidney | Stimulates $\mathrm{Na}^{+}$reabsorption and $\mathrm{K}^{+}$secretion |
|  |  |  | Glucocorticoids (cortisol; corticosterone) | Many tissues | Promotes protein and fat catabolism; raises blood glucose levels; adapts body to stress |
|  |  |  | Androgens (androstenedione; dehydroepiandrosterone [DHEA]; estrone) | Many tissues | Promotes sex drive |
| Adrenal medulla | Gland | Amine | Epinephrine, norepinephrine | Many tissues | Facilitates sympathetic activity; increases cardiac output; regulates blood vessels; increases glycogen catabolism and fatty acid release |
| Gastrointestinal tract (stomach and small intestine) | Cells | Peptide | Gastrin; cholecystokinin (CCK); secretin; glucose-dependent insulinotropic peptide (GIP) | GI tract and pancreas | Assist digestion and absorption of nutrients; regulates gastrointestinal motility |
| Heart | Cells | Peptide | Atrial natriuretic peptide (ANP) | Kidney tubules | Inhibits sodium reabsorption |
| Hypothalamus | Clusters of neurons | Peptide | Trophic hormones (releasing and release-inhibiting hormones: corticotropinreleasing hormone [CRH]; thyrotropinreleasing hormone [TRH]; growth hormone-releasing hormone [GHRH]; gonadrotropinreleasing hormone [GnRH]) | Anterior pituitary | Release or inhibit anterior pituitary hormones |
| Kidney | Cells | Peptide Steroid | Erythropoietin (EPO) <br> 1,25 Dihydroxy- <br> vitamin $D_{3}$ <br> (calciferol) | Bone marrow Intestine | Red blood cell production Increases calcium absorption |
|  |  |  |  |  |  |
| Liver | Cells | Peptide | Angiotensinogen | Adrenal cortex, blood vessels, brain | Aldosterone secretion; increases blood pressure |
|  |  |  | Insulin-like growth factors (IGF-1) | Many tissues | Growth |
| Muscle | Cells | Peptide | Insulin-like growth factors (IGF-1, IGF-II); myogenic regulatory factors (MRFs) | Many tissues | Growth |
| Pancreas | Gland | Peptide | Insulin | Many tissues | Lowers blood glucose levels; promotes protein, lipid, and glycogen synthesis |
|  |  |  | Glucagon | Many tissues | Raises blood glucose levels; promotes glycogenolysis and gluconeogenesis |

TABLE 20.3 Endocrine Organs and Their Secretions, Targets, and Main Effects continued

| Location | Gland or Cells | Chemical Type | Hormone | Target | Main Effect |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  | Somatostatin (SS) | Many tissues | Inhibits secretion of pancreatic hormones; regulates digestion and absorption of nutrients by GI system |
| Parathyroid | Gland | Peptide | Parathyroid hormone (PTH) | Bone, kidney | Promotes $\mathrm{Ca}^{2+}$ release from bone, $\mathrm{Ca}^{2+}$ absorption by intestine, and $\mathrm{Ca}^{2+}$ reabsorption by kidney; raises blood $\mathrm{Ca}^{2+}$ levels; stimulates vitamin $\mathrm{D}_{3}$ synthesis |
| Pineal gland | Gland | Amine | Melatonin | Unknown | Controls circadian rhythms |
| Pituitaryanterior | Gland | Peptides | Growth hormone (GH) | Many tissues | Growth; stimulates bone and soft tissue growth; regulates protein, lipid, and CHO metabolism |
|  |  |  | Adrenocorticotropic hormone (ACTH) | Adrenal cortex | Stimulates glucocorticoid secretion Stimulates secretion of thyroid hormones |
|  |  |  | Thyroid-stimulating hormone (TSH) Prolactin | Thyroid gland |  |
|  |  |  |  | Breast | Milk secretion |
|  |  |  | Follicle-stimulating hormone (FSH) | Gonads | Females: stimulates growth and development of ovarian follicles and estrogen secretion; Males: sperm production by testis |
|  |  |  | Luteinizing hormone (LH) | Gonads | Females: stimulates ovulation, secretion of estrogen and progesterone; Males: testosterone secretion by testis |
| Pituitaryposterior | Extension of hypothalamic neurons | Peptide | Oxytocin (OT) | Breast and uterus | Females: stimulates uterine contractions and milk ejection by mammary glands; Males: unknown function |
|  |  |  | Antidiuretic hormone (ADH or vasopressin) | Kidney | Decreases urine output by kidneys; promotes blood vessel (arteriole) constriction |
| Placenta (pregnant female) | Gland | Steroid | Estrogens and progesterone | Many tissues | Fetal and maternal development |
|  |  | Peptide | Chorionic somatomammotropin (CS) Chorionic gonadotropin (CG) |  | Metabolism |
|  |  |  |  |  | Hormone secretion |
| Skin | Cells | Steroid | Estrogens (estradiol) | hormone form <br> Many tissues | Precursor of 1,25 dihydroxy-vitamin $\mathrm{D}_{3}$ |
| Ovaries (female) | Glands | Steroid |  |  | Egg production; secondary sex characteristics |
|  |  |  | Progestins (progesterone) Ovarian inhibin | Uterus | Promotes endometrial growth to prepare uterus for pregnancy |
|  |  | Peptide |  | Anterior pituitary | Inhibits FSH secretion |
| Testes (male) | Glands | Steroid | Androgen | Many tissues | Sperm production; secondary sex characteristics |
|  |  | Peptide | Inhibin | Anterior pituitary | Inhibits FSH secretion |
| Thymus | Gland | Peptide | Thymosin, thymopoietin | Lymphocytes | Stimulates proliferation and function of T lymphocytes |
| Thyroid | Gland | Iodinated amines Peptide | $\begin{aligned} & \text { Triiodothyronine }\left(\mathrm{T}_{3}\right) ; \\ & \text { thyroxine }\left(\mathrm{T}_{4}\right) \\ & \text { Calcitonin }(\mathrm{CT}) \end{aligned}$ | Many tissues | Increases metabolic rate; normal physical development Promotes calcium deposition in bone; lowers blood calcium levels |
|  |  |  |  | Bone |  |



Figure 20.5 The pituitary gland, its secretions, and targets.

Figure 20.6 outlines the overall metabolic actions of GH; it modulates the metabolic mixture during physical activity by stimulating fatty acid release from adipose tissue while simultaneously inhibiting cellular glucose uptake. This glucosesparing action maintains blood glucose at relatively high levels to augment prolonged exercise performance.

Trained and sedentary individuals show similar increases in GH concentration with exercise to exhaustion. In contrast, the sedentary person maintains higher GH levels for several hours into recovery. During a standard bout of submaximal exercise, sedentary individuals have a greater GH response. The absolute submaximal exercise level represents greater stress for the less fit person allowing GH release to relate more to the relative strenuousness of physical effort.

## Insulin-Like Growth Factors

IGFs (somatomedins) mediate many of GH s effects. In response to GH stimulation, liver cells synthesize IGF-I and IGF-II, a process that requires between 8 and 30 hours. IGFs travel in the blood attached to one of five types of binding proteins for release as free hormones to interact with specific receptors. The factors that influence IGF transport include binding proteins within muscle, nutritional status, and plasma insulin levels.

## Thyrotropin

Thyrotropin, also known as thyroid-stimulating hormone (TSH), controls hormone secretion by the thyroid gland. TSH maintains growth and development of the thyroid gland and increases thyroid cell metabolism. Considering the important role of thyroid hormones in regulating overall body metabolism, one would expect TSH output from the pituitary to increase during physical activity, but this response does not occur consistently.

## Adrenocorticotropic Hormone

ACTH, known as corticotropin, functions as part of the hypothalamic pituitary adrenal axis that regulates adrenal cortex output of hormones in a manner similar to TSH control of thyroid gland secretion. ACTH acts directly to enhance fatty acid mobilization from adipose tissue, increase gluconeogenesis, and stimulate protein catabolism. Owing to difficulty in assay methods and rapid disappearance of this hormone from the blood, data remain scarce concerning ACTH response during physical activity. ACTH concentrations may increase proportionately with exercise intensity and duration if intensity exceeds $25 \%$ of aerobic capacity. ${ }^{37}$ Corticotropin-releasing hormone ( CRH ) and arginine vasopressin (AVP) mediate ACTH release. CRH exhibits a definite diurnal rhythm, with highest levels in early morning just after rising. As the day progresses, CRH levels decline, essentially blocking ACTH release. Factors that alter the normal ACTH rhythm by triggering CRH release include fever, hypoglycemia, and other stressors. CRH is both an ACTH regulator and a central nervous system neurotransmitter, and often is termed the stress response integrator. High-intensity physical activity favors AVP release while prolonged physical activity favors CRH release, both inhibiting ACTH. ${ }^{68}$

## Prolactin

Prolactin (PRL) initiates and supports milk secretion from the mammary glands. PRL levels increase at high exercise intensities and return toward baseline within 45 minutes during recovery. Owing to its important role in female sexual function, repeated exercise-induced PRL release may inhibit ovarian function and contribute to menstrual cycle alterations when females train intensely. Greater increases in PRL occur in women who run without wearing an undergarment support; ${ }^{130}$ either fasting or consuming a high-fat diet enhances release of


Figure 20.6 Overview of growth hormone (GH) actions. GH stimulates breakdown and release of triacylglycerols from adipose tissue and hinders cellular glucose uptake (antiinsulin effect) to maintain a relatively high blood glucose level. Somatomedins mediate the indirect anabolic effects of GH. Elevated GH levels and somatomedins provide feedback to promote GH -inhibiting hormone (GHIH) release and depress hypothalamic release of GH-releasing hormone (GHRH); this further inhibits GH release by the anterior pituitary gland.
this hormone. ${ }^{73}$ PRL concentration also increases in men following maximal exercise. ${ }^{27}$

## Gonadotropic Hormones

Gonadotropic hormones stimulate the male and female sex organs to grow and secrete their hormones at a faster rate. The two gonadotropic hormones are follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH initiates follicle growth in the ovaries and stimulates these organs to secrete estrogen, one type of female sex hormone. LH
complements FSH action to cause estrogen secretion and rupture of the follicle, which allows the ovum to pass through the fallopian tube for fertilization. In the male, FSH stimulates germinal epithelium growth in the testes to promote sperm development. LH also stimulates the testes to secrete testosterone.

Inconsistent reports describe short-term exercise-associated alterations in FSH and LH. LH release is normally pulsatile, making it difficult to separate any specific exercise-related change from the normal pulsatile pattern. Generally, LH concentration rises before exercise begins and peaks during recovery.

## Posterior Pituitary Hormones

The posterior pituitary gland forms as an outgrowth of the hypothalamus and resembles true neural tissue (see Fig. 20.5). This tissue, often called the neurohypophysis, stores antidiuretic hormone (ADH, or vasopressin) and oxytocin. The posterior pituitary does not synthesize its hormones. Instead, the hypothalamus produces these hormones and secretes them to the neurohypophysis for release as needed via neural stimulation. Damage or surgical removal of the posterior pituitary does not dramatically affect ADH or oxytocin production.

ADH influences water excretion by the kidneys. Its action limits production of large volumes of urine by stimulating water reabsorption in the kidney tubules. Oxytocin initiates muscle contraction in the uterus and stimulates ejection of milk during lactation.

Physical activity provides a potent stimulus for ADH secretion. Increased ADH release, probably stimulated by sweating, helps to conserve body fluids during hot-weather physical activity and accompanying dehydration. This waterconserving effect of ADH contributes to efficient modulation of the cardiovascular response to physical activity. ${ }^{104} \mathrm{ADH}$ release decreases with fluid overload, thus increasing urine volume and producing more dilute urine (i.e., lighter color urine). The effect of short-term physical activity on oxytocin release remains unknown.

## Thyroid Hormones

The $15-$ to $20-\mathrm{g}$ reddish brown thyroid gland, located nearer the first part of the trachea just below the larynx, comes under the influence of TSH produced by the anterior pituitary gland. In addition to secreting the calcium-regulating hormone calcitonin, the thyroid gland secretes two protein-iodine bound hormones, thyroxine $\left(\mathbf{T}_{4}\right)$ and triiodothyronine ( $\mathbf{T}_{3}$, the active form of thyroid hormone). These two hormones are often referred to as major metabolic hormones. More $\mathrm{T}_{4}$ is secreted than $\mathrm{T}_{3}$; although less abundant, $\mathrm{T}_{3}$ acts several times faster than $\mathrm{T}_{4}$. The majority of $\mathrm{T}_{3}$ comes from the deiodination of $\mathrm{T}_{4}$ in peripheral tissues, principally liver and kidney. Most receptor cells for $\mathrm{T}_{4}$ metabolize it to $T_{3} . T_{3}$ and $T_{4}$ are not readily soluble in water, which means they bind to carrier proteins that circulate in blood. Thyroxinebinding globulin (glycoprotein synthesized in the liver) serves as the main transporter of thyroid hormones. This carrier protein (along with two others-transthyretin and albumin) permits a more consistent availability of thyroid hormones from which the active, free hormones release for target cell uptake.

Through its stimulating effect on enzyme activity, $\mathrm{T}_{4}$ secretion raises metabolism of all cells except in the brain, spleen, testes, uterus, and thyroid gland itself. For example, abnormally high $\mathrm{T}_{4}$ secretion raises basal metabolic rate (BMR) up to fourfold. This potent thermogenic effect produces large BMR deviations that often indicate thyroid gland abnormality (see Chapter 9). A person may lose weight rapidly with abnormally high thyroid activity. In contrast, depressed thyroid production blunts BMR, which usually leads to gains in body weight and body fat. However, fewer than 3\% of obese persons show abnormal thyroid functions, so depressed thyroid activity cannot explain excessive body fat
gain in most individuals. For nervous system function, $\mathrm{T}_{3}$ release facilitates neural reflex activity, whereas low $\mathrm{T}_{4}$ levels cause sluggishness, often inducing people to sleep for up to 15 hours a day. Thyroid hormones provide important regulation for tissue growth and development, skeletal and nervous system formation, and maturation and reproduction. They also play a role in maintaining blood pressure by provoking an increase in adrenergic receptors in blood vessels.

Whole-body metabolism influences synthesis of thyroid hormones. Depressing the metabolic rate to some critical value directly stimulates hypothalamic release of TSH. This increases thyroid output and increases resting metabolism. Conversely, a chronic elevation in metabolism reduces TSH production, causing metabolism to slow. Figure 20.7 illustrates this exquisitely regulated feedback system.

During physical activity, blood levels of free $T_{4}$ (thyroxine not bound to plasma proteins) increase by approximately $35 \%$. This increase could occur from an exercise-induced elevation in core temperature, which alters the protein binding of several hormones, including $\mathrm{T}_{4}$. The importance of these transient exercise-induced alterations in thyroid hormone dynamics requires further study.

## Thyroid Hormones Affect Quality of Life

Thyroid hormones are not essential for life but they do affect life s quality. In children, full expression of growth hormone requires thyroid activity. Thyroid hormones provide


Figure 20.7 Feedback system that controls thyroid hormone release.
essential stimulation for normal growth and development, especially of nervous tissue. The actions of thyroid hormones become most noticeable in people who suffer from either hypersecretion or hyposecretion.

Hypersecretion of thyroid hormones (hyperthyroidism) produces the following four effects:

1. Increased oxygen consumption and metabolic heat production during rest (heat intolerance is a common complaint)
2. Increased protein catabolism and subsequent muscle weakness and weight loss
3. Heightened reflex activity and psychological disturbances that range from irritability and insomnia to psychosis
4. Rapid heart rate (tachycardia)

Hyposecretion of thyroid hormones (hypothyroidism) produces the following four effects:

1. Reduced metabolic rate and cold intolerance from reduced internal heat production
2. Decreased protein synthesis produces brittle nails, thinning hair, and dry, thin skin
3. Depressed reflex activity, slow speech and thought processes, and feeling of fatigue (in infancy causes cretinism, marked by decreased mental capacity)
4. Slow heart rate (bradycardia)

## Parathyroid Hormones

Four parathyroid glands, measuring $6-\mathrm{mm}$ long, $4-\mathrm{mm}$ wide, and $2-\mathrm{mm}$ deep, embed in the posterior aspect of the thyroid gland (Fig. 20.8). As many as eight glands have been reported in some people, and glands have been found in other regions of the neck or in the thorax. Parathyroid hormone (PTH, or parathormone) controls blood calcium balance. A decrease in blood calcium levels triggers PTH release; increasing calcium concentrations inhibit its release. PTH s major effect increases ionic calcium levels by stimulating three target organs-bone, kidneys, and small intestine.

PTH release produces the following three effects:

1. Activation of bone-reabsorbing cells (osteoclasts) to digest some of the bone matrix to release ionic calcium and phosphate to the blood


Figure 20.8 Dynamics of parathyroid hormone (PTH) release and its actions.


Figure 20.9 Adrenal gland secretions.
2. Enhancement of calcium ion reabsorption and decreased retention of phosphate by the kidneys
3. Increased calcium absorption by intestinal mucosa

Plasma calcium ion homeostasis modulates nerve impulse conduction, muscle contraction, and blood clotting. Limited evidence suggests that physical activity increases PTH release in young, middle-aged, and older individuals, an effect that contributes to the positive effects of mechanical forces from physical activity on bone mass accretion. ${ }^{6,15,88}$

## Adrenal Hormones

The adrenal glands appear as flattened, caplike tissues situated just above each kidney (Fig. 20.9). The glands have two distinct parts: medulla (inner portion) and cortex (outer portion). Each part secretes different types of hormones; consequently, the cortex and medulla are generally considered two distinct glands.

## Adrenal Medulla Hormones

The adrenal medulla makes up part of the sympathetic nervous system. It acts to prolong and augment sympathetic effects by secreting epinephrine and norepinephrine, hormones collectively called catecholamines. Figure 20.10 shows the chemical structure of epinephrine and norepinephrine and the role of each in substrate mobilization. Norepinephrine, a hormone in its own right, serves as an epinephrine precursor. It also acts as a neurotransmitter when released by sympathetic nerve endings. Epinephrine represents $80 \%$ of adrenal medulla secretions, whereas norepinephrine provides the principal neurotransmitter released from the sympathetic nervous system. An outflow of neural impulses from the hypothalamus stimulates the adrenal medulla to increase catecholamine release. These hormones affect the heart, blood vessels, and glands in the same, albeit sloweracting way as direct sympathetic nervous system stimulation. Epinephrine s primary function in energy metabolism


Figure 20.10 Chemical structure of epinephrine and norepinephrine and their role in mobilizing glucose from the liver and free fatty acids from adipose tissue (and blunting glucose uptake by skeletal muscle). Norepinephrine serves as a hormone and as a precursor of epinephrine. It also functions as a neurotransmitter when released by sympathetic nerve endings.
stimulates glycogenolysis (in the liver and active muscles) and lipolysis (in adipose tissue and active muscles); norepinephrine provides powerful lipolytic stimulation in adipose tissue. ${ }^{39,150}$ Sympathetic nerve endings (including those to the adrenal gland) secrete both epinephrine and norepinephrine, so it is more appropriate to discuss the sympathoadrenal response to exercise and training rather than the adrenal gland response. The sympathoadrenal response to physical activity most closely relates to relative rather than absolute activity intensity.

Figure 20.11 illustrates the catecholamine response at various exercise intensities (expressed as $\% \dot{\mathrm{~V}} \mathrm{O}_{2 \max }$ ) in 10 male subjects. Norepinephrine increases markedly at intensities that exceed $50 \% \dot{\mathrm{~V}} \mathrm{O}_{2 \text { max }}$, whereas epinephrine levels remain unchanged until exercise intensity exceeds the $60 \%$ level. At maximum effort, an approximate two- to sixfold increase in norepinephrine release takes place. More than likely, increased secretion occurs from sympathetic postganglionic nerve endings and relates to cardiovascular and metabolic


## Norepinephrine $\square$ Epinephrine

Figure 20.11 Catecholamine response to exercise of increasing intensity in 10 male subjects. (From Applied Physiology Laboratory, University of Michigan, Ann Arbor.)
adjustments in active tissues. Physical activity also increases epinephrine output from the adrenal medulla, with the magnitude of increase related directly to effort intensity and duration. ${ }^{24,85,105}$ Athletes involved in sprint power training show greater sympathoadrenergic activation during maximal exercise than counterparts trained in aerobic exercise. ${ }^{148}$ This difference relates to the higher anaerobic contribution to maximal exercise energy supply by sprint power athletes. Age does not affect catecholamine response to physical activity among individuals equal in aerobic fitness. ${ }^{79,98}$ The effects of increased adrenal medulla activity on blood flow distribution, cardiac contractility, and substrate mobilization all benefit the physical activity response.

## Adrenocortical Hormones

The adrenal cortex, stimulated by corticotropin from the anterior pituitary, secretes adrenocortical hormones. These corticosteroid hormones fit functionally into one of three groups: (1) mineralocorticoids, (2) glucocorticoids, and (3) androgens-each produced in a different zone (layer) of the adrenal cortex.

Mineralocorticoids. As the name suggests, mineralocorticoids regulate the mineral salts sodium and potassium in the extracellular fluid. Aldosterone, the most physiologically important of the three mineralocorticoids, represents almost $95 \%$ of all mineralocorticoids produced.

Figure 20.12 shows four major controlling factors for aldosterone release from the adrenal cortex. Aldosterone secretion controls total sodium concentration and extracellular fluid volume. It stimulates sodium ion reabsorption (along with fluid) in the distal tubules of the kidneys by increasing synthesis of sodium transporter proteins by the epithelial cells of the tubules and collecting duct. Consequently, little sodium


Figure 20.12 Four major factors control aldosterone release from the adrenal cortex. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.
(and fluid) voids in the urine. Increases in cardiac output and arterial blood pressure also accompany increases in plasma volume with aldosterone secretion. In contrast, sodium and water literally flow into the urine when aldosterone secretion ceases. Aldosterone also helps to stabilize serum potassium and pH because the kidneys exchange either a $\mathrm{K}^{+}$or $\mathrm{H}^{+}$for each $\mathrm{Na}^{+}$reabsorbed. Proper mineral balance maintains nerve transmission and muscle function. As with all steroid hormones, cellular response to increased aldosterone production occurs relatively slowly. It requires physical activity in excess of 45 minutes for aldosterone s effect to emerge; hence, its major effects occur during recovery.

Renin Angiotensin Mechanism. Increased sympathetic nervous system activity during exercise constricts blood vessels that serve the kidneys. Reduced renal blood flow stimulates the kidneys to release the enzyme renin into the blood. Increased renin concentration stimulates production of two kidney hormones,
angiotensin II and angiotensin III. These hormones stimulate arterial constriction and adrenocortical secretion of aldosterone, which causes the kidneys to retain sodium and excrete potassium. Renal absorption of sodium also conserves water, causing plasma volume to expand and blood pressure to increase.

Chronic reduction in renal blood flow at rest, perhaps from abnormal sympathetic stimulation, activates the renin angiotensin system. Hypertension occurs from the prolonged overresponse of this mechanism with resulting excess aldosterone output. High blood pressure associated with increased aldosterone production often occurs in teenage obesity. ${ }^{133}$ Teenage hypertension relates to three factors:

1. Decreased salt sensitivity (hence increased water retention)
2. Increased sodium intake
3. Decreased sensitivity to the effects of insulin (hyperinsulinemia)

These interrelationships suggest a direct link between obesity as a disease and subsequent development of hypertension. Similar relationships occur in adults. ${ }^{32,55}$

Glucocorticoids. The stress of physical activity stimulates hypothalamic secretion of corticotropin-releasing factor, causing the anterior pituitary to release ACTH. In turn, ACTH promotes glucocorticoid release by the adrenal cortex. Cortisol (hydrocortisone), the major glucocorticoid of the adrenal cortex, affects glucose, protein, and free fatty acid metabolism in six ways:

1. Promotes breakdown of protein to amino acids in all cells except the liver; the circulation delivers these liberated amino acids to the liver for synthesis to glucose via gluconeogenesis
2. Supports action of other hormones, primarily glucagon and GH in the gluconeogenic process
3. Serves as an insulin antagonist by inhibiting cellular glucose uptake and oxidation
4. Promotes triacylglycerol breakdown in adipose tissue to glycerol and fatty acids
5. Suppresses immune system function
6. Produces negative calcium balance

Figure 20.13 shows factors that affect cortisol secretion and its effects on target tissues. A strong diurnal pattern governs cortisol secretion. Secretions normally peak in the morning and subside at night. Cortisol secretion increases with stress, making it known as the stress hormone. Even though considered a catabolic hormone, cortisol s important effect counters hypoglycemia and is thus essential for life. Animals whose adrenal glands have been removed die if exposed to severe environmental stress. Cortisol, required for full activity of glucagon and the catecholamines, exerts a facilitating effect on these hormones.

Chronically high-serum cortisol levels initiate excessive protein breakdown, tissue wasting, and negative nitrogen balance. Cortisol secretion also accelerates fat mobilization for energy during starvation and intense, prolonged physical activity. With rapid and large increases in cortisol output, the liver splits mobilized fat into its simple ketoacid components. Excess ketoacid concentrations in the extracellular fluid can lead to the potentially dangerous condition of ketosis (a form of acidosis). Individuals who subsist on very low carbohydrate, low-calorie weight-loss diets (termed ketogenic diets; see Chapter 30) can experience ketosis, augmented by elevated cortisol secretion.

Cortisol turnover (difference between its production and removal) provides a way to study cortisol response to physical activity. Cortisol turnover with physical activity exhibits considerable variability with exercise intensity, fitness level, nutritional status, and even circadian rhythm. ${ }^{30,152}$ Most research indicates that cortisol output increases with exercise intensity; this heightened output accelerates lipolysis, ketogenesis, and proteolysis. Extremely high cortisol levels occur following long-duration physical activity such as marathon
running or an intense bout of resistance training. ${ }^{128}$ Even during moderate physical activity, plasma cortisol concentration rises with prolonged duration. Data for cortisol turnover indicate that highly trained runners maintain a state of hypercortisolism that heightens before competition or intense training. ${ }^{43,73}$ Cortisol levels also remain elevated for up to 2 hours following physical activity. This suggests that cortisol plays a role in tissue recovery and repair. Unlike the direct, active metabolic effect of epinephrine and glucagon on fuel homeostasis during exercise, cortisol exerts a more facilitating effect on substrate use.

Gonadocorticoids. The reproductive organs (gonads) provide the major source of the so-called sex steroids, but the adrenal cortex produces androgen hormones (gonadocorticoids) with similar actions. For example, the adrenal cortex produces dehydroepiandrosterone, which exerts effects similar to the dominant male hormone testosterone. Treatment with 50 mg of dehydroepiandrosterone in women with adrenal insufficiency over a 4-month trial improved well being and sexual responsiveness as well as decreased depression and anxiety compared to placebo treatment. ${ }^{227}$ The adrenal cortex also produces small amounts of the female hormones estrogen and progesterone.

## GONADAL HORMONES

The testes in the male and ovaries in the female are the reproductive glands. These endocrine glands produce hormones that promote sex-specific physical characteristics and initiate and maintain reproductive function. No distinctly male or female hormones exist, but rather general differences in hormone concentrations between the sexes. Testosterone is the most important androgen secreted by the interstitial cells of the testes. Figure 20.14 shows that testosterone initiates sperm production and stimulates development of male secondary sex characteristics. Testosterone s anabolic, tissue-building role contributes to male female differences in muscle mass and strength that emerge at the onset of puberty. As noted in Chapter 2, testosterone conversion to estrogen in peripheral tissues, under control of the enzyme aromatase, provides the male with protection in maintaining bone structure throughout life.

The ovaries provide the primary source of estrogens, particularly estradiol and progesterone. Estrogens regulate ovulation, menstruation, and physiologic adjustments during pregnancy. Estrogen circulating in the bloodstream and generated locally in peripheral tissues also exerts effects on blood vessels, bone, lungs, liver, intestine, prostate, and testes through action on $\alpha$ - and $\beta$-receptor proteins. Progesterone contributes specific regulatory input to the female reproductive cycle, uterine smooth muscle action, and lactation. Controversy exists concerning the role of estrogen and progesterone in substrate metabolism during physical activity. ${ }^{3,107}$ Estradiol-17 $\beta$ (biologically active estrogen synthesized from cholesterol) increases free fatty acid mobilization from adipose tissue and inhibits glucose uptake by peripheral tissues.


Figure 20.13 Factors that affect cortisol secretion and its actions on target tissues. CRH, corticotropic releasing hormone; ACTH, adrenocorticotropic hormone.

In this way, the increases in estradiol-17 $\beta$ and GH during physical activity exert similar metabolic influences.

## Testosterone

Plasma testosterone concentration commonly serves as a physiologic marker of anabolic status. In addition to its direct effects on muscle tissue synthesis, testosterone indirectly affects a muscle fiber s protein content by promoting GH release leading to IGF synthesis and release from the liver.

Testosterone also interacts with neural receptors to increase neurotransmitter release and initiate structural protein changes that alter the size of the neuromuscular junction. These neural effects enhance force-production capabilities of skeletal muscle.

Testosterone s effect on the cell nucleus remains controversial. More than likely, a transport protein (sex-hormone binding globulin) delivers testosterone to target tissues, after which testosterone associates with a membrane-bound or cytosolic receptor. It subsequently migrates to the cell nucleus,


Figure 20.14 Androgens effects in men. Binding with special receptor sites in muscle and various other tissues, androgen (testosterone) contributes to male secondary sex characteristics and sex differences in muscle mass and strength that develop at the onset of puberty. Some androgen converts to estrogen in peripheral tissues and gives males a considerable edge over females in maintaining bone mass throughout life.
where it interacts with nuclear receptors to initiate protein synthesis.

Plasma testosterone concentration in females, although only one-tenth that in males, increases with physical activity. Physical activity also elevates estradiol and progesterone levels. In untrained males, resistance exercise and moderate aerobic exercise increase serum and free testosterone levels after 15 to 20 minutes. ${ }^{72}$ Findings remain equivocal concerning the effect of intense endurance exercise on testosterone levels. ${ }^{128,157}$

Figure 20.15 shows the pattern of plasma cortisol and testosterone 48 hours before swimming and immediately following $15 \times 200-\mathrm{m}$ freestyle at the swimmer s competitive velocity, with a 20 -second rest between swims and 1 hour into recovery. Four 6-week periods formed the training program, with careful monitoring of training volume. The bar graphs (right) show values for swim volume during the four training periods, including average performance during time trials. The results clearly show that postexercise cortisol and testosterone remain elevated. Values remained higher 1 hour after physical activity except for testosterone levels in training weeks 6 through 12 and 18 through 24 . The generalized decrease in cortisol and testosterone concentrations when the
swimmers peaked for the championships (weeks 18 24) indicates long-term adaptation for these hormones, not the immediate result of excess stress induced by overtraining and subsequent poor performance. The depressed performance during weeks 18 through 24 might indicate overtraining; this period corresponded to a large increase in training volume. Chapter 21 provides an in-depth discussion of overtraining and its related syndrome.

## INTEGRATIVE QUESTION

Hormones play crucial roles in normal growth and development and the regulation of physiologic function. Give specific examples of why more is not necessarily better for these chemicals.

## Pancreatic Hormones

The pancreas gland, approximately $14-\mathrm{cm}$ long and weighing about 60 g , lies just below the stomach on the posterior


Figure 20.15 Pattern of plasma cortisol and testosterone concentrations measured at three time intervals (4 h before swimming, immediately after multiple sprint swims, and after 1-h recovery) over a 24 -week swim-training season. Bar graphs on right show values for swim volume, time-trial performance, and blood lactate during the four 6-week training periods. (Modified from Bonifazi M, et al. Blood levels of exercise during the training season. In: Miyashita M. et al., eds. Medicine and science in aquatic sports. Basel: Karger, 1994.)
abdominal wall. Two different types of tissues, acini and islets of Langerhans, named for German pathologist and anatomist Paul Langerhans (1847 1888), who first described this cluster of cells in 1869 (Fig. 20.16), compose the pancreas. The islets are comprised of about $20 \% \alpha$-cells that secrete glucagon and $75 \% \beta$-cells that secrete insulin and a peptide called amylin. The remaining cells are somatostatin-secreting D cells and PP cells that produce pancreatic polypeptide. The acini serve an exocrine function and secrete digestive enzymes.

## Insulin

Insulin regulates glucose entry into all tissues (primarily muscle and adipose) except the brain. Insulin s action mediates facilitated diffusion. In this process, glucose combines with a carrier protein on the cell s plasma membrane (see next section) for transport into cells. In this way, insulin regulates glucose metabolism. Any glucose not immediately catabolized for energy either stores as glycogen or synthesizes to triacylglycerol. Without insulin, only trace amounts of glucose enter the cells. Figure 20.17A illustrates that the anabolic functions of insulin promote glycogen, protein, and fat synthesis; Figure 20.17B outlines the target tissues and specific metabolic responses to insulin s action.

Following a meal, insulin-mediated glucose uptake by cells (and correspondingly reduced hepatic glucose output) decreases blood glucose levels. In essence, insulin exerts a hypoglycemic effect by reducing blood glucose concentration. Conversely, with insufficient insulin secretion (or decreased insulin sensitivity), blood glucose concentration increases from a normal level of about $90 \mathrm{mg} \cdot \mathrm{dL}^{1}$ to a high of $350 \mathrm{mg} \cdot \mathrm{dL}^{1}$. When blood glucose levels remain high, glucose ultimately spills into the urine. Without insulin, fatty acids metabolize as the primary energy substrate.

Insulin also exerts a pronounced effect on fat synthesis. A rise in blood glucose levels (as normally occurs following a meal) stimulates insulin release. This causes some glucose uptake by fat cells for synthesis to triacylglycerol. Insulin s action also triggers intracellular enzyme activity that facilitates protein synthesis. This occurs by one or all of the following actions:

1. Increasing amino acid transport through the plasma membrane
2. Increasing cellular levels of RNA
3. Increasing protein formation by ribosomes

Insulin Transport of Glucose into Cells: Glucose Transporters. Cells possess different glucose transport proteins (termed glucose transporters or GLUTs), depending on the variation in insulin and glucose concentrations. ${ }^{97,135}$ Muscle


Figure 20.16 The pancreas, its secretions, and their actions.
fibers contain GLUT-1 and GLUT-4, with most glucose entering by the GLUT-1 carrier during rest. With high blood glucose or insulin concentrations (as occur after eating or during physical activity), muscle cells receive glucose via the insulin-dependent GLUT-4 transporter. GLUT-4 action is mediated through a second messenger, which permits migration of the intracellular GLUT-4 protein to the surface to promote glucose uptake. The fact that GLUT-4 moves to the cell surface through a separate, insulin-independent mechanism coincides with observations that active muscles absorb glucose without insulin.

Glucose Insulin Interaction. Blood glucose levels within the pancreas directly control insulin secretion. Elevated blood glucose levels cause insulin release. This, in turn, induces glucose entry into cells (lowers blood glucose), removing the stimulus for insulin release. In contrast, a decrease in blood glucose concentration dramatically lowers blood insulin levels to provide a favorable milieu to increase blood glucose. The interaction between glucose and insulin serves as a feedback mechanism to maintain blood glucose concentration within narrow limits. Rising levels of plasma amino acids also increase insulin secretion.

Figure 20.18 relates plasma insulin concentration to exercise duration for cycling at $70 \% \dot{\mathrm{VO}}_{2 \text { max }}$. The inset graph shows insulin response as a function of exercise intensity $\left(\% \dot{\mathrm{~V}}_{2 \text { max }}\right)$. The decreased insulin concentration (below rest values) as exercise duration extends or intensity increases results from inhibitory effects of an exercise-induced
catecholamine release on pancreatic $\beta$-cell activity. Catecholamine suppression of insulin relates directly to physical activity intensity. Physical activity inhibition of insulin output explains why no excessive insulin release (and possible rebound hypoglycemia) occurs with a concentrated glucose feeding during physical activity. Prolonged physical activity derives progressively more energy from free fatty acids mobilized from the adipocytes from reduced insulin output and decreased carbohydrate reserves. Blood glucose lowering with prolonged physical activity directly enhances hepatic glucose output and sensitizes the liver to the glucose-releasing effects of glucagon and epinephrine, whose actions help to stabilize blood glucose levels.

Diabetes Mellitus. Diabetes mellitus consists of subgroups of disorders with different pathophysiologies. The current statistics regarding diabetes prevalence in the United States are staggering (see Fig. 20.19). Between 2003 and 2006, $25.9 \%$ of the United States population 20 years and older had diabetes; for those older than 60 years of age the prevalence was $34 \%$. About 12.0 million, or $11.2 \%$, of all men and 11.5 million, or $10.2 \%$, of women aged 20 years or older have diabetes. Nearly 15 million, or $9.8 \%$, of non-Hispanic whites and 3.7 million, or $14.7 \%$, of non-Hispanic blacks aged 20 years or older are diabetics.

From 2005 to 2007 there was an unprecedented $13.5 \%$ increase in diabetes prevalence; 2007 alone saw 1.6 million newly diagnosed cases, which brought the total number of


Figure 20.17 A. Primary functions of insulin in the body. The show where insulin exerts its influence in metabolism. B. Target tissues and specific metabolic responses to insulins action. The anabolic functions of increased insulin promote glycogen, protein, and fat synthesis.


Figure 20.18 Plasma insulin levels during 30 minutes of cycle ergometer exercise at $70 \% \dot{V O}_{2 \text { max }}$. Inset, data show insulin



Figure 20.19 Prevalence of diagnosed and undiagnosed diabetes among people aged 20 years or older, United States, 2007. Age 20 years or older: 23.5 million, or $10.7 \%$, of all people in this age group have diabetes. Age 60 years or older: 12.2 million, or $23.8 \%$, of all people in this age group have diabetes. (From 20042006 National Health Interview Survey estimates projected to year 2007.)
diabetics to 23.6 million men and women, or about $8 \%$ of the U.S. population, with at least another $10 \%$ undiagnosed. Most importantly, roughly one-third of all new cases are under the age of 20: Truly, diabetes has become a childhood disease !

Diabetes is the seventh leading cause of death in the United States and directly related to heart disease, hypertension, blindness, kidney failure, nervous system disease, amputations, dental disease, complications of pregnancy, and pneumonia, Additionally, over $90 \%$ of all diabetics are hopelessly sedentary; they cannot walk continuously for a quarter mile or climb one flight of stairs!

Diabetes: A Global Epidemic and a Worldwide Healthcare Problem

By 2025, the largest increases in diabetes prevalence will take place in developing countries. Every 10 seconds a person dies from diabetesrelated causes.
Every 10 seconds two people develop diabetes.
Diabetes is the fourth leading cause of global death by disease.
Diabetes currently affects 246 million people worldwide and will affect 380 million by 2025 . In 2007, the five countries with the largest number of diabetics were India ( 40.9 million), China (39.8 million), the United States ( 19.2 million), Russia ( 9.6 million) and Germany ( 7.4 million). In 2007, the five countries with the highest diabetes prevalence in the adult population were

Nauru (30.7\%), United Arab Emirates (19.5\%), Saudi Arabia ( $16.7 \%$ ), Bahrain ( $15.2 \%$ ), and Kuwait (14.4\%).
Each year 3.8 million deaths are attributable to diabetes. An even greater number die from cardiovascular disease made worse by diabetesrelated lipid disorders and hypertension.
At least $50 \%$ of all people with diabetes are unaware of their condition. In some countries this figure reaches $80 \%$.
$10 \%$ to $20 \%$ of people with diabetes die of renal failure.
More than 2.5 million people worldwide are affected by diabetic retinopathy; it is the leading cause of vision loss in adults of working age (20 to 65 years) in industrialized countries. On average, people with type 2 diabetes die 5 to 10 years before people without this disease.
Cardiovascular disease is the major cause of death in diabetes, accounting for some $50 \%$ of all diabetes fatalities.
Type 2 diabetics are over twice as likely to have a heart attack or a stroke as people without diabetes.

Sources:

1. Diabetes atlas, third edition, International Diabetes Federation, 2007.
2. World Health Organization diabetes unit: www.who.int/diabetes.

The terms type 1 (absolute insulin deficiency that develops early in life and represents 5\% to $10 \%$ of the diabetic population) and type 2 (relative insulin resistance and deficiency that develops later in life and associates with obesity, diet, and sedentary living) identify the two major diabetic subgroups.

Diabetes symptoms include:
Presence of glucose in the urine (glycosuria)
Frequent urination (polyuria)
Excessive thirst (polydipsia)
Extreme hunger (polyphagia)
Unexplained weight loss
Increased fatigue
Irritability
Blurry vision
Numbness or tingling in the extremities (hands, feet)
Slow-healing wounds or sores
Abnormally high frequency of infection
Use the following Internet site to calculate your diabetes risk: www.diabetes.org/risk-test.jsp.

Tests for Diabetes Mellitus. Different tests diagnose diabetes, including the laboratory-based glucose and insulin clamp methodology, an oral glucose-tolerance test, and a simple 8 -hour fasting plasma glucose test.

The clamp procedure involves maintaining insulin at a constantly above-normal blood concentration using infusion technology (termed hyperinsulinemic clamp). Once insulin stabilizes at the higher level, the body s use of glucose is measured by infusing a known amount of glucose into the patient s blood. A euglycemic clamp maintains blood glucose at nearnormal concentration with insulin production measured. A euglycemic hyperinsulinemic clamp combines both clamp procedures. A large glucose uptake for a given insulin concentration reflects increased insulin sensitivity. Increased insulin release to a constant glucose condition relates to augmented insulin responsiveness. Decreased insulin sensitivity indicates inability of cells to adequately respond to insulin to increase glucose uptake. Type 2 diabetes commonly reflects inadequacies in either insulin receptors or cellular response to insulin binding (i.e., there is relative insulin resistance). Decreased insulin responsiveness indicates impaired $\beta$-cell function evident in some type 2 diabetics and is the primary cause of type 1 diabetes. [The term impaired fasting glucose (IFG) indicates fasting blood glucose values are $\geq 100 \mathrm{mg} \cdot \mathrm{dL}^{1}\left(5.6 \mathrm{mmol} \cdot \mathrm{L}^{1}\right)$, but $<126 \mathrm{mg} \cdot \mathrm{dL}^{1}\left(7 \mathrm{mmol} \cdot \mathrm{L}^{1}\right)$.]
Oral glucose-tolerance test evaluates blood sugar levels 2 hours after drinking 75 grams of a concentrated glucose solution. Delayed removal of ingested glucose indicates diabetes. [The term impaired glucose tolerance (IGT) indicates a 2-h glucose clearance between $\geq 140 \mathrm{mg} \cdot \mathrm{dL}^{1}\left(7.8 \mathrm{mmol} \cdot \mathrm{L}^{1}\right)$ but $<200 \mathrm{mg} \cdot \mathrm{dL}^{1}\left(11.1 \mathrm{mmol} \cdot \mathrm{mL}^{1}\right)$.]
Fasting plasma glucose (FPG) test measures plasma glucose following an 8-hour fast. The American Diabetes Association (http://www.diabetes .niddk.gov/) currently recommends the FPG test.

## Classification Categories for Fasting <br> Blood Glucose

| Category | Fasting Plasma Glucose |
| :--- | :--- |
| Normal | $<110 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ |
| Impaired range | $110125 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ |
| Suspected diabetes | $>125 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ |

Considerable risks exist for impaired glucose homeostasis—probably a genetic trait that manifests itself in adolescence-in which blood glucose remains elevated, but not high enough for diabetic classification. Nondiabetic, middle-aged men whose FPG falls in the upper range of normal show a higher risk of death from heart disease than those in the low normal range. ${ }^{7}$ Men with fasting blood glucose levels above $85 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ have a $40 \%$ higher risk of cardiovascular death than men with lower values, even
after adjusting for age, smoking habits, blood pressure, and fitness status. The current plasma glucose cutoff for suspected diabetes is an FPG of $126 \mathrm{mg} \cdot \mathrm{dL}^{-1}$, down from the previous standard of $140 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ set in 1979 . This lower cutoff acknowledges that patients can remain asymptomatic despite microvascular complications (damaged small blood vessels) with FPG values in the low- to mid- $120 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ range. The impaired range represents a transition between normal and overt diabetes. In this situation, the body no longer responds properly to insulin and/or secretes inadequate insulin to achieve a more desirable blood glucose concentration.

## Metabolic Syndrome

Metabolic syndrome, first mentioned in the late 1980s, represents a multifaceted grouping of coronary artery disease risks. ${ }^{9,41,92}$ Diet-induced insulin resistance/hyperinsulinemia often occurs before manifestations of the metabolic syndrome of obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension. ${ }^{4,110,144}$ In essence, the syndrome reflects a concurrence of four factors:

1. Disturbed glucose and insulin metabolism (fasting glucose $\geq 110 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ )
2. Overweight with abdominal fat distribution (waist circumference: men $>102 \mathrm{~cm}$ [40 in]; women $>88 \mathrm{~cm}$ [35 in])
3. Mild dyslipidemia (triacylglycerols $\geq 150 \mathrm{mg} \mathrm{dL}^{-1}$; high-density lipoprotein cholesterol: men, $<40 \mathrm{mg} \cdot \mathrm{dL}^{-1}$; women $<50 \mathrm{mg} \cdot \mathrm{dL}^{-1}$
4. Hypertension ( $\geq 130 / \geq 85 \mathrm{~mm} \mathrm{Hg}$ )

## fyi <br> Common Characteristics of the Metabolic Syndrome <br> Insulin resistance <br> Glucose intolerance <br> Dyslipidemia (high triacylglycerols, low HDL, high LDL) <br> Stroke <br> Upper-body obesity <br> Type 2 diabetes mellitus <br> Hypertension <br> Coronary artery disease <br> Reduced ability to dissolve blood clots

Individuals with metabolic syndrome exhibit high risk for cardiovascular disease, type 2 diabetes, Alzheimer s disease, and all-cause mortality. ${ }^{91}$ Some researchers maintain that inappropriate food consumption (high levels of refined sugars), sedentary lifestyle, and poor levels of muscular strength and cardiorespiratory fitness not only associate with the metabolic syndrome but represent features of this disease. ${ }^{75,90,132}$ Estimates place the age-adjusted prevalence of the metabolic syndrome in the United States at nearly $25 \%$, or about 47 million men
and women. ${ }^{41}$ The age-adjusted prevalence is similar for men ( $24 \%$ ) and women ( $23.4 \%$ ). Mexican Americans have the highest age-adjusted prevalence of the syndrome (31.9\%). The lowest prevalence occurs among whites (23.8\%), African Americans (21.6\%), and people reporting other for race or ethnicity (20.3\%). Among African Americans, women exhibit a $57 \%$ higher prevalence than men; Mexican American women have a $26 \%$ higher prevalence.

This disease of modern civilization afflicts a large number of adults (more common in men than women) in western industrialized countries. Disease occurrence relates to genetic, hormonal, and lifestyle factors of obesity, physical inactivity, and nutrient excesses, including high intakes of saturated and trans-fatty acids. Although characterized by the clustering of insulin resistance and hyperinsulinemia, dyslipidemia (atherogenic plasma lipid profile), essential hypertension, abdominal (visceral) obesity, and glucose intolerance, the syndrome also relates to abnormalities of blood coagulation, hyperuricemia, and microalbuminuria. Psychosocial stress, socioeconomic disadvantage, and abnormal psychiatric traits also link to the syndrome s pathogenesis. ${ }^{8,9}$

Table 20.4 provides percentage body fat ranges and associated risk equivalent to the traditional BMI cutoffs for the metabolic syndrome for black and white men and women. Lifestyle modifications that include increased regular physical activity represent the cornerstone of national recommendations to prevent the metabolic syndrome. ${ }^{110,175}$

## Insulin Actions and Impaired Glucose Homeostasis

Figure 20.20 summarizes insulin s normal response and under insulin-resistant and type 2 diabetes conditions. The increase in blood glucose concentration following a meal induces insulin release from the $\beta$-cells in the islets of Langerhans. Insulin then migrates in the blood to target cells throughout the body, where it binds to receptor molecules on the cell surface. Insulin receptor interaction triggers a series of events within the cell that enhance glucose uptake and subsequent catabolism or storage as glycogen and/or fat. A defect anywhere along the pathway for glucose uptake signals diabetes. Seven possible causes include:

1. Destruction of $\beta$-cells
2. Abnormal insulin synthesis
3. Depressed insulin release
4. Inactivation of insulin in the blood by antibodies or other blocking agents
5. Altered insulin receptors or a decreased number of receptors on peripheral cells
6. Defective processing of the insulin message within the target cells
7. Abnormal glucose metabolism

## Type 1 Diabetes

Type 1 diabetes, formerly called juvenile-onset diabetes, typically occurs in younger individuals and represents

TABLE 20.4 Thresholds of Percentage Body Fat (\%BF) Corresponding to Established Body Mass Index Cutoffs Associated with Metabolic Syndrome Risk
\%BF and Corresponding Percentiles

| BMI <br> Cutoffs $\left(K G / M^{2}\right)$ | Men |  |  |  | Mean ${ }^{\text {a }}$ | Women |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Black |  | White |  |  | Black |  | White |  |
|  | Cutoff | Percentile | Cutoff | Percentile |  | Cutoff | Percentile | Cutoff | Percentile |
| 18.5 | 12.7 | 8.9 | 11.0 | 3.9 | 12 | 25.4 | 11.7 | 22.5 | 24 |
| 25 | 21.7 | 43.5 | 21.2 | 41.0 | 21 | 32.0 | 29.3 | 30.8 | 31 |
| 30 | 28.3 | 80.9 | 29.1 | 87.6 | 29 | 37.1 | 52.5 | 37.2 | 37 |
| 35 | 35.0 | 97.6 | 37.0 | 99.4 | 36 | 42.1 | 75.9 | 43.5 | 43 |

${ }^{a}$ Values were rounded.
From Zhu S, et al. Percentage body fat ranges associated with metabolic syndrome risk: results based on the third National Health and Nutrition Examination Survey (1988 1994). Am J Clin Nutr 2003;78:228.
between 5 and $10 \%$ of all diabetes cases. This diabetes form represents an autoimmune response, possibly from a single protein that renders the $\beta$-cells incapable of producing insulin and often other pancreatic hormones. Type 1 diabetic patients present a more severe abnormality for glucose homeostasis than individuals in the type 2 subgroup. Physical activity exerts more pronounced effects on the metabolic state in type 1 individuals, and the management of exercise-related problems requires greater attention (see In a Practical Sense, p. 428).

## Type 2 Diabetes

Type 2 diabetes tends to occur after age 40, but a sharp increase now occurs in much younger individuals (often less than 10 years of age). This alarming new health trend signals that type 2 diabetes may represent a pediatric disease. Recent estimates indicate that diabetes has more than tripled in children over the last 3 to 5 years. Physicians consider the spiraling rate of childhood obesity-particularly among African Americans, Native Americans, and Hispanics (most notably children of Mexican descent)—as the predominant factor in the rising number of children with type 2 diabetes. Type 2 diabetes accounts for nearly $95 \%$ of all diabetes cases in the United States; it represents the leading cause of death from the disease. Treatment costs exceed $\$ 105$ billion annually.

Three factors can produce high blood glucose levels in type 2 diabetes:

1. Inadequate insulin produced by the pancreas to control blood sugar (relative insulin deficiency)
2. Decreased insulin effects on peripheral tissue (insulin resistance), particularly skeletal muscle (Fig. 20.20)
3. Combined effect of factors 1 and 2

A dysregulation in glycolytic and oxidative capacities of skeletal muscle also relates to insulin resistance in type 2 diabetes. ${ }^{143}$ The disease most likely results from the interaction of genes and lifestyle factors-physical inactivity, weight gain
(up to $80 \%$ of type 2 diabetes are obese), aging, and possibly a high-fat diet. No doubt, these lifestyle factors have contributed to the $70 \%$ increase in the disorder among persons in their 30 s during the last decade of the 20th century, and a $33 \%$ overall increase nationally. Also, the form of insulin resistance in type 2 diabetes has a strong genetic component. Diabetic-prone individuals possess a gene that directs synthesis of a protein that inhibits insulin s action in cellular glucose transport.

fyi

## Risk Factors for Type 2 Diabetes

Body mass exceeds $20 \%$ of ideal First-degree relative with diabetes (genetic influence)
Member of a high-risk ethnic group (black, Hispanic American, Pacific Islander, American Indian, Asian)
Delivered a baby weighing more than 9 pounds or developed gestational diabetes Blood pressure at or above $140 / 90 \mathrm{~mm} \mathrm{Hg}$ HDL cholesterol level of $35 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ or below and/or a triacylglycerol level of $250 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ or above
Impaired fasting plasma glucose or impaired glucose tolerance on previous testing

Obesity, particularly upper-body fat distribution, and physical inactivity represent major risks for type 2 diabetes in adults and children. ${ }^{164}$ An estimated 60 to 80 million Americans show insulin resistance but have not developed overt symptoms of type 2 diabetes. One-third of these individuals will eventually become full-blown diabetics, and many others are at heightened risk of cardiovascular disease. ${ }^{52}$ Failure of insulin to exert its normal effect increases glucose conversion to triacylglycerol and storage as body fat. For the insulin-resistant individual, a diet high in simple sugars and


Figure 20.20 A. Normal insulin glucose interaction, B. with insulin resistance, and $\mathbf{C}$. type 2 diabetes.

## IN A PRACTICAL SENSE

## Diabetes, Hypoglycemia, and Physical Activity

Persons with type 1 or type 2 diabetes should exercise regularly as part of a comprehensive treatment regimen. Hypoglycemia represents the major risk of physical activity for individuals who take insulin or oral hypoglycemic agents. A physically active diabetic person needs to pay particular attention to the following:

1. Warning signs of hypoglycemia
2. Immediate response to a hypoglycemia attack
3. Treatment of late-onset hypoglycemia

## HYPOGLYCEMIA WARNING SIGNS

Symptoms of moderate and severe hypoglycemia (see Table) result from inadequate glucose supply to the brain. In general, hypoglycemic symptoms appear only after blood glucose concentration drops below $60 \mathrm{mg} \cdot \mathrm{dL}^{-1}$.

Symptoms of low blood glucose vary considerably. Some diabetic persons with autonomic neuropathy who lose the ability to secrete adrenaline-like hormones in response to hypoglycemia experience hypoglycemic unawareness. They require regular blood glucose monitoring during and after physical activity. Individuals who take $\beta$-blocker medication also have increased risk for hypoglycemic unawareness.

## HYPOGLYCEMIA ATTACK: WHAT TO DO

1. Respond quickly: Hypoglycemic reactions appear suddenly and progress rapidly.
2. Stop exercising: Test blood glucose to confirm hypoglycemia.
3. Eat or drink carbohydrate: Immediately consume 10 to 15 g of simple sugar. A diabetic person should always carry highglycemic carbohydrate while exercising (e.g., hard candy, sugar cubes, raisins, juice). Consuming ice cream or chocolates is a poor choice; their high fat content depresses the glycemic index and impedes glucose absorption.
4. Rest 10 to 15 minutes: This allows for intestinal absorption of glucose. Test blood glucose levels before resuming physical activity. If blood glucose registers below $100 \mathrm{mg} \cdot \mathrm{dL}^{-1}$, do not exercise but eat more sugar.
5. Remonitor during physical activity: After resuming physical activity, pay close attention to further signs of hypoglycemia. If possible, measure blood glucose within 30 to 45 minutes.
6. Replenish carbohydrate immediately after physical activity: Consume complex carbohydrates. If carbohydrate intake does not increase blood glucose concentration, be prepared to administer glucagon subcutaneously to boost glucose levels.

## LATE-ONSET HYPOGLYCEMIA

Late-onset hypoglycemia describes the condition of excessively low blood glucose more than 4 hours (and up to 48 h ) after physical activity. It occurs more frequently in new exercisers or after a strenuous workout. Insulin sensitivity remains high for 24 to 48 hours after physical activity, so late-onset hypoglycemia poses a particular problem for many medicated diabetics. The following precautions can guard against late-onset hypoglycemia:

Adjust insulin dosage or other medication before exercising. If needed, increase food intake before and during physical activity.

If exercise lasts beyond 45 minutes, monitor blood glucose at 2 -hour intervals for 12 hours into recovery or until sleep. Consider reducing insulin or oral hypoglycemic agents until bedtime. Before retiring, eat some lowglycemic food to increase blood glucose levels. Use caution when initiating a physical activity program. Start slowly and gradually increase exercise intensity and duration over a 3 - to 6 -week period.
If planning to exercise longer than 45 to 60 minutes, exercise with a friend who can assist in an emergency. Always carry snacks and important phone numbers (doctor, hospital, home), and wear a medical ID bracelet.

## ADJUSTING INSULIN LEVELS

For intense physical activity, consider the following:
Intermediate-acting insulin: Decrease dose by 30 to $35 \%$ on the day of exercise.
Intermediate- and short-acting insulin: Omit dose if it normally precedes physical activity.
Multiple doses of short-acting insulin: Reduce dose before exercise by $30 \%$ and supplement with carbohydrate-rich food.
Continuous subcutaneous insulin infusion: Eliminate mealtime bolus or insulin increment that precedes or follows physical activity.
Avoid exercising for 1 hour the muscles that receive the short-acting insulin injection.
Avoid exercising in late evening.

## Warning Signs of Hypoglycemia

## Mild hypoglycemic reaction

Trembling or shakiness
Nervousness
Rapid heart rate
Palpitations
Increased sweating
Excessive hunger

## Moderate hypoglycemic reactions

Headache
Irritability and abrupt mood changes
Impaired concentration and attentiveness
Mental confusion
Drowsiness

## Severe hypoglycemic reactions

Unresponsiveness
Unconsciousness and coma
Convulsions
refined carbohydrates (with a relatively high glycemic index) facilitates body fat accumulation. Fat cell enlargement further exacerbates the situation because these cells exhibit insulin resistance from their reduced insulin receptor density. Interestingly, women with excess body fat and high cardiorespiratory fitness are more insulin sensitive than equally obese but sedentary counterparts. ${ }^{44}$

## fyi

Characteristics of Type 1 and Type 2 Diabetes

| Characteristics | Type 1 Diabetes | Type 2 Diabetes |
| :---: | :---: | :---: |
| Age of onset | Usually $<20 \mathrm{y}$ | Usually $>40$ y (but increasing in children) |
| Proportion of all diabetics | <10\% | >90\% |
| Appearance of symptoms | Acute or subacute | Slow |
| Metabolic ketoacidosis | Frequent | Rare |
| Obesity at onset | Uncommon | Common |
| $\beta$-cells | Decreased | Variable |
| Insulin | Decreased | Variable |
| Inflammatory cells in islets | Present initially | Absent |
| Family history | Uncommon | Common |

As with type 1 diabetes, adequate glucose fails to enter the cells of a person with type 2 diabetes. This triggers abnormally high levels of blood glucose that the kidney tubules filter and void in the urine (glycosuria). Excessive glucose particles in renal filtrate create an osmotic effect that diminishes water reabsorption, which results in loss of large amounts of fluid (polyuria). With decreased cellular glucose uptake, a diabetic person relies largely on fat catabolism for energy. This produces an excess of ketoacids and a tendency toward acidosis. In extreme situations, diabetic coma occurs as plasma pH falls as low as 7.0. Arteriosclerosis, small blood vessel and nerve disease, and susceptibility to infection occur at increased rates in type 2 diabetes. Obese diabetic women also face an almost threefold greater risk of endometrial cancer than diabetic women of normal weight, perhaps from their persistently high insulin levels (insulin insensitivity). ${ }^{140}$

Diabetes and Physical Activity. Hypoglycemia remains the most common disturbance in glucose homeostasis during physical activity in diabetic persons who take exogenous insulin. Hypoglycemia most frequently occurs during prolonged, intense physical activity when hepatic glucose release does not match increased glucose use by active muscle. In addition, persons with type 2 diabetes often have reduced exercise tolerance independent of glycemic control. Contributing factors include genetics, undesirable lifestyle characteristics, excessive body fat, and poor physical fitness.

INTEGRATIVE QUESTION
Explain the sweet-smelling breath of individuals who suffer from poorly regulated diabetes mellitus or malnutrition from starvation.

## Glucagon

The $\alpha$-cells of the islets of Langerhans secrete glucagon, the insulin antagonist hormone. In contrast to insulin s effect in lowering blood sugar levels, glucagon primarily stimulates both glycogenolysis and gluconeogenesis by the liver and increases lipid catabolism. (Fig. 20.21). The glucose generated by glucagon action then moves into the blood. Glucagon exerts its effect by activating adenylate cyclase. This enzyme stimulates cyclic AMP in liver cells and causes hepatic glycogen breakdown to glucose (glycogenolysis). Glucagon also stimulates gluconeogenesis by promoting the liver s uptake of amino acid uptake.

As with insulin, plasma glucose concentration controls glucagon output by the pancreas. A decrease in blood glucose concentration from prolonged intense physical activity or food (or carbohydrate) restriction stimulates glucagon release.

Autonomic nervous stimulation does not mediate glucagon release, unlike its effects on insulin secretion. Also, no gender differences exist in the glucagon response to exercise when individuals exercise at the same percentage of aerobic capacity. ${ }^{29,154}$ Because glucagon release occurs later in exercise, this hormone exerts little influence in the early regulation of hepatic glycogenolysis. More than likely, it primarily


Figure 20.21 Glucogen secretion and its action on target tissues.
contributes to blood glucose regulation as exercise progresses and glycogen reserves deplete.

## Other Glands and Hormones

Other hormones also influence bodily functions. The liver secretes somatomedins, which affect growth of muscle, cartilage, and other tissues. The mucosal lining of the small intestine secretes secretin, gastrin, and cholecystokinin to promote and coordinate digestive processes. The hypothalamus itself constitutes an important endocrine gland that secretes stimulating or releasing hormones that activate or release anterior pituitary hormones. The hypothalamus also releases somatoliberin, which stimulates somatotropin secretion from the anterior pituitary gland.

## EXERCISE TRAINING AND ENDOCRINE FUNCTION

Table 20.5 lists select hormones and their general response to exercise training. Only limited research has evaluated multiple hormone secretions and changes consequent to exercise training because of the complex interactions between endocrine secretions and the nervous system. The magnitude of hormonal response to a standard exercise load generally declines with endurance training. For example, when highly trained athletes perform at the same absolute exercise level as sedentary subjects, hormonal responses remain lower in the athletes.

Improved target tissue sensitivity and/or responsiveness to a given amount of hormone accounts for much of this efficiency in response. ${ }^{26,65}$ A similar level of hormonal response occurs regardless of training state when subjects exercise at the same relative exercise intensity (i.e., same percentage of maximum [lower absolute load for the untrained]). With maximal exercise, trained subjects have an identical or somewhat greater hormonal response than untrained subjects.

## Anterior Pituitary Hormones

## Growth Hormone

GH stimulates lipolysis and inhibits carbohydrate breakdown, so some have argued that exercise training enhances GH secretion and conserves glycogen reserves. However, this does not occur. Compared with untrained counterparts, en-durance-trained individuals show less rise in blood GH levels at a given physical activity intensity-a response attributed to reduced exercise stress as training progresses and fitness improves. Regardless of training status, women typically maintain higher GH levels at rest than men; this difference disappears during prolonged exercise. ${ }^{17}$ Figure 20.22A illustrates the training-induced depression of GH response of a representative subject from a group of six men during 20 minutes of constant-load, intense exercise before and after 3 and 6 weeks of endurance training. Integrated GH concentrations (exercise plus recovery) for the group averaged $45 \%$ lower

## TABLE 20.5 Hormones and Their Responses to Endurance Training

## Hormone Training Response

## Hypothalamus-pituitary hormones

Growth hormone
Thyrotropin
ACTH
Prolactin
FSH, LH, and testosterone
Posterior pituitary hormones
Vasopressin (ADH)
Oxytocin
Thyroid hormones
Thyroxine ( $T_{4}$ )
Triiodothyronine ( $T_{3}$ )
Adrenal hormones
Aldosterone
Cortisol
Epinephrine and norepinephrine

## Pancreatic hormones

Insulin
Glucagon

No effect on resting values; less dramatic rise during exercise
No known training effect
Increased exercise values
Some evidence that training lowers resting values
Trained females have depressed values; reduced testosterone in males (testosterone levels may increase in males with long-term resistance training)

Slightly reduced ADH at a given workload
No research results available

Reduced concentration of total $T_{3}$ and increased free thyroxine at rest
Increased turnover of $T_{3}$ and $T_{4}$ during exercise

No training adaptation
Slight elevation during exercise
Decreased secretion at rest and at the same absolute exercise intensity after training

Increased sensitivity to insulin; normal decrease in insulin during exercise greatly reduced with training
Smaller increase in glucose levels during exercise at absolute and relative workloads

## Kidney enzyme and hormone

Renin and angiotensin
No apparent training effect

than pretraining values at both training measures. Responses for plasma catecholamines (Fig. 20.22B and C) and blood lactate (Fig. 20.22D) paralleled the decrease in GH. Because the constant-load exercise test represented less physiologic demand after training (reflected by lower catecholamine and lactate levels), a similar release of GH after training probably requires higher absolute exercise intensity. The effect of exercise training on GH release also may occur under nonexercise conditions. For example, aerobic training above the lactate threshold level amplifies the 24 -hour pulsatile GH release during rest (see Focus on Research, p. 433).

## ACTH (Adrenocorticotropic Hormone)

ACTH secreted by the posterior pituitary gland provides potent stimulation to the adrenal cortex and thus increases free fatty acid mobilization for energy. Training increases ACTH release during physical activity-a response that stimulates adrenal gland activity to promote fat catabolism and spare glycogen. ${ }^{13,95}$ This effect would certainly benefit prolonged, high-intensity exercise performance.

## PRL (Prolactin)

Little information exists concerning exercise training changes in PRL. It does appear that resting PRL levels of male runners average below values for sedentary nonrunners. ${ }^{54,167}$

## FSH (Follicle-Stimulating Hormone), LH (Leuteinizing Hormone), and Testosterone

Regular physical activity depresses reproductive hormone responses in women and men. ${ }^{33,168}$ Male endurance athletes generally maintain resting testosterone levels between 60 and $85 \%$ of values for sedentary men.

Women. Women with a long history of exercise participation have altered FSH and LH levels at different times in their menstrual cycles, which may contribute to menstrual dysfunction. For example, FSH levels remain depressed in trained females throughout an abbreviated anovulatory menstrual cycle, whereas LH and progesterone concentrations rise in the cycle s follicular phase. Variations in the menstrual

Figure 20.22 Top. Serum growth hormone (GH) concentrations in a representative subject during 20 minutes of constant-load exercise and 45 minutes of recovery at pretraining, after 3 weeks of training, and after 6 weeks of training. Bottom. Effects of 6 weeks of training on integrated GH concentration (A), and end-exercise concentrations of epinephrine (B), norepinephrine (C), and blood lactate (D) in response to constant-load cycle ergometry exercise ( $n=6$, mean). Pre-week 3, after 3 weeks of training; Post, after 6 weeks of training. * $P<.05$ versus pretraining; ** $P<.05$ versus week 3. (From Weltman A, et al. Exercise training decreases the growth hormone (GH) response to acute constant-load exercise. Med Sci Sports Exerc 1997;29:669.)
cycle do not affect metabolic and hormonal responses to acute bouts of physical activity. ${ }^{43,76}$

Men. Endurance training affects a man s pituitary gonadal function, including levels of testosterone and PRL. Figure 20.23 compares 46 male runners (average weekly running distance: 64 km ) and 18 nonrunners matched for age, stature, and body mass. The runners showed lower testosterone than nonrunners, with no differences in LH and FSH levels. Reduced testosterone concentration (both increased clearance and lower production) in endurance-trained men parallels the sex-steroid reductions observed in women who undergo endurance training and associated reductions in body fat. ${ }^{149}$ No difference exists in LH and FSH levels between trained and untrained men; thus, impaired gonadotropin release from the anterior pituitary does not cause the lower testosterone levels during standard physical activity in the trained state.

## Posterior Pituitary Hormones

## ADH (Antidiuretic Hormone)

Intense physical activity to exhaustion or prolonged submaximal activity at the same relative intensity produces no difference in ADH levels between trained and untrained individuals. ADH concentration decreases with training when exercising at the same absolute submaximal intensity.

## PTH (Parathyroid Hormone)

Endurance training enhances exercise-related increases in PTH in young and elderly adults. ${ }^{137,176}$ The significance of a training-induced augmented rise in PTH for preserving bone mass with aging awaits further study.

## Thyroid Hormones

Exercise training produces a coordinated pituitary thyroid response that reflects increased turnover of thyroid hormones. Increased thyroid turnover often reflects excessive hormonal
action that ultimately leads to hyperthyroidism (i.e., overproduction of $\mathrm{T}_{3}$ and $\mathrm{T}_{4}$ hormones). However, no evidence indicates a higher incidence of hyperthyroidism in highly trained individuals. For example, inordinately high BMR levels and basal body temperatures rarely occur in the trained state. Consequently, the greater $\mathrm{T}_{4}$ turnover that accompanies physical training occurs through a mechanism that differs from normal thyroid hormone dynamics.

Research on women who endurance train yields interesting results regarding thyroid turnover. Changing from a baseline of relatively sedentary living to running 48 km per week produced a mild thyroid impairment reflected by decreased $\mathrm{T}_{3}$ and $\mathrm{T}_{4}$ levels. ${ }^{14}$ In contrast, nearly doubling the weekly distance increased plasma hormone levels. To explain these apparent conflicting effects of regular physical activity, the researchers suggested that greater body fat loss with more intense training produced an exercise-induced increase in thyroid output. Six months of resistance training in men slightly reduced the concentrations of $T_{4}$ and plasma-free $T_{4}$, without change in TSH. However, the magnitude of the change was of no clinical or physiologic significance. ${ }^{124}$

## Adrenal Hormones

## Aldosterone

The renin angiotensin aldosterone system contributes to homeostatic control of body fluid volumes, electrolytes, and blood pressure, but exercise training does not affect resting levels of these compounds or their normal response to physical activity.

## Cortisol

Plasma cortisol levels increase less in trained subjects than in sedentary subjects who perform the same absolute level of submaximal exercise. Adrenal gland enlargement results from both cellular hypertrophy and hyperplasia with repeated bouts of intense exercise training and correspondingly high cortisol output.


Figure 20.23 Comparison of testosterone, LH, and FSH levels in trained male runners and untrained controls. Runners show lower testosterone levels than controls and no significant difference in LH and FSH. (From Wheeler GD, et al. Reduced serum testosterone and prolactin levels in male distance runners. JAMA 1984;252:514.)

## FOCUS ON RESEARCH

## Training Intensity Affects Growth Hormone Release

Weltman A, et al. Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. J Appl Physiol 1992;72:2188.
$>$ Research has focused on growth hormone (GH) responses to a single session of physical activity and longterm training. The dynamics of GH secretions during exercise training takes on clinical importance because of the causal relationship between GH availability and maintenance of lean body tissue during aging and weight loss.

Weltman and colleagues studied GH dynamics with 52 weeks of aerobic run training in two groups of 21 healthy, eumenorrheic women. One group ran at a speed corresponding to lactate threshold ( @LT) and the other at a faster speed above the lactate threshold level $(>L T)$. Nontraining women served as controls $(C)$. Both training groups completed similar weekly mileage. The distance covered during the first week was 5 miles. Weekly mileage then gradually increased to 24 miles by week 20 and continued at 24 miles per week until week 40 . Thereafter, weekly mileage increased by 1.25 miles for three of the weeks. Subjects ran between 35 and 40 miles per week by the end of the study.

Yearlong training increased $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ by $9.9 \%$ for the @LT group and $11.8 \%$ for the $>$ LT group. In addition, the @LT group increased exercise $\dot{\mathrm{V}} \mathrm{O}_{2}$ at $\mathrm{LT}\left(\dot{\mathrm{VO}}_{2-\mathrm{LT}}\right)$ by $21.5 \%$, while the $>$ LT group s $\dot{\mathrm{V}} \mathrm{O}_{2-\mathrm{LT}}$ increased by $28 \%$. The C group remained unchanged on all measures. No differences in body mass, fat mass, or percentage body fat emerged within or among groups, although the $>$ LT group showed a trend toward body fat reduction. Both exercise groups increased fat-free body mass with training.

The figure illustrates the effects of the run training program on resting 24 -hour integrated serum GH concentrations. Training induced a $50 \%$ increase in resting GH concentration for the $>$ LT group. GH concentrations remained unchanged for the C and @LT groups. The
investigators speculated that the release of endogenous opiates and catecholamines and inhibition of somatostatin release in more intense exercise performed by the $>$ LT group facilitated GH release.

This research showed that exercise training augments resting pulsatile GH release by amplitude enhancement, but only with training intensity above LT. Training at intensities above the LT may provide a natural and healthful means to increase pulsatile GH secretion under conditions that depress GH release, as in aging. Increased GH release through regular physical activity can conserve the lean tissue mass during weight loss.


## > $\mathrm{LT} \square$ @LT $\square \mathrm{C}$

Integrated 24-hour resting GH concentrations for the control group $(C)$ and groups that exercised either at an intensity equivalent to the lactate threshold (@LT) or greater than the lactate threshold $(>L T)$. Note the large (50\%) increase in GH concentration for the >LT group compared with the @LT and C groups.

## Epinephrine and Norepinephrine

Sympathoadrenal activity (principally norepinephrine release) in response to an absolute submaximum workload remains lower in trained than untrained individuals. ${ }^{36}$ Epinephrine and norepinephrine output in standard exercise falls dramatically during the first several weeks of training. The appearance of bradycardia and a smaller rise in blood pressure during submaximal exercise represent the most familiar consequences of the sympathoadrenal training adaptation. Reductions in exercise heart rate and blood pressure
reflect favorable adaptations because they lower myocardial oxygen demands during physical activity and possibly other forms of stress. For equivalent relative exercise intensities, a higher sympathoadrenal response occurs following aerobic training. ${ }^{51}$ Figure 20.24 illustrates norepinephrine and epinephrine during physical activity at intensities that ranged between 60 to $85 \%$ of aerobic capacity by three adult men and six women prior to and following 10 weeks of aerobic training that increased $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ by $20 \%$. Plasma norepinephrine levels (Fig. 20.24, top) increased progressively with exercise


## $\square$ Untrained $\square$ Trained

Figure 20.24 Plasma norepinephrine (top) and epinephrine concentrations (bottom) at rest and after 15 minutes of exercise at the same relative exercise intensity $\left(\% \dot{V V O}_{2 \text { max }}\right)$ before and after 10 weeks of endurance exercise training. (From Greiwe JS, et al. Norepinephrine response to exercise at the same relative intensity before and after endurance training. J Appl Physiol 1999;86:531.)
intensity before and after training. Training produced higher plasma norepinephrine levels, particularly at higher intensities. Consistently higher epinephrine values also emerged following training (Fig. 20.24, bottom), but the differences did not reach statistical significance. More than likely, greater catecholamine output at the same relative exercise intensity following training reflects three factors requiring greater sympathetic nervous system activation:

1. Greater absolute demand for substrate use via glycogenolysis and lipolysis
2. Increased overall cardiovascular response
(e.g., cardiac output)
3. Larger muscle mass activation

Whether exercise training alters resting catecholamine levels remains unclear.

## Pancreatic Hormones

Endurance training maintains blood levels of insulin and glucagon during physical activity closer to resting levels. In essence, the trained state requires less insulin at any stage


Pre-training $\square$ Post-training
Figure 20.25 Pre post differences in plasma glucagon and insulin responses to exercise before and after 20 weeks of an aerobic training program. (From Applied Physiology Laboratory, University of Michigan.)
from rest through light to moderately intense physical activity. Figure 20.25 shows insulin and glucagon responses in 10 young adults before and after 20 weeks of training at 60 to $80 \%$ $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$. Aerobic training depressed the exercise response of both hormones, with glucagon showing the most pronounced reduction. These findings agree with previous reports for adults who trained for 10 weeks by running and cycling. ${ }^{53}$

## Regular Physical Activity and Type 2 Diabetes Risk

Cross-sectional, retrospective, prospective, and interventional epidemiologic research provide strong evidence that regular physical activity reduces type 2 diabetes prevalence in adolescents and adults with or without concomitant body composition changes. ${ }^{2,16,61,86,162}$ (Refer to http://www. acsm-msse.org/pt/pt-core/template-journal/msse/ media/0700.pdf for the ACSM position stand on physical activity and type 2 diabetes.) Those individuals at greatest risk for type 2 diabetes (obese, hypertensive, family history, sedentary lifestyle) gain the greatest benefit from regular physical activity. ${ }^{1,100,125}$ For adult men and women, low
fitness levels coincide with increased clustering of the metabolic abnormalities associated with the Metabolic Syndrome (see p. 425), the deadly quartet of insulin resistance, glucose intolerance, upper-body obesity, and dyslipidemia. For sedentary, middle-aged men, aerobic exercise plus weight loss lowers blood pressure and improves glucose and fat metabolism. ${ }^{31,87}$ It may even reduce the amount of antidiabetic medication a patient currently takes to control the disease. ${ }^{172}$ A 6-year clinical trial evaluated the effects of diet and physical activity lifestyle interventions on the occurrence of type 2 diabetes in individuals with impaired glucose tolerance. Men and women were randomly assigned to either control, dietonly, exercise-only, or diet-plus-exercise groups. Diet modification consisted of 25 to 30 kCal per kg of body mass ( 55 to $60 \%$ carbohydrate, 25 to $30 \%$ lipid, and 10 to $15 \%$ protein) for individuals with a BMI below 25. Those with a BMI above 25 maintained the same macronutrient mixture as the leaner group while gradually losing weight at a rate of 0.5 to 1.0 kg per month until their BMI decreased to 23. Physical activity intervention required a progressive increase in the quantity of mild-to-moderate regular physical activity. The diet exercise intervention combined the major components of both diet and exercise treatments. Figure 20.26 shows that diet, physical activity, and combined diet exercise interventions decreased incidence of diabetes after the 6-year intervention.

A large prospective study evaluated diabetes risk for a cohort of 70,102 female nurses aged 40 to 65 years without diabetes, cardiovascular disease, or cancer at baseline measurements in 1986. ${ }^{67}$ In agreement with previous prospective research on men, an 8-year follow-up found increased physical activity correlated with a substantially reduced relative risk for type 2 diabetes. Figure 20.27 indicates that after adjustment for smoking, alcohol use, history of hypertension, and elevated cholesterol levels, relative risk across physical


Figure 20.26 Effects of dietary and exercise lifestyle interventions on the occurrence of type 2 diabetes in individuals with impaired glucose tolerance. (From Xiao-ren P, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes Care 1997;20:537.)


Figure 20.27 Multivariate relative risks of type 2 diabetes according to MET-hours for total physical activity quintile (ascending 20-percentile units) within strata of (A) body mass index (BMI), (B) history of hypertension, and (C) parental history of diabetes. MET-hours for total physical activity represents average time per week spent in each of eight physical activities multiplied by the MET value of each activity. The MET value equals energy need per kilogram of body mass per hour of activity divided by the energy need per kilogram of body mass per hour at rest. (From Hu GB, et al. Walking compared with vigorous physical activity and the risk of type 2 diabetes in women: a prospective study. JAMA 1999;282:1433.)
activity quintiles (20-percentile units) related inversely to diabetes risk in lean and overweight women. The dose response relationship remained consistent in those at low or high risk for diabetes and stayed significant after BMI adjustment. Women who walked regularly achieved greater benefits with a brisker walking pace; the most vigorous exercise lowered diabetes risk by $46 \%$. Equivalent energy expenditures from walking or other forms of physical activity produced comparable risk reduction.


Control of Blood Glucose
Figure 20.28 Possible mechanisms of how regular physical activity improves insulin action and blood glucose homeostasis in type 2 diabetes. TNF-alpha, tumor necrosis factor-alpha, a hormonelike substance released from active adipocytes in the abdominal region, which may depress insulin-regulated glucose transport. (Modified from Ivy JL, et al. Prevention and treatment of noninsulindependent diabetes mellitus. Exerc Sport Sci Rev 1999;27:1.)

Figure 20.28 outlines the possible mechanisms of how exercise training-via its effects on skeletal muscle, adipose tissue, liver, and pancreatic hormone output-improves insulin action and blood glucose control in type 2 diabetes.

Physical Activity Benefits for Type 2 Diabetes. Exercise training provides considerable benefits for persons with type 2 diabetes. ${ }^{59,129}$

Glycemic Control. Skeletal muscle consumes the major amount of glucose transported in blood. Muscle, for example, generally clears between 70 and $90 \%$ of the glucose in an oral or intravenous glucose challenge. A single bout of moderate or intense physical activity abruptly decreases plasma glucose levels, an effect that persists for up to several days. Extending the duration of weekly physical activity from 115 minutes to 170 minutes produces the greatest increase in insulin
sensitivity. ${ }^{66}$ Most likely, the immediate effects of each exercise session on increasing the active muscles insulin sensitivity causes long-term improvement in glycemic control, not any exercise-induced chronic adaptations in tissue function. When resuming a sedentary lifestyle, the muscles sensitivity to insulin decreases, thus requiring more insulin to clear a given quantity of blood glucose. ${ }^{117}$ Improved insulin sensitivity with regular physical activity provides type 2 diabetics with important therapy that ultimately lowers their insulin requirement. Three factors account for the improved insulin sensitivity for glucose transport in skeletal muscle and adipose tissue after a bout of physical activity:

1. Translocation of the glucose transporter protein GLUT-4 from the endoplasmic reticulum to the cell surface
2. Increase in total quantity of GLUT-4
3. Increase in glycogen synthase activity and subsequent glycogen storage (independent of any effect on insulin signaling $)^{23,58,64,69,131}$

The hyperinsulinemic patient who requires the largest insulin release for glucose regulation derives the greatest benefits from regular physical activity. ${ }^{159}$ This observation supports the theory that regular physical activity acts by reversing insulin resistance (i.e., physical activity increases insulin sensitivity).

Combining resistance exercise and endurance training improves markers of insulin resistance and body composition for insulin-resistant individuals more than endurance training alone. ${ }^{87,158}$ Benefits of resistance plus endurance training for hyperinsulinemia most likely come from the specific effects of activating a relatively larger muscle mass (than with endurance training alone) and additional caloric expenditure. Improvements in blood glucose homeostasis with regular physical activity rapidly decrease once training ceases and completely dissipate within several weeks of inactivity. Interestingly, recent research indicates that reliance on intensive pharmacologic therapy to lower blood glucose levels in high-risk type 2 diabetics increased mortality and did not significantly reduce cardiovascular events compared with standard therapy. ${ }^{156}$

Cardiovascular Disease. Excess morbidity and mortality in type 2 diabetes results from coronary heart disease, stroke, and peripheral vascular disease from accelerated atherosclerosis. Disease risk factors that improve with regular physical activity include hyperinsulinemia, hyperglycemia, abnormal plasma lipoproteins, some blood coagulation parameters, and hypertension.

Weight Loss. Weight loss and accompanying reduction in body fat and its distribution enhance glucose tolerance and insulin sensitivity. ${ }^{5,86}$ The beneficial effects of physical activity on fat loss often are underestimated because body weight changes per se with exercise do not necessarily reflect the even more favorable, exercise-induced body composition changes (fat loss and muscle gain). Combining diet and regular physical activity reduces body fat in diabetic persons more effectively than either treatment alone.

Psychologic Profile. Improved exercise capacity in diabetic persons relates to decreased anxiety, improved mood and self-esteem, increased sense of well-being and psychologic control, enhanced socialization, and improved quality of life. ${ }^{106}$

Occurrence of Type 2 Diabetes. Regular physical activity contributes to delaying and even preventing the onset of insulin resistance and type 2 diabetes in persons at high risk for developing this disease. Exercise benefits are particularly pronounced for obese individuals and perhaps all persons with increased abdominal fat deposition.

Exercise Risks for Type 2 Diabetes. Figure 20.29 lists potential adverse effects of exercise in type 2 diabetics. One can minimize these risks by properly screening patients before they start an exercise program and carefully monitoring them during exercise when the program begins.

Exercise Guidelines for Type 1 Diabetes. The clinical usefulness of regular exercise to improve glucose control in type 1 diabetes remains uncertain. To complicate matters for type 1 diabetics, physical activity can trigger a potentially dangerous dual response: (1) enhanced glucose uptake by active muscles and (2) greater than anticipated exogenous insulin distributed by more rapid circulation that accompanies physical activity. These two factors could worsen the imbalance between glucose supply and use, increasing the risk of serious complications from hypoglycemia. In a Practical Sense on page 428 offers physical activity guidelines for the diabetic patient, including those with well-controlled type 1 diabetes who wish to perform prolonged and strenuous exercise while minimizing the principal risk of hypoglycemia.

## RESISTANCE TRAINING AND ENDOCRINE FUNCTION

Muscle remodeling in resistance training reflects a complex process of cell receptor interaction with different hormones and DNA-mediated production of new contractile proteins. The specific exercise response to muscular overload initially links to configuration of the exercise stimulus-intensity, frequency, volume, sequence, mode, and recovery interval. Figure 20.30 proposes how resistance exercise training improves overall muscular size, strength, and power. Hormonal factors responsible for exercise-induced changes in muscle size and function include the following:

1. Changes in hepatic and extrahepatic hormone clearance rates
2. Differential rates of hormone secretion (and accompanying fluid shifts around the receptor sites)
3. Altered receptor-site activation via neurohumoral control. In general, early-phase adaptations to resistance training reflect a hormonal response that mediates neuromuscular system adaptations that improve muscle strength


Figure 20.29 Potential physical and physiologic problems and problem areas faced by type 2 diabetics who begin a physical activity program.

Testosterone and GH are two primary hormones that affect adaptations to resistance training. Testosterone augments GH release and interacts with nervous system function to increase muscle force production. These roles may be more important than any direct anabolic effect of testosterone per se. A single session of resistance training generally elicits a short-term rise in serum testosterone and decrease in cortisol, with a greater response in men than women. ${ }^{29,49,83}$ Concurrently, catecholamine release from the adrenal medulla increases with the acute stress of high-force and high-power exercise protocols. ${ }^{18}$

Resistance training in men increases frequency and amplitude of testosterone and GH secretion, thereby creating a favorable
hormonal environment for muscular growth (hypertrophy). In contrast, most studies fail to demonstrate changes in testosterone and GH concentrations with training in females. Thus, gender differences in hormone output with resistance training may ultimately explain variations in responsiveness of muscle strength and size to prolonged muscular overload.

Testosterone response to resistance exercise reveals several factors that increase its release. Most effective include intense activation of large-muscle groups with dead lifts, power cleans, and squats, and other forms of heavy resistance exercise (i.e., 85 to $95 \%$ 1-RM) or high-volume (total quantity) training with multiple sets and/or physical activity with less


Figure $\mathbf{2 0 . 3 0}$ Schematic model of how heavy resistance training produces favorable adaptations in muscle structure and maximal strength performance. (Modified from Kraemer WJ. Endocrine responses and adaptations to strength training. In: Komi PV, ed. Strength and power in sport. London: Blackwell Scientific, 1992.)
than 1-minute rest intervals. ${ }^{84}$ Long-term resistance training in men increases resting testosterone levels, which correlates with the pattern of strength improvement over time. ${ }^{56}$

## OPIOID PEPTIDES AND PHYSICAL ACTIVITY

Scientists who studied the pain-relieving effects of opioid peptides (e.g., morphine) on brain function in the 1970s reported these substances exhibited neurotransmitter effects and targeted specific opioid brain receptor sites. With this finding came the realization that perhaps the brain itself produced endogenous opioid, mood-altering substances. Evidence for existence of endogenous substances with opiate-like behavior first emerged with the isolation and purification of two opioid pentapeptides, methionine and leucine enkephalin (Greek, meaning in the brain ). These opioids form part of a larger propiocortin precursor molecule produced in the anterior pituitary. Other opioid substances include $\beta$-lipotropin, $\beta$-endorphin, and dynorphin, (the most potent of the opioid peptides).

The various endogenous opioids exert widespread effects with a range in function from neurohormones to neurotransmitters. Endogenous opiates strongly inhibit hormonal release from the anterior pituitary, principally LH and FSH release. This inhibition may play a key role in menstrual cycle disturbances observed among many physically active womendelay in menarche, dysfunctional uterine bleeding, secondary amenorrhea, and inadequacy of the luteal phase. In contrast to their inhibitory role, the opioid peptides stimulate GH and PRL release.

Endorphins also regulate other hormones including ACTH, the catecholamines, and cortisol. Serum concentrations of $\beta$-endorphin and/or $\beta$-lipotropin generally increase with physical activity similarly in men and women, although the response varies among individuals and varies inversely with exercise intensity. ${ }^{35,48,81}$ Physical activity increases $\beta$ endorphin up to five times the resting level and probably even more in the brain itself, ${ }^{74}$ particularly region-specific effects in frontolimbic brain areas that are involved in the processing of affective states and mood. ${ }^{11}$ With resistance exercise, $\beta$ endorphin release varies with the exercise protocol; longer duration (lighter resistance) and longer interset rest intervals elicit the greatest response. ${ }^{82}$

The precise physiologic significance of the response of the various endogenous opioid peptides to physical activity remains unclear, but several noteworthy effects emerge. These include the postulated opioid effect in triggering the exercise high, a state described as euphoria and exhilaration as the duration of moderate-to-intense aerobic exercise increases. Endorphin secretion also may increase pain tolerance, improve appetite control, and reduce anxiety, tension, anger, and confusion. Interestingly, these effects generally reflect the documented psychologic benefits of regular physical activity.

The effect of exercise training on endorphin response remains controversial. One study reported no significant change in $\beta$-endorphin response to prolonged exercise following

8 weeks of endurance training. Contrasting research showed that general physical conditioning augmented $\beta$-endorphin and $\beta$-lipotropin release in exercise. ${ }^{20}$ Greater endorphin release also occurs with sprint-type training, suggesting that anaerobic factors also affect endorphin dynamics. ${ }^{81}$

Exercise training can increase an individual s sensitivity to opioid effects, thus reducing the amount of hormone required to induce a specific effect. Regular physical activity causes the opioids produced during physical activity to degrade more slowly than in the pretraining condition. ${ }^{70} \mathrm{~A}$ slower rate of hormone disposal facilitates and prolongs an opioid response and possibly augments one stolerance for extended physical activity. Taken in total, one could view the endogenous opioid response to regular physical activity as a form of positive addiction.

## INTEGRATIVE QUESTION

List four supplements at your local health food store that claim to enhance exercise performance. Which supplements purport to stimulate hormone release? Based on hormonal regulation and function, explain whether these products can deliver on their claims.

## PHYSICAL ACTIVITY, INFECTIOUS ILLNESS, CANCER, AND IMMUNE RESPONSE

Don $t$ exercise when fatigued or you ll get sick reflects the common perception of parents, athletes, and coaches that excessive intense exercise increases susceptibility to certain illnesses. In contrast, some also believe that regular, more moderate physical activity improves health and reduces susceptibility to the common cold.

Studies as early as 1918 reported that most cases of pneumonia in boys in boarding school occurred among athletes, and respiratory infections seemed to progress toward pneumonia after intense sports training. Anecdotal reports also related the severity of poliomyelitis to participation in intense physical activity at the critical time of infection. Current epidemiologic and clinical findings from the field of exercise immunology-the study of the interactions of physical, environmental, and psychologic factors on immune func-tion-support the contention that short-term, unusually strenuous physical activity affects immune function to increase susceptibility to illness, particularly upper respiratory tract infection (URTI). Repeated URTI may signal a state of overtraining (see Chapter 21).

The immune system comprises a highly complex and self-regulating grouping of cells, hormones, and interactive modulators that defend the body from invasion from outside microbes (bacterial, viral, and fungal), foreign macromolecules, and abnormal cancerous cell growth. This system has two functional divisions: (1) innate immunity and (2) acquired immunity. The innate immune system includes anatomic and


Figure 20.31 Theoretical model of the interrelationships between stress, physical activity, illness, and the immune system. (From MacKinnon LT. Current challenges and future expectations in exercise immunology: back to the future. Med Sci Sports Exerc 1994;26:191.)
physiologic components (skin, mucous membranes, body temperature, and specialized defenses such as natural killer cells, diverse phagocytes, and inflammatory barriers). The acquired immune system consists of specialized B- and T-lymphocyte cells. When activated these cells regulate a highly effective immune response to a specific infectious agent. If infection does occur, an optimal immune system diminishes the severity of illness and speeds recovery.

Figure 20.31 shows a proposed model for the interactions of physical activity, stress, illness, and the immune system. Within this framework, physical activity, stress, and illness interact, each exerting its separate effect on immunity. For example, physical activity affects susceptibility to illness, while certain illnesses clearly affect exercise capacity. Likewise, psychologic factors (via links between the hypothalamus and immune function) and other forms of stress, including nutritional deficiencies and acute alterations in normal sleep schedule, influence resistance to illness. Concurrently, physical activity can either positively or negatively modulate the response to stress. Each factor-stress, illness, and short- and long-term exercise-exerts an independent effect on immune status, immune function, and resistance to disease.

## Upper Respiratory Tract Infections

Figure 20.32 describes the general J-shaped curve relating exercise volume and/or intensity and susceptibility to URTI. Different immune function markers generally follow an inverted J-shaped curve. ${ }^{123,174}$ Implications drawn from this relationship may be simplistic, but light to moderate physical activity offers more protection against URTI and possibly diverse cancers than a sedentary life-style. ${ }^{96,99,141}$ Moderate physical activity does not exacerbate the severity and duration of illness when an infection occurs. ${ }^{163}$ In contrast, a marathon run or intense training session provides an open window ( 3 to 72 h ) that decreases antiviral and antibacterial resistance


Figure 20.32 General model showing the relationship between intensity of physical activity and susceptibility to upper respiratory tract infection (URTI). Moderate exercise reduces risk of URTI, whereas exhaustive competition or training places the participant at increased risk. (From Nieman DC. Exercise, upper respiratory tract infection, and the immune system. Med Sci Sports Exerc 1994;26:128.)
and increases risk of URTI that manifests itself within 1 to 2 weeks, ${ }^{28,114}$ particularly for athletes prone to illness. ${ }^{25}$ Approximately $13 \%$ of the participants in a Los Angeles marathon reported an episode of infectious URTI during the week following the race. For runners of comparable ability who did not compete for reasons other than illness, the infection rate approximated just $2 \%{ }^{115}$

## Short-Term Exercise Effects

Moderate exercise: Moderate exercise boosts natural immune functions and host defenses for up to several hours. ${ }^{45}$ Noteworthy effects include increases in natural killer (NK) cell activity. These phagocytic lymphocyte subpopulations enhance the blood s cytotoxic capacity and provide the first line of defense against pathogens. The NK cell does not require prior or specific sensitization to foreign bodies or neoplastic cells. Rather, these cells demonstrate spontaneous cytolytic activity that ultimately ruptures and/or inactivates viruses and depresses the metastatic potential of tumor cells.
Exhaustive exercise: Prolonged exhaustive exercise (and other forms of extreme stress or increased training) severely depresses the body s first line of defense against infection. ${ }^{80,93,112,126,165}$ Repeated cycles of unusually intense exercise and sports participation
further compound the risk. Impaired immune function from strenuous exercise carries over to a second bout of exercise on the same day to augment negative changes in neutrophils, lymphocytes, and select CD cells. ${ }^{136}$ Elevated temperature, cytokines, and various stress-related hormones (epinephrine, GH, cortisol, $\beta$-endorphins) in exhaustive exercise may mediate the transient depression of innate (NK cell and neutrophil cytotoxicity) and depress adaptive immune defenses (T- and B-cell function). ${ }^{148,153}$ Reduced immunity following strenuous exercise remains in the mucosal immune system of the upper respiratory tract. ${ }^{47,109,160}$ and associates with increased URTI risk. ${ }^{113}$ This negative effect on immune response clearly supports advising individuals with URTI symptoms to refrain from physical activity (or at least go easy ) to optimize normal immune mechanisms that combat infection. Table 20.6 summarizes components of the immune system that exhibit transient changes after prolonged intense exertion.

## Long-Term Exercise Effects

Aerobic training positively affects natural immune functions in young and old individuals and obese persons during

## TABLE 20.6 Immune System Components that Exhibit Negative Change after Prolonged, Intense Exercise

High neutrophil and low lymphocyte blood counts, induced by high concentrations of plasma cortisol
Increase in blood granulocyte and monocyte phagocytosis (engulfing of infectious agents and of breakdown products of muscle fiber); decrease in nasal neutrophil phagocytosis
Decrease in granulocyte oxidative-burst activity (killing activity)
Decrease in nasal mucociliary clearance (sweeping movement of cilia)
Decrease in NK-cell cytotoxic activity (the ability to kill infected cells or cancer cells)
Decrease in mitogen-induced lymphocyte proliferation (a measure of T-cell function)
Decrease in the delayed-type hypersensitivity skin response
(the ability of the immune system to produce hard red lumps
after the skin is pricked with antigens)
Increase in plasma concentrations of pro- and
antiinflammatory cytokines (e.g., interleukin-6 and interleukin- 1 receptor antagonist)
Decrease in ex vivo production of cytokines (interferon-8, interleukin-1, and interleukin-6) to mitogens and endotoxin
Decrease in nasal and salivary IgA concentration (an important antibody)
Blunted expression of major histocompatibility complex (MHC) II in macrophages (an important step in recognition of foreign agents by the immune system)

From Nieman DC. Immunity in athletes: current issues. Sports Sci Exchange, Gatorade Sports Science Institute 1998;11(2).
weight loss. ${ }^{38,40,146}$ Areas of improvement include enhanced functional capacity of natural cytotoxic immune mechanisms (e.g., antitumor actions of NK cell activity) and diminished age-related decrease in T-cell function and associated cytokine production. ${ }^{74}$ The cytotoxic T cells defend directly against viral and fungal infections and help regulate other immune mechanisms.

If exercise training enhances immune function, one might ask why trained individuals show increased susceptibility to URTI after intense competition. The open window hypothesis maintains that an inordinate increase in training or competition exposes highly conditioned athletes to abnormal stress that transiently but severely depresses NK cell function. This period of immunodepression (open window) decreases natural resistance to infection. The inhibitory effect of strenuous physical activity on ACTH and cortisol s maintenance of optimal blood glucose concentrations may negatively affect the immune process. For individuals who exercise regularly but only at moderate levels, the window of opportunity for infection remains closed, thus maintaining the protective benefits of regular physical activity on immune function.

Resistance Training. Nine years of prior resistance exercise training did not affect resting NK cell activity or number compared to sedentary controls. ${ }^{116}$ Comparisons also indicated that resistance training activated monocytes more than typically observed for aerobic training. Monocyte activation releases prostaglandins that downregulate NK cells following physical activity, thus blunting the long-term positive effect of physical activity on NK cells. These researchers had previously reported a $225 \%$ increase in NK cells following a short-term bout of resistance exercise, ${ }^{177}$ a response similar to the short-term effect of moderate aerobic exercise. ${ }^{42}$

Perhaps a Role for Nutritional Supplements. Nutrition may optimize immune system function with strenuous exercise and training. ${ }^{46,62,101,138}$

Macronutrients. Consuming a high-fat diet (62\% energy from lipids) negatively affected the immune system compared to a carbohydrate-rich diet ( $65 \%$ energy from carbohydrates). In general, endurance athletes who ingest carbohydrate during a race or prolonged trial experience lower disruption in hormonal and immune measures (indicating a diminished level of physiologic stress) than athletes not consuming carbohydrate. ${ }^{139}$ Supplementing with a $6 \%$ carbohydrate beverage ( 0.71 L before; 0.25 L every 15 min during; 500 mL every h throughout a 4.5 -h recovery) depressed cytokine levels in the inflammatory cascade after 2.5 hours of running at $77 \%$ $\dot{\mathrm{V}} \mathrm{O}_{2 \max }{ }^{111}$ Consuming carbohydrates $(4 \mathrm{~mL}$ per kg of body mass) every 15 minutes during 2.5 hours of high-intensity running or cycling maintained higher plasma glucose levels in 10 triathletes during exercise than a placebo. ${ }^{119}$ A blunted cortisol response and diminished pro- and antiinflammatory cytokine responses accompanied the higher plasma glucose levels with supplementation in both forms of exercise. Similar benefits from carbohydrate ingestion for cortisol and select
antiinflammatory cytokines occur following marathon competition, regardless of age or gender. ${ }^{120}$ This suggests a carbohy-drate-induced reduction in overall physiologic stress in prolonged high-intensity exercise. In contrast, carbohydrate ingestion during two hours of intense resistance training produced no effect on immune changes compared to similar training with placebo ingestion. ${ }^{121}$

Micronutrients. Combined supplementation with antioxidant vitamins C and E produces more prominent immunopotentiating effects (enhanced cytokine production) in young, healthy adults than supplementation with either vitamin alone. ${ }^{71}$ Also, a 200-mg daily vitamin E supplement enhanced several clinically relevant indices of T-cell mediated function in healthy elderly subjects. ${ }^{102}$ Long-term daily supplementation with a physiologic dose of vitamins and minerals or with 200 mg of vitamin E did not lower the incidence and severity of acute respiratory tract infections in noninstitutionalized persons aged 60 and older. For individuals with infections, those receiving vitamin E had longer total illness duration and restriction of activity. ${ }^{50}$

Daily supplementation with vitamin $C$ benefits individuals engaged in intense exercise, particularly those predisposed to frequent URTI. ${ }^{60,127}$ Runners who received a $600-\mathrm{mg}$ daily vitamin C supplement before and for 3 weeks following a $90-\mathrm{km}$ ultramarathon competition experienced fewer symptoms of URTI-running nose, sneezing, sore throat, coughing, fever-than runners given a placebo. Interestingly, infection risk inversely related to race performance; those with the fastest times suffered more symptoms. URTI also appeared most frequently in runners with strenuous training regimens. For these individuals, additional vita$\min \mathrm{C}$ and E and perhaps carbohydrate ingestion before, during, and after prolonged stressful exercise may boost immune mechanisms for combating this type of infection. ${ }^{118}$ More than likely, other stressors-sleep deficit, mental stress, poor nutrition, or weight loss-magnify stress on the immune system from a single or repeated bout of exhaustive physical activity.

Glutamine and the Immune Response. The nonessential amino acid glutamine plays an important role in normal immune function. One protective aspect concerns glutamine s role as an energy fuel for nucleotide synthesis by disease fighting cells, particularly lymphocytes and macrophages that defend against infection. ${ }^{19,142}$ In humans, sepsis, injury, burns, surgery, and endurance exercise lower plasma and skeletal muscle glutamine levels. Lowered plasma glutamine levels most likely occur because glutamine demand by the liver, kidneys, gut, and immune system exceeds its supply from the diet and skeletal muscle. The lowered plasma glutamine concentration may contribute to the immunosuppression that accompanies extreme physical stress. ${ }^{10,63,145}$ Thus, glutamine supplementation might reduce susceptibility to URTI following prolonged competition or a bout of exhaustive training.

Marathoners who ingested a glutamine drink (5 g L-glutamine in 330 mL mineral water) at the end of a race and then 2 hours later reported fewer URTI symptoms than unsupplemented athletes. ${ }^{21}$ In subsequent studies by the same researchers to determine a possible protective mechanism, glutamine s effect on postexercise infection risk did not relate to any change in blood lymphocyte distribution. ${ }^{22}$ Appearance of URTI in athletes during intense training does not fluctuate with changes in plasma glutamine concentration. Preexercise glutamine supplementation does not affect the immune response following repeated bouts of intense exercise. ${ }^{89}$ Glutamine supplements taken $0,30,60$, and 90 minutes after a marathon race prevented the drop in glutamine concentrations following the race but did not influence lymphokine-activated killer cell activity, proliferative responses, or exercise-induced changes in leukocyte subpopulations. ${ }^{134}$ Based on current evidence, we cannot recommend glutamine supplements to reliably blunt immunosuppression from exhaustive exercise.

## A General Recommendation to Optimize Immunity

A lifestyle that emphasizes regular physical activity, maintenance of a well-balanced diet, reducing stress to a minimum, and obtaining adequate sleep generally optimizes immune function. For weight loss, we recommend a gradual approach because more rapid weight loss with accompanying severe caloric restriction suppresses immune function. ${ }^{15}$ With prolonged intense exercise, ingesting about $1 \mathrm{~L} \cdot \mathrm{~h}^{1}$ of a typical carbohydrate-rich sports drink lessens negative changes in immune function from the stress of physical activity and accompanying carbohydrate depletion. In general, endurance athletes who consume carbohydrate during a race experience a lower disruption in hormonal and immune measures than athletes who do not consume carbohydrate.

## The Physical Activity Cancer Connection

Epidemiologic studies generally demonstrate a protective association between regular physical activity and risk of breast, colon, lung, and prostate cancers (see Chapter 31). ${ }^{94,103}$ Longterm enhancement of other natural immune functions may contribute to the cancer-protective effect of regular physical activity in addition to its beneficial effect on NK cell activity. Upgraded defenses include augmented phagocytic capacity of the monocyte macrophage lineage combined with more robust cytotoxic and intracellular killing capacities (T-cell activity) that inhibit tumor growth and destroy cancer cells. ${ }^{173}$ Other potential effects of regular physical activity on aspects of cancer development include beneficial changes in the bodys antioxidant functions; endocrine profiles; prostaglandin metabolism; body composition; and, in the case of colon cancer, a beneficial increase in intestinal transit time. In Chapter 31, we review the role of physical activity in the prevention and treatment of different cancers.

## Summary

1. The endocrine system consists of a host organ, a transmitted substance (hormone), and a target or receptor organ. Hormones consist of steroids or amino acid (polypeptide) derivatives.
2. Hormones alter rates of cellular reactions by acting at specific receptor sites to enhance or inhibit enzyme function.
3. The amount of hormone synthesized, the amount released or taken up by the target organ, and the removal rate from the blood influence blood hormone concentration.
4. Most hormones respond to peripheral stimulus on an as-needed basis; others release at regular intervals. Some secretory cycles span several weeks; others pattern on a 24 -hour cycle.
5. The anterior pituitary secretes at least six hormones: PRL, the gonadotropic hormones FSH and LH, corticotropin, TSH, and GH.
6. GH promotes cell division and cellular proliferation. IGFs (or somatomedins) mediate many of GH s effects.
7. TSH controls the amount of hormone secreted by the thyroid gland; ACTH regulates output of hormones from the adrenal cortex; PRL affects reproduction and development of secondary sex characteristics of females; FSH and LH stimulate the ovaries to secrete estrogen in females and the testes to secrete testosterone in males.
8. The posterior pituitary secretes ADH, which controls water excretion by the kidneys. It also secretes oxytocin, an important hormone in birthing and lactation.
9. PTH controls blood calcium balance. It increases ionic (free) calcium levels by stimulating three target organs: bone, kidneys, and the small intestine.
10. TSH stimulates metabolism of all cells and increases carbohydrate and fat breakdown in energy metabolism.
11. The medulla of the adrenal gland secretes epinephrine and norepinephrine. The adrenal cortex secretes mineralocorticoids (regulate extracellular sodium and potassium levels), glucocorticoids (stimulate gluconeogenesis and serve as insulin antagonists), and androgens (control male secondary sex characteristics).
12. Testes in the male produce testosterone and ovaries in the female produce the estrogens estradiol and progesterone.
13. Moderate aerobic and resistance exercise increases testosterone in untrained males. For females, plasma testosterone and estrogen levels increase during moderate physical activity.
14. Insulin increases glucose transport into cells to control blood glucose levels and carbohydrate metabolism.
15. Total lack of insulin or decreased sensitivity or increased resistance to this hormone produces diabetes mellitus.
16. The $\beta$-cells of the pancreas secrete glucagon, an insulin antagonist that raises blood sugar levels.
17. Exercise training exerts differential effects on resting and exercise-induced hormone production and release. Trained persons have elevated hormone response during physical activity for ACTH and cortisol, and depressed values for GH, PRL, FSH, LH, testosterone, ADH, thyroxine, catecholamines, and insulin. No training response occurs for aldosterone, renin, and angiotensin.
18. Exercise-induced elevation of $\beta$-endorphins and other opioid-like hormones contributes to euphoria, increased pain tolerance, exercise high, and altered menstrual function.
19. Unusually intense physical activity increases susceptibility to URTI. Moderate physical activity upgrades immune responses to protect against URTI.
20. Regular exercise training positively affects natural immune functions. An enhanced immune profile protects against URTI and various cancers.
21. References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

World Health Organization: Diabetes Programme www.who.int/diabetes
American Diabetes Association: Diabetes Risk Calculator www.diabetes.org/risk-test.jsp
National Diabetes Information Clearinghouse (NDIC) http://www.diabetes.niddk.nih.gov/


## Applied <br> Exercise <br> Physiology



## SECTION



##  of Energy Transfer Capacity

## OVERVIEW

Throughout this book, we emphasize that different physical activities, depending on duration and intensity, activate highly specific energy transfer systems. We acknowledge the difficulty in placing certain activities into one category. For example, as a person increases aerobic fitness, an activity previously classified as anaerobic may become aerobic. In many cases, all three energytransfer systems-adenosine triphosphate phosphocreatine (ATP PCr) system, lactic acid system, and aerobic system-operate predominantly at different times during exercise, but each remains functional throughout the activity. Their relative contributions to the energy continuum directly relate to the duration and intensity (power output) of a specific activity.

Brief power activities for up to 6 seconds duration rely almost exclusively on immediate energy generated from the breakdown of stored intramuscular high-energy phosphates, ATP and PCr. Consequently, power athletes (e.g., sprinters, football players, shot putters, pole vaulters) must gear training toward improving this energy-transfer capacity, including the force-generating capacity of targeted muscles that power their sport. As all-out movement progresses to 60 seconds in duration and power output decreases, most of the energy for movement still arises through fast and slow anaerobic pathways. These metabolic reactions also involve the glycolytic short-term energy system with subsequent lactate accumulation. As exercise intensity diminishes and duration extends to 2 to 4 minutes, reliance on energy from the intramuscular phosphagens and anaerobic glycolysis decreases, and aerobic ATP production becomes increasingly more important. As prolonged exercise duration increases, aerobic metabolism generates more than $99 \%$ of the total energy requirement. Clearly, an efficient training program allocates a proportionate commitment to targeted training of specific energy and physiologic systems activated in the activity. The chapters in this section discuss anaerobic and aerobic conditioning (Chapter 21), including procedures for training muscles to become stronger (Chapter 22), with emphasis on principles, methods, and short-term responses and longer-term training adaptations. In the final chapter (Chapter 23), we explore the safety and efficacy of diverse chemical, nutritional, and physiologic aids to enhance exercise training and physical performance.

# Interview with Dr. Bengt Saltin 



Education: S dert lje Gymnasium (1955); Medical School, Karolinska Institute, Stockholm (1956 62); thesis in physiology, Karolinksa Institute, Stockholm (1964)

Current Affiliation: Director, Copenhagen Muscle Research Centre at Rigshospitalet and the University of Copenhagen; Adjunct Professor, August Krogh Institute, University of Copenhagen

Honors and Awards: See Appendix E, available online at
http://thepoint.lww.com/mkk7e.
Research Focus: Exploration of integrative cardiovascular and metabolic response to physical exercise, including studies on skeletal muscle in humans by direct needle biopsy

Memorable Publication: Saltin B, et al. Response to exercise after bed rest and after training: a longitudinal study of adaptive changes in oxygen transport and body composition. Circulation 1968;38(Suppl 7):79.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

In recognition of his studies, which provide a better understanding of maximal oxygen uptake in human subjects under different physiological and pathophysiological conditions, particularly thermal stress and dehydration.

Dr. Saltins classic study on exercise after bed rest and after training was the scientific foundation for the current early ambulation and exercise treatment of patients with coronary heart disease and the understanding of deconditioning that occurs in space travel.

In the late 1960s, Dr. Saltin began his seminal studies on skeletal muscle in humans, obtained by direct needle
biopsy. This pioneering work has had a profound influence on our understanding of the anatomical, physiological, and biochemical behavior of skeletal muscle and its interactions with the cardiovascular system. His recent work has determined the maximal flow capacity in active skeletal muscle and shows that the limiting factor in maximal oxygen uptake is the pumping capacity of the heart.

Dr. Saltin has provided training for many of the current leaders in exercise and sports science, and they have greatly benefited from his unique ability to acquire new knowledge by studying at all levels of integration.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

> In January of 1958, I had my oral examination in physiology as part of my medical studies. The examiner was Professor Ulf von Euler (later the 1970 Nobel Prize winner in physiology or medicine for discoveries concerning humoral transmitters in the nerve terminal and the mechanisms for their storage, release, and inactivation). At the end of the examination, I was asked whether I would be interested in staying on as a student instructor. My answer was yes. As I had an interest in orienteering (a common sport in Scandinavia), I wanted to be associated with exerciserelated research. Professor Euler called Erik Hohw -

Christensen, who was the professor of physiology at the Royal School of Gymnastics. The week after I met with Professor Hohw -Christensen in the summer of 1958, I started to work with him on a project that evaluated energy demands in intermittent exercise. During the semesters, I helped with teaching while at the same time continuing my medical studies. In the fall of 1961 , I decided to go for a doctoral thesis in physiology, which I defended in May 1964.

Who were the most influential people in your career, and why?
> Two people played a very important role in my scientific career. I would like to acknowledge Professor Erik Hohw -Christensen and Professor Per-Olof
strand. Professor Hohw -Christensen had been a student of Johannes Lindhard, the first Docent of the equivalent of an endowed Chair in Anatomy, Physiology, and Theory of Gymnastics at the University of Copenhagen, and had also done cooperative research with 1920 Nobel Prize winner August Krogh. Professor Per-Olof strand at the Karolinska Institute was the equivalent of my PhD dissertation research advisor. My projects were concerned with trying to better understand maximal oxygen uptake in human subjects and its determinants under different physiological and pathophysiological conditions, particularly thermal stress and dehydration. The knowledge and passion of these two pioneer scientists encouraged a younger generation of researchers-tobe to focus on human integrative physiology.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

This is a difficult question to answer. I have been very fortunate to work with many scientists from all over the world. For example, in 1965, I spent 1 year in the Department of Medicine at the University of Texas in Dallas. Later, I worked for 5 months at the John B. Pierce Institute and Department of Physiology at Yale University in New Haven, Connecticut. In 1972, I spent 2 months in the Department of Medicine at the University of California, San Francisco, and then in 1976, I spent 3 months working with David Costill in The Human Performance Laboratory at Ball State University in Muncie, Indiana. I also spent 4 months at Cumberland College and the Department of Physiology at New South Wales University in Sydney, Australia. For my interest in high-altitude physiology and temperature regulation, I was fortunate to spend from 1 to 5 months between the years of 1960 and 1989 in laboratories in Northern Norway studying the physical profile and health of Nomadic Lapps, and at the following locations studying high-altitude physiology: Mt. Evans (Colorado), Mexico City, the Andes and Himalayan mountains, and Kenya. I also had a wonderful experience studying the physiological responses to exercise in racing camels in the Arabian desert.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

- To try to better understand, not only to describe, basic phenomena concerned with physiological responses to exercise under various environmental conditions. Exercise science was a key area in science in the latter part of the nineteenth century and in the first three decades of the twentieth century. There are many reasons for the lack of major contributions since then. One reason could be that the majority of exercise

scientists describe a phenomenon, but they do not try hard enough to penetrate the mechanisms and thereby contribute to the fundamental understanding of the phenomenon.


## What advice would you give to students who express an interest in pursuing a career in exercise science research?

> Become very focused and learn basic techniques. Today, exercise science is to a large extent the study of acute and chronic adaptations. Thus, one route I would highlight is to identify the exercise stimulus and the intracellular signalling of genes of importance for muscle adaptation. In an article in Scientific American (September 2000), we pointed out that Olympic athletes depend on how well their muscles adapt to the stress of high-intensity aerobic, anaerobic, and resistance training. However, recent research suggests that the ratio of fast- to slow-twitch muscle fibers depends on inherited characteristics. Unfortunately, future genetic technologies could change even that as athletes experiment with methods to enhance muscle performance.

## 450 Section 4

## What interests have you pursued outside your professional career?

$>$ I have been heavily involved in the sport of orienteering, both as a runner and administrator. From 1982 to 1988, I served as a Board Member and President of the International Orienteering Federation. I am a theater freak and have an interest in literature. Ibsen and Strindberg are my favorites, but most classical plays from antique Greece onwards will bring me to the theater. Throughout life my reading companions have been Katherine Mansfield, Albert Camus, Joseph Brodsky, and, to name a Dane, J. P. Jacobsen.

## You have the opportunity to give a last lecture. Describe its primary focus.

> I have given my last lecture. It focused on how young exercise physiologists could best serve an area in research and also make a major contribution to science. A major point was to identify an important phenomenon. If there are ample methods to study it, then stay with it until it has been solved. In other words, be mechanistic, carefully explain the phenomena, and then do whatever you can to understand it.



## CHAPTER 21

## Training for Anaerobic and Aerobic Power

## CHAPTER OBJECTIVES

> Discuss and provide examples of the exercise training principles of (1) overload, (2) specificity, (3) individual differences, and (4) reversibility
> Outline the metabolic adaptations to anaerobic exercise training
> Outline the metabolic, cardiovascular, and pulmonary adaptations to aerobic exercise training
> Discuss factors that expand the $\mathrm{a}-\mathrm{vO}_{2}$ difference during graded exercise, and how endurance training affects each component

- Explain the effects of endurance training on regional blood flow
- Explain the term athletes heart; contrast structural and functional characteristics of the heart of an endurance athlete versus a resistance-trained athlete
> Describe the influence of (1) initial fitness level, (2) genetics, (3) training frequency, (4) training duration, and (5) training intensity on the aerobic training response
> Discuss the rationale for using heart rate to establish exercise intensity for aerobic training
- Discuss the term training-sensitive zone, including its rationale, advantages, limitations, and application for men and women of different ages
> Give the reason for adjusting the training-sensitive zone for swimming and other forms of upperbody exercise
> Justify the rating of perceived exertion to establish exercise intensity for aerobic training
> Outline advantages of training at the lactate threshold
> Contrast continuous and intermittent aerobic exercise training and advantages and disadvantages of each
- Summarize current recommendations by the American College of Sports Medicine concerning the quantity and quality of exercise to develop and maintain cardiorespiratory and muscular fitness and joint flexibility in healthy adults
> Outline the application of the overload principle to train the (1) intramuscular high-energy phosphates and (2) glycolytic energy system
> Summarize important factors about the exercise prescription for interval training
$>$ Describe the most common form of overtraining syndrome and summarize interacting factors that contribute to overtraining in endurance athletes
> Summarize current recommendations for regular physical activity during pregnancy


## EXERCISE TRAINING PRINCIPLES

Stimulating structural and functional adaptations to improve performance in specific physical tasks remains a major objective of exercise training. These adaptations require adherence to carefully planned programs, with focus on frequency and length of workouts, type of training, speed, intensity, duration, and repetition of the activity, rest intervals, and appropriate
competition. Application of these factors varies depending on performance and fitness goals. Several principles of physiologic conditioning are common to improving performance in the diverse physical activity classifications illustrated in Figure 21.1. The basic approach to physiologic conditioning applies similarly to men and women within a broad age range; both respond and adapt to training in essentially the same way.


Figure 21.1 Classification of physical activity based on duration of all-out exercise and the corresponding predominant intracellular energy pathways.

## Overload Principle

Regular application of a specific exercise overload enhances physiologic function to induce a training response. Exercising at intensities greater than normal stimulates highly specific adaptations so the body functions more efficiently. Achieving the appropriate overload requires manipulating training frequency, intensity, and duration, with focus on exercise mode.

The concept of individualized and progressive overload applies to athletes, sedentary persons, disabled persons, and even cardiac patients. An increasing number in this latter group have applied appropriate exercise rehabilitation to walk, jog, and eventually run and compete in marathons and triathlons. As we discuss in Chapter 31, achieving healthrelated benefits of regular physical activity requires lower exercise intensity (but greater volume) than required to improve maximum aerobic fitness. ${ }^{107,126,203}$

## Specificity Principle

Exercise training specificity refers to adaptations in metabolic and physiologic functions that depend upon the type and mode of overload imposed. A specific anaerobic exercise stress (e.g., strength power training) induces specific strength power adaptations; specific endurance exercise stress elicits specific aerobic system adaptations-with only a limited interchange of benefits between strength power training and aerobic training. Nonetheless, the specificity principle extends beyond this broad demarcation. Aerobic training, for example, does not represent a singular entity that requires only cardiovascular overload. Aerobic training that relies on specific muscles in the desired performance most effectively improves aerobic fitness for swimming, ${ }^{57}$ bicycling, ${ }^{150}$ running, ${ }^{129}$ or upper-body exercise. ${ }^{112}$ Some evidence even suggests a temporal specificity in training response such that indicators of training improvement peak when measured at the time of day when training regularly occurred. ${ }^{81}$ The most
effective evaluation of sport-specific performance occurs when the laboratory measurement most closely simulates the actual sport activity and/or uses the muscle mass and movement patterns required by the sport. ${ }^{12,57,111}$ Simply stated, specific exercise elicits specific adaptations to promote specific training effects. Put another easy-to-remember way: specificity refers to Specific Adaptations to Imposed Demands (SAID).

## Specificity of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$

Table 21.1 presents evidence for the specificity of endurance swim training on aerobic capacity improvements. Fifteen men trained 1 hour daily, 3 days a week for 10 weeks. For all subjects, $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ before and after training was measured during treadmill running and tethered swimming. Vigorous swimming elicits a general circulatory overload, so the researchers expected at least minimal improvement (or transfer ) in aerobic power from swimming to running. This did not occur. Almost total specificity accompanied the $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ improvement with swim training. Use of treadmill running alone to assess swim training effects would have mistakenly concluded no swim training effect!

When training for specific aerobic activities such as cycling, swimming, rowing, or running, the overload must (1) engage the appropriate muscles required by the activity and (2) provide exercise at a level sufficient to stress the cardiovascular system. Little improvement occurs when measuring aerobic capacity with dissimilar exercise; the greatest improvement occurs when the test exercise duplicates the training exercise. These results also apply in exercise rehabilitation of patients with coronary artery disease. ${ }^{145}$ The data in Table 21.1 also indicate that while swimming $\dot{\mathrm{V}}_{2 \text { max }}$ improved $11 \%$ with swim training, maximum exercise time increased $34 \%$ during the swim test. Improvements in $\mathrm{VO}_{2 \max }$ probably reach a peak during training. Thereafter, other

TABLE 21.1 Effects of 10 Weeks of Interval Swim Training on Changes in $\mathrm{VO}_{2 \text { max }}$ and Endurance Performance During Running and Swimming

| Subjects | Measure | Running Test |  |  | Swimming Test |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Swim Training |  | Pretraining | Posttraining | \% Change | Pretraining | Posttraining | \% Change |
|  | $\mathrm{VO}_{2 \text { max }}$ |  |  |  |  |  |  |
|  | $\mathrm{L} \cdot \mathrm{min}^{-1}$ | 4.05 | 4.11 | 1.5 | 3.44 | 3.82 | 11.0 |
|  | $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | 54.9 | 55.7 | 1.5 | 46.6 | 51.8 | 11.0 |
|  | Max work time $\min$ | 19.6 | 20.5 | 4.6 | 11.9 | 15.9 | 34.0 |
| Nontraining |  |  |  |  |  |  |  |
|  | $\mathbf{V O}_{2 \text { max }}$ |  |  |  |  |  |  |
|  | $L \cdot \min ^{-1}$ | $4.12$ | $4.18$ | $1.5$ |  | 3.40 | -3.1 |
|  | $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | $55.1$ | $55.5$ | $0.7$ | $46.8$ | 45.0 | -3.8 |
|  | Max work time min | 20.7 | 19.7 | -4.8 | 11.5 | 11.5 | 0 |

From Magel JR, et al. Specificity of swim training on maximum oxygen uptake. J Appl Physiol 1975;38:151.

## FOCUS ON RESEARCH

## Highly Specific Nature of the Training Response

Saltin B, et al. The nature of the training response: peripheral and central adaptations to one-legged exercise. Acta Physiol Scand 1976;96:289.

> In 1976, Saltin and colleagues performed one of the first studies to document that regular exercise induces marked local adaptations in trained muscle. Importantly, these adjustments enhance local blood flow and metabolism in response to physical activity and also contribute to general cardiovascular function during exercise.

An elegant series of experiments separated local and general training effects. They applied different combinations of one-legged bicycle exercise to study simultaneously adaptations of skeletal muscles and central circulatory functions with training. Healthy but otherwise sedentary males with pretraining $\dot{\mathrm{V}}_{2_{\text {max }}}$ of $46 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}$ (range: 3754 ) were placed into three training groups: group A-one-legged endurance training ( E ) and the other leg sprint training (S); group B-one-legged S and the other leg no training (NT); group C-one-legged E and the other leg NT. Exercise training performed on a bicycle ergometer with intensity adjusted to heart rate lasted 4 weeks, with an average of 5 workouts per leg each week. The exercise intensity throughout training represented $75 \%$ for E and $150 \%$ for S of the one-legged $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ assessed pretraining and at week 3 to ensure proper training progression. Intensity and duration of each type of training produced similar total work output for each training bout. Total weekly energy output averaged $12,558 \mathrm{kCal}$ per trained leg, with all groups achieving within 5 to $10 \%$ of this value; group A, however, performed 90 to $95 \%$ more work than group B because their training required both legs.

Pre- and posttraining measurements included needle biopsy samples from the quadriceps femoris for histochemical identification of muscle fiber type and area, glycogen concentration, and succinate dehydrogenase (SDH) and ATPase activity. Subjects performed submaximal and maximal exercise for each leg and during twolegged maximal cycling ( 8 of 13 subjects provided data to evaluate local metabolic adaptations to training). Measures included oxygen consumption, heart rate, arteriovenous oxygen difference ( $a-\bar{v} \mathrm{O}_{2}$ diff) in muscle blood flow (catheters inserted in the two femoral arteries and veins to measure each leg s blood flow), and glucose and lactate. The three major findings were:

[^33]- Training induced no change in muscle fiber composition but produced pronounced metabolic adaptations reflected by enhanced SDH activity of the S- and E-trained legs, with no change in the NT leg. These changes generally paralleled increases in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$.
- Glycogen use during two-legged exercise remained lowest in the trained leg. Moreover, only the untrained leg continuously released lactate during submaximal exercise.


## 1. One-legged exercise

Figure 1 shows that $\mathrm{V}_{\mathrm{O}_{2 \text { max }}}$ increased nearly $20 \%$ with training in the E-trained leg, $11 \%$ in the S-trained leg, and $8 \%$ when exercising both legs (group A). S training of one leg only (group B) increased $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ by $15 \%$, whereas $\dot{\mathrm{V}}{ }_{2 \text { max }}$ of the nontrained leg increased less than $2 \%$. Onelegged endurance training for group $C$ increased $\dot{\mathrm{V}} \mathrm{O}_{2_{\text {max }}}$ by $24 \%$ in the trained leg while $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ with the NT leg increased just $6 \%$. These results confirmed that training only one leg exerts little effect on the nontrained leg, thus indicating considerable training specificity.

## 2. Two-legged exercise

Analysis of pre- and posttraining two-legged $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ revealed mean increases for groups $\mathrm{A}(9 \%)$, B ( $10 \%$ ), and C ( $8 \%$ ). Figure 2 shows similar leg blood flow (left panel) in trained and untrained legs and in E-trained legs compared with S-trained legs. In addition, similarity existed for $\mathrm{a}-\mathrm{v}_{2}$ difference (middle panel) for S - and E-trained legs during exercise. In the four subjects with one trained and one untrained leg, the slightly higher $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ differences in the trained leg resulted from a lower oxygen content in the femoral blood draining the trained leg (greater $\mathrm{O}_{2}$ extraction). Endurance- and sprint-trained legs showed similar calculated oxygen consumptions during exercise (right panel); some subjects, however, showed higher values in the trained leg than in the untrained leg.

The study s major impact was demonstrating that an exercise training regimen elicits a distinct pattern of local adaptations only in the trained muscles. These specific local changes provide essential stimulation for the central cardiovascular response to exercise. Saltin and coworkers concluded that peripheral adaptations to training probably contribute as much to the training response as the welldocumented improvement in central circulatory function.

## FOCUS ON RESEARCH



Figure 1 Mean percentage changes in $\mathrm{VO}_{2 \text { max }}$ in groups $\mathrm{A}, \mathrm{B}$, and C during onelegged exercise. Pretraining $\mathrm{VO}_{2 \text { max }}$ values $\left(L \cdot \min ^{-1}\right)$ are indicated below each bar. The four bars on the far right indicate average values for all untrained, sprint- or endurance-trained limbs and values for two-legged exercise regardless of training group.


Rest $\square$ Untrained (NT)-Trained (T) $\square$ Endurance trained (E)-Sprint trained (S)
Figure 2 Leg blood flow (left panel), leg a- $\mathrm{vO}_{2}$ difference (middle panel), and oxygen consumption (right panel) in each leg for subjects performing two-legged exercise for 1 hour at $70 \% \mathrm{VO}_{2 \max }$. Comparisons are between the legs of four untrained subjects (NT) and four trained subjects (endurance-trained [T] or sprinttrained [S]). The panels also show trained and untrained leg comparisons for the four subjects who trained one leg with the endurance regimen and the other leg with sprint training.
mechanisms (only partly related to oxygen transport system capacity) support performance improvements. These adaptations most likely take place within the active musculature rather than the central circulatory system (see Focus on Research, p. 454).

Whereas aerobic exercise training induces a highly specific $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ improvement, more general improvements take place in cardiac function. Ventricular contractility, for example, that improves with one mode of exercise training also improves when exercising the untrained limbs. ${ }^{205}$

Individuals apparently can train the myocardium per se with diverse big-muscle exercise modes.

## Specificity of Local Changes

Overloading specific muscle groups with endurance training enhances exercise performance and aerobic power by facilitating oxygen transport and oxygen use at the local level of the trained muscles. ${ }^{82,122}$ For example, the vastus lateralis muscle of well-trained cyclists has greater oxidative capacity than that of endurance runners; oxidative capacity in this muscle improves considerably following training on a bicycle ergometer. Such local metabolic adaptations increase the capacity of trained muscles to generate ATP aerobically before the onset of lactate accumulation. The specificity of
aerobic improvement also may result from greater regional blood flow in active tissues from (1) increased microcirculation, (2) more effective redistribution of cardiac output, or (3) the combined effect of both factors. Regardless of the mechanism, these adaptations occur only in specifically trained muscles and only become apparent in exercise that activates this musculature.

## Individual Differences Principle

All individuals do not respond similarly to a given training stimulus. For example, a person s relative fitness level at the start of training exerts an influence. This subprinciple of initial values reveals that individuals with lower fitness deliver the greatest training improvement. This principle operates

TABLE 21.2 Changes in Measures of Physiologic and Metabolic Function with Various Durations of Detraining ${ }^{a}$

| Variable | Trained | Detrained | Change, \% Short-Term Detraining ${ }^{b}$ | Change, \% Longer-Term Detraining ${ }^{\text {c }}$ |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | 62.2 | 57.3 | -8 |  |
|  | 62.1 | 50.8 |  | -18 |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{L} \cdot \min ^{-1}$ | 4.45 | 4.16 | -7 |  |
| Cardiac output, $\mathrm{L} \cdot \mathrm{min}^{-1}$ | 27.8 | 25.5 | -8 |  |
|  | 27.8 | 25.2 |  | -10 |
| Stroke volume, mL | 155 | 139 | -10 |  |
|  | 148 | 129 |  | -13 |
| Heart rate, b $\cdot \mathrm{min}^{-1}$ | 186 | 193 | 4 |  |
|  | 187 | 197 |  | 5 |
| Oxygen pulse, mL $\cdot \mathrm{b}^{-1}$ | 12.7 | 10.9 |  | -14 |
| Sum 3-min recovery HR | 190 | 237 |  | 25 |
| Plasma volume, L | 2.91 | 2.56 | -12 |  |
| $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff, $\mathrm{mL} \cdot 100 \mathrm{~mL}^{-1}$ | 15.1 | 15.4 | -2 (NS) |  |
|  | 15.1 | 14.1 |  | -7 |
| $\mathrm{PCr}, \mathrm{mM} \cdot(\mathrm{g} \text { wet wt })^{-1}$ | 17.9 | 13.0 |  | -27 |
| ATP, mM $\cdot(\mathrm{g} \text { wet } \mathrm{wt})^{-1}$ | 5.97 | 5.08 |  | -15 |
| Glycogen, mM - $(\mathrm{g} \text { wet } \mathrm{wt})^{-1}$ | 113.9 | 57.4 |  | -50 |
| Capillary density, cap $\cdot \mathrm{mm}^{-2}$ | 511 | 476 | -7 |  |
|  | 464 | 476 |  | -2 (NS) |
| Oxidative enzyme capacity |  |  | -29 | -32 |
| Myoglobin, mg (g protein) ${ }^{-1}$ | 43.3 | 41.0 | -5 (NS) |  |
|  | 43.3 | 40.7 |  | -6 |
| Insulin (rest) |  |  | 17120 |  |
| Norepinephrine/epinephrine (rest) |  |  | No change |  |
| Norepinephrine/epinephrine (exercise) |  |  |  | 65100 |
| Blood lactate |  |  | 88 |  |
| Lactate threshold |  |  | -7 | -18 |
| Exercise lipolysis |  |  | -52 |  |
| Muscle glycogen synthesis |  |  | -29 | -40 |
| Time to fatigue, min |  |  | -10 |  |
| Swim power, W |  |  |  | -14 |
| Elbow extension strength, ft-lb | 39.0 | 25.5 |  | -35 |

[^34]for healthy individuals as well as those with cardiovascular disease or at high risk for the disease. ${ }^{18,166,224}$ When a relatively homogenous group begins a regimen of exercise training, one cannot expect each person to achieve the same state of fitness (or exercise performance) after 10 or 12 weeks. A coach should not insist that all athletes on the same team (or even in the same event) train the same way or at the same relative or absolute exercise intensity. Optimal training benefits occur when exercise programs focus on individual needs and capacities of participants. Chapter 11 and page 476 of this chapter emphasize that genetic factors interact to impact the training response.

## Reversibility Principle

Loss of physiologic and performance adaptations (detraining) occurs rapidly when a person terminates participation in regular physical activity. Only 1 or 2 weeks of detraining reduces both metabolic and exercise capacity, with many training improvements fully lost within several months. ${ }^{140}$ Table 21.2 shows the biologic consequences of various durations of short-term ( $<3$ weeks) and longer-term (3 12 weeks) detraining in endurance-trained individuals. The data represent average responses reported in the literature. One
research group confined five subjects to bed for 20 consecutive days. ${ }^{180} \dot{\mathrm{VO}}_{2 \max }$ decreased by $25 \%$. This decrease accompanied a similar decrement in maximal stroke volume and cardiac output, which decreased maximal aerobic power an average of $1 \%$ per day. Additionally, the number of capillaries within trained muscle decreased between 14 and $25 \%$ within 3 weeks immediately following training. ${ }^{179}$ For elderly subjects, 4 months of detraining completely negated endurance training adaptations on cardiovascular functions and body water distribution. ${ }^{155}$

Even among highly trained athletes, the beneficial effects of many years of prior exercise training remain transient and reversible. For this reason, most athletes begin a reconditioning program several months prior to the start of the competitive season or, at a minimum, maintain some moderate level of off-season, sport-specific training to slow the decline in physiologic functions from detraining.

## PHYSIOLOGIC CONSEQUENCES OF EXERCISE TRAINING

The following sections present a more detailed listing of the diverse adaptations to the anaerobic and aerobic exercise training responses outlined in Table 21.3.
$\begin{array}{cl}\text { TABLE 21.3 } & \begin{array}{l}\text { Typical Metabolic and Physiologic Values for Healthy, Endurance-Trained and } \\ \text { Untrained Men }\end{array} \text { a }\end{array}$

| Variable | Untrained | Trained | Percentage Difference ${ }^{b}$ |
| :---: | :---: | :---: | :---: |
| Glycogen, mM - $(\mathrm{g} \text { wet muscle) })^{-1}$ | 85.0 | 120 | 41 |
| Number of mitochondria, $\mathrm{mmol}^{3}$ | 0.59 | 1.20 | 103 |
| Mitochondrial volume, \% muscle cell | 2.15 | 8.00 | 272 |
| Resting ATP, mM $\cdot(\mathrm{g} \text { wet muscle) })^{-1}$ | 3.0 | 6.0 | 100 |
|  | 11.0 | 18.0 | 64 |
| Resting creatine, $\mathrm{mM} \cdot(\mathrm{g} \text { wet muscle })^{-1}$ | 10.7 | 14.5 | 35 |
| Glycolytic enzymes |  |  |  |
| Phosphofructokinase, $\mathrm{mM} \cdot(\mathrm{g} \text { wet muscle })^{-1}$ | 50.0 | 50.0 | 0 |
| Phosphorylase, mM - $\mathrm{g}^{\text {wet muscle })^{-1}}$ | 46 | 69 | 60 |
| Aerobic enzymes |  |  |  |
| Succinate dehydrogenase, mM $\cdot\left(\mathrm{kg}\right.$ wet muscle) ${ }^{-1}$ | 510 | 1520 | 133 |
| Max lactate, mM - $\mathrm{kg}^{\text {wet muscle })^{-1}}$ | 110 | 150 | 36 |
| Muscle fibers |  |  |  |
| Fast twitch, \% | 50 | 2030 | -50 |
| Slow twitch, \% | 50 | 60 | 20 |
| Max stroke volume, mL | 120 | 180 | 50 |
| Max cardiac output, L $\cdot \mathrm{min}^{-1}$ | 20 | 3040 | 75 |
| Resting heart rate, $\mathrm{b} \cdot \mathrm{min}^{-1}$ | 70 | 40 | -43 |
| Max heart rate, $\mathrm{bmin}^{-1}$ | 190 | 180 | -5 |
| Max $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff, mL $\cdot \mathrm{dL}^{-1}$ | 14.5 | 16.0 | 10 |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ | 3040 | 6580 | 107 |
| Heart volume, L | 7.5 | 9.5 | 27 |
| Blood volume, L | 4.7 | 6.0 | 28 |
| $\mathrm{V}_{\text {Emax }}, \mathrm{L} \cdot \mathrm{min}^{-1}$ | 110 | 190 | 73 |
| Percentage body fat | 15 | 11 | -27 |

[^35]TABLE 21.4 Changes in Resting Concentrations of PCr, Creatine, ATP, and Glycogen Following 5 months of HeavyResistance Training in 9 Male Subjects

| Variable ${ }^{\boldsymbol{a}}$ | Control | Posttraining | Percentage <br> difference |
| :--- | :---: | :---: | :---: |
| PCr | 17.07 | 17.94 | +5.1 |
| Creatine | 10.74 | 14.52 | +35.2 |
| ATP | 5.07 | 5.97 | +17.8 |
| Glycogen | 86.28 | 113.90 | +32.0 |

From MacDougall JD, et al. Biochemical adaptation of human skeletal muscle to heavy resistance training and immobilization. J Appl Physiol 1977;43:700.
${ }^{a}$ All values are averages expressed in mM per gram of wet muscle.
${ }^{b}$ All percentage differences are statistically significant.

## ANAEROBIC SYSTEM CHANGES WITH TRAINING

Figure 21.2 summarizes generalized responses for metabolic adaptations in anaerobic function that accompany anaerobic training. Consistent with the concept of training specificity, activities that demand a high level of anaerobic metabolism induce specific changes in the immediate and short-term energy systems without concomitant increases in aerobic functions. Three important changes occur with anaerobic power training:

1. Increased levels of anaerobic substrates. Muscle biopsy specimens taken before and after resistance


Figure 21.2 Generalized potential for increases in anaerobic energy metabolism of skeletal muscle with shortterm sprint power training.
training (TABLE 21.4) show increases in the trained muscle s resting levels of ATP, PCr , free creatine, and glycogen, accompanied by a $28 \%$ improvement in muscular strength. Other studies have shown higher levels of ATP and total creatine content in trained muscles of sprint runners and track speed cyclists compared to distance runners and road racers. ${ }^{144}$ Speed power training also increases PCr content of the trained skeletal muscle.
2. Increased quantity and activity of key enzymes that control the anaerobic (glycolytic) phase of glucose catabolism. These changes do not achieve the magnitude observed for oxidative enzymes with aerobic training. The most dramatic increases in anaerobic enzyme function and fiber size occur in fast-twitch muscle fibers.
3. Increased capacity to generate high levels of blood lactate during all-out exercise. This adaptation probably results from (1) increased levels of glycogen and glycolytic enzymes and (2) improved motivation and tolerance to pain in fatiguing physical activity. Research has not yet demonstrated that exercise training augments buffering capacity mechanisms. Motivational factors probably improve traininginduced tolerance to elevated plasma acidity.

## AEROBIC SYSTEM CHANGES WITH TRAINING

Figure 21.3 shows the diverse physiologic and metabolic factors related to oxygen transport and use. With adequate training stimulus, the positive adaptations in many of these factors remain independent of race, gender, age and, in some instances, health status. ${ }^{25,31,186,223}$

## Metabolic Adaptations

Aerobic training improves the capacity for respiratory control in skeletal muscle.


Figure 21.3 Physiologic factors that limit $\mathrm{VO}_{2 \max }$ and aerobic exercise performance. Hb , hemoglobin.

## Metabolic Machinery

To some extent, mitochondrial potential and not oxygen supply limits the oxidative capacity of untrained muscle. ${ }^{72}$ Endurance-trained skeletal muscle fibers contain larger and more numerous mitochondria than less active fibers. The enlarged mitochondrial structural machinery and enzyme activity adaptations with aerobic training (up to $50 \%$ increase in just a few weeks) greatly increase the capacity of subsarcolemmal and intermyofibrillar muscle mitochondria to generate ATP aerobically. ${ }^{65,84,198}$ A nearly twofold increase in aerobic system enzymes within 5 to 10 days of training coincides with increased mitochondrial capacity to generate ATP aerobically.

Increases in total mitochondrial material, not increased enzymatic activity per unit of mitochondrial protein, account for the enzyme changes. The increase in mitochondrial protein by a factor of two exceeds the typical 10 to $20 \%$ increases in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ with endurance training. More than likely, enzymatic changes allow a person to sustain a higher percentage
of aerobic capacity during prolonged exercise without blood lactate accumulation.

Fat Metabolism. Endurance training increases the oxidation of fatty acids for energy during rest ${ }^{148}$ and submaximal exercise (FIG. 21.4). ${ }^{49,85,214}$ Enhanced fat catabolism becomes particularly apparent at the same absolute submaximal exercise workload without regard to fuel input (fed or fasted), ${ }^{9,11,30}$ and the effect occurs within two weeks of training. ${ }^{201}$ Impressive increases also occur in trained muscle s capacity to use intramuscular triacylglycerols as the primary source for fatty acid oxidation. ${ }^{127}$ Four factors contribute to a heightened training-induced increased lipolysis:

1. Greater blood flow within trained muscle
2. More fat-mobilizing and fat-metabolizing enzymes
3. Enhanced muscle mitochondrial respiratory capacity
4. Decreased catecholamine release for the same absolute power output


## $\square$ Before training $\square$ After training

Figure 21.4 Aerobic exercise training enhances fat catabolism in submaximal exercise. During constant-load, prolonged exercise, total energy derived from fat oxidation increases considerably following training. The carbohydratesparing adaptation results from facilitated release of fatty acids from adipose tissue depots (augmented by a reduced blood lactate level) and an increased amount of triacylglycerol within the endurance-trained muscle fibers. (From Hurley BF, et al. Muscle triglyceride utilization during exercise: effect of training. J Appl Physiol 1986;60:562.)

Enhanced fat catabolism in submaximal exercise benefits endurance athletes because it conserves the glycogen stores so important during prolonged, intense exercise. Improved fatty acid $\beta$-oxidation and respiratory ATP production contribute to a cell s integrity and high level of function. This enhances endurance capacity independent of increases in glycogen reserves or aerobic power.

Carbohydrate Metabolism. Trained muscle exhibits enhanced capacity to oxidize carbohydrate during maximal exercise. Consequently, large quantities of pyruvate flow through aerobic energy pathways in this type of exercise, an effect consistent with increased mitochondrial oxidative capacity and enhanced glycogen storage within muscles. Reduced carbohydrate as fuel and increased fatty acid
combustion in submaximal exercise with endurance training results from the combined effects of the following:

1. Decreased muscle glycogen use
2. Reduced glucose production (decreased hepatic glycogenolysis and gluconeogenesis)
3. Reduced use of plasma-borne glucose ${ }^{30}$

Training-enhanced hepatic gluconeogenic capacity provides further resistance to hypoglycemia during prolonged exercise. ${ }^{32,41}$

## Muscle Fiber Type and Size

Aerobic training elicits metabolic adaptations in each muscle fiber type. The basic fiber type probably does not change to any great extent; rather, all fibers maximize their already existing aerobic potential.

Selective hypertrophy occurs in the different muscle fiber types with specific overload training. Highly trained endurance athletes have larger slow-twitch fibers than fasttwitch fibers in the same muscle. Conversely, the fast-twitch fibers of athletes trained in anaerobic power activities occupy a greater portion of the muscle s cross-sectional area.

Myoglobin. As might be expected, slow-twitch muscle fibers with high capacity to generate ATP aerobically contain relatively large quantities of myoglobin. Among animals, a muscle s myoglobin content relates to their level of physical activity. The leg muscles of hunting dogs, for example, contain more myoglobin than the muscles of sedentary house pets; similar findings exist for grazing cattle compared with penned animals. ${ }^{222}$ The effect of regular physical activity on myoglobin levels in humans remains undetermined, but any effect is likely negligible.

## Cardiovascular Adaptations

Figure 21.5 summarizes important adaptations in cardiovascular function with aerobic exercise training that increase oxygen delivery to active muscle.

## Cardiac Hypertrophy: The Athletes Heart

Long-term aerobic training generally increases the heart s mass and volume with greater left-ventricular enddiastolic volumes during rest and exercise. Moderate cardiac hypertrophy secondary to longitudinal myocardial cell enlargement reflects a fundamental and normal training adaptation of muscle to an increased workload independent of age. ${ }^{137}$ This enlargement is characterized by an increased size of the left ventricular cavity (eccentric hypertrophy) and modest thickening of its walls (concentric hypertrophy).

Exercise training alters the contractile properties of cardiac muscle fibers that include increased sensitivity to activation by $\mathrm{Ca}^{2+}$, changes in force length relationship, and increased power output. ${ }^{38}$ Myocardial overload stimulates greater cellular protein synthesis with concomitant reductions


Figure 21.5 Adaptations in cardiovascular function with aerobic exercise training that increase oxygen delivery to active muscles.
in protein breakdown. Increasing trained muscle s RNA content accelerates protein synthesis. Individual myofibrils thicken, while the number of contractile filaments increases.

The heart volume of sedentary men averages about 800 mL . In athletes, increases in heart volume relate to the aerobic nature of the sport-endurance athletes average a $25 \%$ larger heart volume than their sedentary counterparts. The degree to which the large heart volumes of endurance athletes reflect genetic endowment, training adaptations, or a combined effect remains unanswered.

Training duration affects cardiac size and structure. Several studies report no changes in cardiac dimensions with short-term training despite improvements in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ and submaximal exercise heart rate response. ${ }^{167,205}$ When endurance training increases left ventricular size, the enlargement does not reflect a permanent adaptation. Instead, heart size decreases to pretraining levels-with no deleterious effectsas training intensity decreases. ${ }^{37,80}$ Figure 21.6 depicts the general trend for cardiac enlargement (reflected by leftventricular mass) in untrained and strength power- and endurance-trained athletic groups.

Specific Nature of Cardiac Enlargement. The ultrasonic technique of echocardiography incorporates sound
waves to map myocardial dimensions and heart chamber volume (see Chapter 32). This technique has evaluated the structural characteristics of hearts of male and female athletes (and other species of mammals) to determine how various modes of exercise training differentially affect cardiac enlargement. ${ }^{151,199}$

Cardiac dimensions of male swimmers, water polo players, distance runners, wrestlers, and shot putters were compared during their competitive seasons with those of untrained college men. The swimmers and runners represented athletes in isotonic or endurance events; the wrestlers and shot putters represented isometric or resistance-trained power athletes. Table 21.5 shows clear distinctions in structural characteristics of the hearts of healthy athletes and untrained individuals. Heart structure differences among athletes relate to the nature of exercise training. In swimmers, left-ventricular volume averaged 181 mL and mass equaled 308 g . In wrestlers, left-ventricular volume averaged 110 mL and mass averaged 330 g ; the nonathletic controls averaged 101 mL for ventricular volume and 211 g for ventricular mass. The resistance-trained athletes had thicker ventricular walls, whereas the walls of the hearts of endurance athletes remained within a normal range. Cardiac morphologic and functional adaptations, including resting bradycardia, increased


## $\square$ Male $\square$ Female

Figure 21.6 General trend toward cardiac enlargement (left-ventricular mass) among the untrained and various groups of strength power- and endurance-trained male and (where applicable) female athletes.
stroke volume, and enlarged ventricular internal dimensions also occur in prepubertal children who undergo intense endurance training. ${ }^{146}$

Figure 21.7 shows the distribution of left-ventricular enddiastolic dimensions in 1309 elite Italian athletes ages 13 to 59 years. These dimensions ranged from 38 to 66 mm (average: 48.4 mm ) in women and 43 to 70 mm (average: 55.5 mm ) in men. Ventricular cavity size of the majority of athletes remained within normal range, but $14 \%$ showed substantially enlarged dimensions. A large body surface area and participation in endurance cycling, cross-country skiing, and canoeing represented the major determinants of enlarged cavity dimension. The subjects remained free of heart problems over the 12 -year study period. Other athletic groups also show an enlarged ventricular cavity (increased end-diastolic volume)
with normal wall thickness, ${ }^{133,170}$ with the effect less pronounced among females. ${ }^{151}$

Training-Induced Plasma Volume Provides a Possible Explanation. Myocardial structural and dimensional adaptations to regular exercise generally reflect specific training demands. ${ }^{19,158}$ As discussed in the section titled Plasma Volume on page 463, a plasma volume increase within a day or two of the onset of endurance training contributes to intraventricular enlargement, or eccentric hypertrophy. ${ }^{189}$ Increased plasma volume, coupled with a decreased heart rate and increased myocardial compliance, dilates or stretches the left-ventricular cavity analogous to filling a balloon with water.

In contrast to endurance athletes, male and female resistance-trained athletes possess the largest intraventricular

TABLE 21.5 Comparative Average Cardiac Dimensions in College Athletes, World-Class Athletes, and Normal Subjects

| Dimension ${ }^{\text {a }}$ | College Runners ( $\mathrm{n}=15$ ) | College Swimmers ( $\mathrm{n}=15$ ) | World-Class Runners ( $\mathrm{n}=10$ ) | College Wrestlers ( $\mathrm{n}=12$ ) | World-Class Shot Putters $(n=4)$ | Normals $(n=16)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| LVID | 54 | 51 | $4859^{\text {b }}$ | 48 | $4352^{\text {b }}$ | 46 |
| LVV, mL | 160 | 181 | 154 | 110 | 122 | 101 |
| SV, mL | 116 | NR | 113 | 75 | 68 | NR |
| LV wall, mm | 11.3 | 10.6 | 10.8 | 13.7 | 13.8 | 10.3 |
| Septum, mm | 10.9 | 10.7 | 10.9 | 13.0 | 13.5 | 10.3 |
| LV mass, g | 302 | 308 | 283 | 330 | 348 | 211 |

[^36]
$\square$ Male $\square$ Female

Figure 21.7 Distribution of left-ventricular end-diastolic cavity dimensions in 1309 highly trained athletes without evidence of structural cardiovascular disease. Fourteen percent of the athletes had markedly enlarged left ventricular cavities that ranged in size from 60 to 70 mm . (From Pelliccia A, et al. Physiologic left ventricular cavity dilation in elite athletes. Ann Intern Med 1999;130:23.)
septum, ventricular wall thickness, and ventricular mass, with little enlargement in the left ventricles internal cavity. ${ }^{56,110}$ These athletes do not experience volume overload with training. Instead, their training produces short-term episodes of elevated arterial blood pressure (see Chapter 15) from high forces generated by a limited mass of skeletal muscle. An increase in ventricular wall thickness (that generally falls within the normal range when expressed as ventricular mass per unit body size, particularly fat-free body mass) ${ }^{151,152}$ compensates for additional afterload on the left ventricle without affecting ventricular cavity size. More than likely, considerable intraindividual variability exists for the hearts structural response to different forms of training. When changes do occur, the implications for myocardial blood supply and long-term cardiovascular health remain unknown. No compelling scientific evidence indicates that specific modes of arduous physical activity and training damage a healthy heart. ${ }^{95}$ The same also pertains to cardiac patients who undergo a proper exercisebased cardiac rehabilitation program. ${ }^{21}$

Functional Versus Pathologic Cardiac Hypertrophy. Disease can induce considerable cardiac enlargement. In hypertension, for example, the heart chronically works against excessive resistance to blood flow (afterload). This stretches the heart muscle, which, in accord with the Frank-Starling mechanism, generates compensatory force to overcome the added resistance to systolic ejection. In addition to ventricular dilation, individual muscle cells enlarge (hypertrophy) to adjust to the increased myocardial work imposed by a hypertensive state. In untreated hypertension, myocardial fibers stretch beyond their optimal length, so the enlarged, dilated heart weakens and eventually fails. To the pathologist, this hypertrophied heart represents an enlarged, distended, and functionally inadequate organ unable to deliver sufficient blood to satisfy minimal resting requirements.

Exercise training, on the other hand, imposes only a temporary myocardial stress, so rest periods provide time for recuperation. Also, dilation and weakening of the left ventricle, a frequent response to chronic hypertension, does not accompany compensatory myocardial adaptations with exercise training. The enlarged heart size of elite athletes generally falls within the upper range of normal for either body size or increased end-diastolic volume. The athletes heart does not represent a dysfunctional organ. Rather, it demonstrates normal systolic and diastolic functions and superior functional capacity for stroke volume and cardiac output. One possible exception concerns resistance-trained athletes who abuse anabolic steroids. An increase in both systolic and diastolic blood pressure, including exacerbation of the normal cardiac hypertrophy, occurs with steroid use. ${ }^{64,70,93}$

## INTEGRATIVE QUESTION

Explain how cardiac hypertrophy with pressure overload training (e.g., resistance training) could affect oxygenation of myocardial tissues?

## Plasma Volume

A 12 to $20 \%$ increase in plasma volume, in the absence of changes in red blood cell mass, occurs after three to six aerobic training sessions. In fact, a measurable change occurs within 24 hours of the first exercise bout, with expansion of extracellular fluid volume requiring several weeks. ${ }^{181}$ Intravascular volume expansion directly relates to increased synthesis and retention of plasma albumin. ${ }^{135,142}$ A plasma volume increase enhances circulatory reserve and increases end-diastolic volume, stroke volume, oxygen transport, $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, and temperature-regulating ability during exercise. ${ }^{61,66}$

An expanded plasma volume returns to pretraining levels within 1 week following training. ${ }^{189,218}$ For endurance athletes in different sports, hemoglobin mass and blood volume averaged $35 \%$ higher than that of untrained subjects, with little difference in hemoglobin concentration among groups. ${ }^{75}$

## Heart Rate

Endurance training creates an imbalance between tonic activity of sympathetic accelerator and parasympathetic depressor neurons in favor of greater vagal dominance-a response mediated primarily by increased parasympathetic activity and a small decrease in sympathetic discharge. ${ }^{60,106}$ Training also decreases the intrinsic firing rate of sinoatrial (SA) nodal pacemaker tissue. ${ }^{182}$ These adaptations contribute to the resting and submaximal exercise bradycardia in highly conditioned endurance athletes or previously sedentary individuals who train aerobically.

Exercise Heart Rate: Training Effects. Submaximal heart rate for a standard exercise task frequently decreases by 12 to $15 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ with endurance training, while a much smaller decrease occurs for resting heart rate. Such heart rate reductions reflect the magnitude of training improvement because they generally coincide with increased maximum stroke volume and cardiac output. Figure 21.8 illustrates the


$$
\begin{aligned}
& \square \text { Endurance athletes } \\
& \square \text { Sedentary college students } \\
& \square \text { sedentary college students after training }
\end{aligned}
$$

Figure 21.8 Heart rate and oxygen consumption during upright exercise in endurance athletes ( $\square$ ) and sedentary college students before ( $\quad$ ) and after ( $\square$ ) 55 days of aerobic training ( $\boldsymbol{\top}=$ maximal values).
relationship between heart rate and oxygen consumption during graded exercise for athletes and sedentary students. ${ }^{178}$ The group of six endurance athletes trained for several years; the other group consisted of three sedentary college students. The researchers evaluated the students exercise responses before and after a 55-day training program designed to improve aerobic fitness. The lines relating heart rate and oxygen consumption remain essentially linear for both groups throughout the major portion of the exercise range. Whereas the untrained students heart rates accelerate rapidly as exercise intensity and oxygen consumption increase, the athletes heart rates rise much less; that is, the slope, or rate of change, of the $\mathrm{HR} \dot{\mathrm{V}} \mathrm{O}_{2}$ lines differs considerably between trained and untrained. Consequently, an athlete (or trained student) performs more intense exercise and achieves a higher oxygen consumption before reaching a specific submaximal heart rate than does a sedentary student. At an oxygen consumption of $2.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, the athletes heart rate averaged $70 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ less than for sedentary students. After 55 days of training, the difference in submaximal heart rate decreased to about $40 \mathrm{~b} \cdot \mathrm{~min}^{-1}$. In each instance, cardiac output remained essentially unchanged-an increase in stroke volume compensated for the lower heart rate.

## Stroke Volume

Endurance training causes the heart s stroke volume to increase during rest and exercise regardless of age or gender. Four factors produce this change ${ }^{44,98,131}$ :

1. Increased internal left ventricular volume (consequent to the training-induced plasma volume expansion) and mass
2. Reduced cardiac and arterial stiffness
3. Increased diastolic filling time (from traininginduced bradycardia)
4. Possibly, improved intrinsic cardiac contractile function
Exercise Stroke Volume: Trained Versus Untrained. Figure 21.9 shows the stroke volume response during exercise for the men depicted in Figure 21.8. Five important trainingrelated observations emerge:
5. The endurance athlete $s$ heart exhibits a considerably larger stroke volume during rest and exercise than an untrained person of similar age.
6. The greatest stroke volume increase during upright exercise for trained and untrained persons occurs in transition from rest to moderate exercise. Only small increases in stroke volume accompany further increases in exercise intensity.
7. Maximum stroke volume generally occurs between 40 and $50 \%$ of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ (untrained persons); this takes place at a heart rate of 110 to $120 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ in young adults. Debate currently focuses on whether the stroke volume decreases, plateaus, or gradually increases during graded exercise to maximum, particularly among endurance athletes where the stroke

```
\squareEndurance athletes
Sedentary college students
    Sedentary college students
    after training
```

Figure 21.9 Stroke volume and oxygen consumption during upright exercise in endurance athletes ( $\square$ ) and sedentary college students before ( $\square$ ) and after ( $\square$ ) 55 days of aerobic training ( $\boldsymbol{\uparrow}=$ maximal values).
volume may benefit from an enlarged plasma volume. ${ }^{62,219}$ More than likely, endurance training minimizes the small decrease in stroke volume often observed during maximal exercise. Even at nearmaximal heart rates, sufficient time exists for the trained heart s ventricles to fill during diastole without reduction in stroke volume. ${ }^{59,197,228}$
4. For untrained persons, only a small increase in stroke volume occurs during transition from rest to exercise. Consequently, a cardiac output increase occurs from acceleration in heart rate. For endurance athletes, heart rate and stroke volume both increase to increase cardiac output; the athlete s stroke volume generally expands $60 \%$ above resting values.
Relatively large stroke volume increases in transition from rest to exercise also occur in endurance-trained children and older men compared with healthy but untrained counterparts. ${ }^{66,176}$
5. Eight weeks of aerobic training by previously sedentary individuals substantially increases stroke volume, but these values remain below values for elite athletes.

Stroke Volume and $\dot{\mathbf{V}} \mathbf{O}_{\text {2max }}$. The data in Table 21.6 am plify the importance of stroke volume in differentiating persons with high and low $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ values. These data represent three groups: (1) athletes, (2) healthy but sedentary men, and (3) patients with mitral stenosis, a valvular heart disease that causes inadequate emptying of the left ventricle. The differences in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ among groups relate closely to differences in maximal stroke volume. Patients with mitral stenosis achieved an aerobic capacity and maximum stroke volume one-half that of sedentary subjects. The importance of stroke volume also emerges in comparisons among healthy groups. Athletes achieved an average $62 \%$ larger $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ than sedentary subjects, almost entirely from the athletes $60 \%$ larger stroke volume and cardiac output (Figs. 21.9 and 21.10).

## Cardiac Output

An increase in maximum cardiac output represents the most significant adaptation in cardiovascular function with aerobic training. Maximal heart rate generally decreases slightly with training; thus, increased cardiac output capacity results directly from improved stroke volume. A large maximum cardiac output (stroke volume) distinguishes champion endurance athletes from other well-trained athletes and from untrained counterparts.

Figure 21.10 illustrates the important role of cardiac output in achieving a high level of aerobic metabolism. In trained athletes and students, cardiac output increases linearly with oxygen consumption throughout the major portion of the exercise intensity range with the athletes achieving the highest values for both variables. A linear relationship between cardiac output and oxygen consumption in graded exercise also occurs in children and adolescents. For these young persons, increased stroke volume (and proportionate increase in cardiac output) closely matches the added oxygen requirement of exercise during growth. ${ }^{34}$

Exercise Training and Submaximal Cardiac Output. Early reports showed that endurance training, while improving

TABLE 21.6 Maximal Values for Oxygen Consumption, Heart Rate, Stroke Volume, and Cardiac Output in Three Groups with Low, Normal, and High Aerobic Capacities

| Group | $\mathbf{V O}_{\mathbf{2 m a x}}$ <br> $\left(\mathbf{L} \cdot \mathbf{m i n}^{\mathbf{1}} \mathbf{)}\right.$ | Max Heart Rate <br> $\left(\mathbf{B} \cdot \mathbf{m i n}^{\mathbf{1}} \mathbf{)}\right.$ | Max Stroke Volume <br> $\left(\mathbf{m L} \cdot \mathbf{B}^{\mathbf{- 1}}\right)$ | Max Cardiac Output <br> $\left(\mathbf{L} \cdot \mathbf{m i n}^{\mathbf{- 1}}\right)$ |
| :--- | :---: | :---: | :---: | :---: |
| Mitral stenosis | 1.6 | 190 | 50 | 9.5 |
| Sedentary | 3.2 | 200 | 100 | 20.0 |
| Athlete | 5.2 | 190 | 160 | 30.4 |

[^37]

Figure 21.10 Cardiac output and oxygen consumption during upright exercise in endurance athletes ( $\square$ ) and sedentary college students before ( $\square$ ) and after ( $\square$ ) 55 days of aerobic training ( $\boldsymbol{\Lambda}=$ maximal values).
maximal cardiac output, reduced the heart s minute volume during moderate exercise. In one study, average cardiac output of young men after 16 weeks of aerobic training decreased by 1.1 and $1.5 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at a specific submaximal oxygen consumption. ${ }^{42}$ As expected, maximal cardiac output increased $8 \%$, from 22.4 to $24.2 \mathrm{~L} \cdot \mathrm{~min}^{-1}$. With reduced submaximal cardiac output, a corresponding increase in oxygen extraction in the active muscles achieves the exercise oxygen requirement. A training-induced reduction in submaximal cardiac output presumably reflects two factors:

1. More effective redistribution of blood flow
2. Trained muscles enhanced capacity to generate ATP aerobically at a lower tissue $\mathrm{PO}_{2}$

## Oxygen Extraction ( $a-\bar{v} \mathrm{O}_{2}$ Difference)

Aerobic training increases the quantity of oxygen extracted (measured as arterio-venous oxygen differences, or $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference) from circulating blood. ${ }^{183}$ An increase in the maximum $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference results from more effective cardiac output distribution to active muscles combined with enhanced capacity of trained muscle fibers to extract and process available oxygen, The $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference takes on even greater importance in contributing to improved aerobic capacity with training in older men and women because the elderly often show diminished capacity to improve cardiac output with training. ${ }^{100,185}$

Figure 21.11 compares the relationship between oxygen extraction ( $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference) and exercise intensity for the trained athletes and untrained students depicted in Figure 21.8.


Endurance athletes
Sedentary college students
Sedentary college students after training
Figure 21.11 The $\mathrm{a}-\mathrm{v} \mathrm{O}_{2}$ difference and oxygen consumption during upright exercise in endurance athletes $(\square)$ and sedentary college students before ( $\square$ ) and after ( $\square$ ) 55 days of aerobic training ( $\mathbf{1}=$ maximal values).

The $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference for the students increases steadily during graded exercise to a maximum of 15 mL per deciliter of blood. Following 55 days of training, the students maximum oxygen extraction increased $13 \%$ to 17 mL of oxygen. This means that during intense exercise, arterial blood released approximately $85 \%$ of its oxygen content. Actually, the active muscles extract even more oxygen because the $a-\bar{v} \mathrm{O}_{2}$ difference reflects an average based on sampling of mixed-venous blood, which contains blood returning from tissues that use much less oxygen during exercise than active muscle. The posttraining value for maximal $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference for the students equals the value of the endurance athletes. Obviously, the students lower cardiac output capacity explains the rather large difference in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ that clearly differentiates athletes from students.

## Blood Flow and Distribution

Submaximal Exercise. Trained persons perform submaximal exercise with a lower cardiac output (and unchanged or slightly lower muscle blood flow) than untrained persons. A relatively larger portion of submaximal cardiac output flows to high oxidative skeletal muscles (composed primarily of type I fibers) at the expense of blood flow to muscles with a large percentage of type IIb fibers with low oxidative capacity. ${ }^{35}$ Two factors contribute to reduced muscle blood flow in submaximal exercise: ${ }^{103,204,217,225}$

1. Relatively rapid training-induced changes in vasoactive properties of large arteries and local resistance vessels within skeletal and cardiac muscle, mediated by the dilation effects of endothelium-derived nitric oxide
2. Changes within muscle cells that enhance oxidative capacity

Both of these adaptations support the principle of training specificity. As the muscle s ability to deliver, extract, and use oxygen increases, the active tissue s oxygen needs require proportionally less blood flow.

Maximal Exercise. Three factors affect how aerobic training increases total skeletal muscle blood flow during maximal exercise:

1. Larger maximal cardiac output
2. Distribution of blood to muscle from nonactive areas that temporarily compromise blood flow during allout effort
3. Enlargement of cross-sectional areas of large and small arteries (arteriogenesis) and veins, and 10 to $20 \%$ increase in capillarization per gram of muscle (angiogenesis). ${ }^{77,164,168}$ This effect begins rapidly from increased vascular endothelial growth factorsproduced by skeletal muscle cells (partly in response to vascular sheer stress and wall stress in response to the hemodynamic forces imposed by exercise) to induce angiogenesis-after a single bout of exercise in trained and untrained persons. ${ }^{54,97,104}$

Training-induced decreases in splanchnic and renal blood flow in exercise occur from reduced sympathetic nervous system outflow to these tissues. ${ }^{128}$ This frees a relatively large quantity of blood for distribution to active muscles. Concurrently, exercise training and accompanying exposure to elevated core temperatures produces heat loss adaptations via enhanced endothelium-dependent increases in skin blood flow for a given internal temperature. ${ }^{89,99}$ Augmented cutaneous blood flow facilitates the endurance-trained person $s$ capacity to dissipate the metabolic heat generated in exercise.

The observation that oxygen extraction in skeletal muscle remains near maximal in intense exercise supports the hypothesis that oxygen supply (blood flow), not oxygen use (extraction), limits the maximal respiratory rate of muscle tissue. ${ }^{10,139,168}$

Myocardial Blood Flow. For both normal persons and cardiac patients, structural and functional changes in the heart s vasculature, including modifications in mechanisms that regulate myocardial perfusion, parallel a modest traininginduced myocardial hypertrophy. ${ }^{69,102}$ Structural vascular modifications include an increase in cross-sectional area of the proximal coronary arteries, possible arteriolar proliferation and longitudinal growth, recruitment of collateral vessels, and increased capillary density. These adaptations provide adequate perfusion to support the increased blood flow and energy demands of the functionally improved myocardium.

Two mechanisms help explain how aerobic training increases coronary blood flow and capillary exchange capacity:

1. Ordered progression of structural remodeling that improves myocardial vascularization when new capillaries form and develop into small arterioles ${ }^{101}$
2. More effective control of vascular resistance and blood distribution within the myocardium ${ }^{211,217}$

The significance of vascular and cellular adaptations to the hearts functional capacity during exercise remains unclear-mainly because the healthy, untrained heart does not suffer from reduced oxygen during maximal exercise. Training adaptations may provide some cardioprotection by enabling myocardial tissue to better tolerate and recover from transient episodes of ischemia (i.e., become more resistant to ischemic injury). The trained tissue also functions at a lower percentage of its total oxidative capacity during exercise. Vascular adaptations do not accompany the myocardial hypertrophy that occurs with chronic resistance training. ${ }^{137}$

## Blood Pressure

Regular aerobic training reduces systolic and diastolic blood pressure during rest and submaximal exercise. The largest reduction occurs in systolic pressure, particularly in hypertensive subjects (see Chapters 15 and 32 for a more complete discussion).

## Pulmonary Adaptations with Training

Aerobic training stimulates adaptations in pulmonary ventilation dynamics during submaximal and maximal exercise. The adaptations generally reflect a breathing strategy that minimizes respiratory work at a given exercise intensity. This frees oxygen for use by the nonrespiratory active musculature.

## Maximal Exercise

Maximal exercise ventilation increases from increased tidal volume and breathing rate as maximal oxygen consumption increases. This makes sense physiologically because any increase in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ raises the body s oxygen requirement and corresponding need to eliminate additional carbon dioxide via alveolar ventilation.

## Submaximal Exercise

Several weeks of aerobic training reduce the ventilatory equivalent for oxygen $\left(\dot{\mathrm{V}}_{\mathrm{E}} / \dot{\mathrm{V}} \mathrm{O}_{2}\right)$ during submaximal exercise and lower the percentage of the total exercise oxygen cost attributable to breathing. Reduced oxygen consumption by the ventilatory musculature enhances exercise endurance for two reasons:

1. It reduces fatiguing effects of exercise on the ventilatory musculature.
2. Any oxygen freed from use by the respiratory musculature becomes available to active locomotor muscles.

In general, exercise training increases tidal volume and decreases breathing frequency. Consequently, air remains in the lungs for a longer time between breaths; this increases oxygen extraction from inspired air. For example, the exhaled air of trained individuals during submaximal exercise contains


Figure 21.12 Ventilation equivalents during light (L) and intense (I) submaximal arm and leg exercise before and after arm training (top) and leg training (bottom). (From Rasmussen B, et al. Pulmonary ventilation, blood gases, and blood pH after training of the arms and the legs. J Appl Physiol 1975;38:250.)
only 14 to $15 \%$ oxygen, whereas the expired air of untrained persons averages $18 \%$ at the same exercise intensity. This translates to the common observation that untrained persons ventilate proportionately more air to achieve the same submaximal oxygen consumption.

Substantial specificity exists for ventilatory responses relative to the type of exercise and training adaptations. When subjects performed arm-only and leg-only exercise, consistently higher ventilatory equivalents occurred with the arms (Fig. 21.12). As expected, the ventilatory equivalent decreased in each mode with exercise training. However, the reduction occurred only with exercise that used specifically trained muscles. For the group trained by arm-crank ergometry, the ventilation equivalent decreased only during arm exercise and vice versa for the leg-trained group. The ventilatory training adaptation linked closely to a less pronounced rise in blood lactate and heart rate during the specific training exercise. This suggests that local adaptations in specifically trained muscles affect the ventilatory adjustment to training. In this regard, lower lactate levels with training remove the drive to breathe from any additional carbon dioxide produced from lactate buffering.

## Training May Benefit Ventilatory Endurance

Prolonged, intense exercise causes the inspiratory muscles to fatigue. ${ }^{8,86}$ Such exercise also reduces the abdominal muscles capacity to generate maximal expiratory pressure. ${ }^{51}$

Exercise training allows for sustained, exceptionally high levels of submaximum ventilation. ${ }^{19,88,193}$ Endurance training stabilizes the body s internal milieu during submaximal exercise. Consequently, exercise causes less disruption in whole-body hormonal and acid base balance that could negatively impact inspiratory muscle function. The ventilatory muscles also benefit directly from exercise training. For example, 20 weeks of run training by healthy men and women improved ventilatory muscle endurance by approximately $16 \%$ (less lactate accumulation during standard breathing exercise). The training-induced increase in aerobic enzyme levels and oxidative capacity of the respiratory musculature contribute to enhanced ventilatory muscle function. ${ }^{163,196}$ Exercise training also increases inspiratory muscle capacity to generate force and sustain a given level of inspiratory pressure. ${ }^{26}$ These adaptations benefit exercise performance in three ways:

1. Reduce overall exercise energy demands because of less respiratory work
2. Reduce lactate production by the ventilatory muscles during intense, prolonged exercise
3. Enhance how ventilatory muscles metabolize circulating lactate as metabolic fuel

## Blood Lactate Concentration

Figure 21.13 illustrates the generalized effect of endurance training in lowering blood lactate levels and extending exercise before onset of blood lactate accumulation (OBLA)


Figure 21.13 Generalized response for pre- and posttraining lactate accumulation during graded exercise. (Plots based on data from the Applied Physiology Laboratory, University of Michigan, Ann Arbor, MI.)
during exercise of increasing intensity. The underlying explanation centers on three possibilities related to central and peripheral adaptations to aerobic training discussed in this chapter:

1. Decreased rate of lactate formation during exercise
2. Increased rate of lactate clearance (removal) during exercise
3. Combined effects of decreased lactate formation and increased lactate removal

## Other Aerobic Training Adaptations

- Body composition changes: Regular aerobic exercise for the obese or overweight person reduces body mass and body fat and augments a more favorable body fat distribution (see Chapter 30). Exercise only or combined with calorie restriction reduces body fat more than weight loss with dieting by promoting conservation of lean tissue.
- Body heat transfer: Well-hydrated, trained individuals exercise more comfortably in hot environments because of a larger plasma volume and more responsive thermoregulatory mechanisms; in other words, they dissipate heat faster and more economically than sedentary individuals.
- Performance changes: Enhanced endurance performance accompanies physiologic adaptations with training. Figure 21.14 depicts cycling performance prior to and following 10 weeks of cycling training for 40 to 60 minutes, 4 days per week for 10 weeks at $85 \%$


Figure 21.14 Percentage drop-off from initial exercise intensity before and after 10 weeks of endurance cycling training. (From the Applied Physiology Laboratory, University of Michigan, Ann Arbor, MI.)
$\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$. In the performance test, subjects attempted to maintain a constant power output of 265 watts for 8 minutes. Training produced less drop-off in power output during the prescribed 8 -minute exercise test.

- Psychologic benefits: Regular exercise, regardless of age, creates important potential benefits on psychologic state. Adaptations often occur to a degree equal to that achieved with other therapeutic interventions, including pharmacologic therapy. ${ }^{45,206}$


## Six Potential Psychologic Benefits from Regular Exercise

1. Reduction in state of anxiety (i.e., the level of anxiety at the time of measurement)
2. Decrease in mild-to-moderate depression
3. Reduction in neuroticism (long-term exercise)
4. Adjunct to professional treatment of severe depression
5. Improvement in mood, self-esteem, and selfconcept
6. Reduction in the various indices of stress

## Summary View

Figure 21.15 summarizes adaptive changes in active muscle that accompany $\dot{\mathrm{V}}_{2 \text { max }}$ improvements with endurance training and detraining. Aerobic capacity generally increases 15 to $25 \%$ over the first 3 months of intensive training and may improve by $50 \%$ over a 2 -year interval. When training ceases, $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ rapidly decreases toward the pretraining level. Even more impressive training effects occur for aerobic enzymes of the citric acid cycle and electron-transport chain within the mitochondria of trained muscles. These enzymes increase rapidly and substantially throughout training in both fiber types and subdivisions. Conversely, a few weeks of detraining substantially reduce a large portion of enzymatic adaptations. The number of muscle capillaries increases during training. When training ceases, this adaptation in blood supply probably decreases relatively slowly. The ultimate detraining occurs with aging. Although it is possible to produce substantial improvements in physiologic function in the elderly, regular exercise slows but cannot halt the muscle atrophy, weakness, and fatigability that accompanies an increase in chronological age. ${ }^{43}$

Local metabolic improvement greatly exceeds improvements in capacity to circulate, deliver, and use oxygen (reflected by $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ and cardiac output) during intense exercise. With local training adaptations, a muscle s lactate flux remains at lower levels (lower production and/or greater removal rate) than similar submaximal exercise before training. These cellular adjustments account for how a trained person performs steady-rate exercise at a greater percentage of $\dot{V} O_{2 \max }$.


Figure 21.15 Generalized summary of increase in aerobic capacity and muscle adaptations with endurance training. (Modified from Saltin B, et al. Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners. Ann NY Acad Sci 1977;301:3.)

## FACTORS THAT AFFECT AEROBIC TRAINING RESPONSES

Four factors influence the aerobic training response:

1. Initial level of aerobic fitness
2. Training intensity
3. Training frequency
4. Training duration

## Initial Level of Aerobic Fitness

The magnitude of the training response depends on initial fitness level. Someone who rates low at the start has considerable room for improvement. If capacity already rates high, the magnitude of improvement remains relatively small. Studies of sedentary, middle-aged men with heart disease showed that $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ improved by $50 \%$, while similar training in normally active, healthy adults improved 10 to $15 \%$. ${ }^{168}$ Of course, a relatively small improvement in aerobic capacity represents as crucial a change for an elite athlete (where even a 1 to $2 \%$ performance change could be the difference between winning and losing) as a much larger increase in physiologic and performance capacity for a sedentary person. As a general guideline, aerobic fitness improvements with endurance training range between 5 and $25 \%$. Some of this improvement occurs within the first week of training.

## INTEGRATIVE QUESTION

Respond to the question, How long must I exercise to get in shape?

## Training Intensity

Training-induced physiologic adaptations depend primarily on intensity of overload. At least seven different ways express exercise intensity:

1. Energy expended per unit time (e.g., $9 \mathrm{kCal} \cdot \min ^{-1}$, or $37.8 \mathrm{~kJ} \cdot \mathrm{~min}^{-1}$ )
2. Absolute exercise level or power output (e.g., cycle at $900 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$, or 147 W )
3. Relative metabolic level expressed as percentage of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ (e.g., $85 \% \dot{\mathrm{~V}}_{2 \text { max }}$ )
4. Exercise below, at, or above the lactate threshold, or OBLA (e.g., 4 mM lactate)
5. Exercise heart rate, or percentage of maximum heart rate (e.g., $180 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, or $80 \% \mathrm{HR}_{\max }$ )
6. Multiples of resting metabolic rate (e.g., 6 METs)
7. Rating of perceived exertion (e.g., $\mathrm{RPE}=14$ )

An example of absolute training intensity involves having all individuals exercise at the same power output, or energy expenditure (e.g., $9.0 \mathrm{kCal} \cdot \min ^{-1}$ ) for 30 minutes. When everyone performs at the same intensity, the task can elicit considerable stress for one person yet fall short of training threshold for another more fit person. For this reason, the relative stress on a person s physiologic systems establishes exercise intensity. The assigned exercise intensity usually relates to some breakpoint for steady-rate exercise (e.g., lactate threshold, OBLA) or some percentage of maximum physiologic capacity (e.g., $\% \dot{\mathrm{~V}} \mathrm{O}_{2 \max }, \% \mathrm{HR}_{\max }$ ), or maximum exercise capacity. General practice establishes aerobic training intensity via direct measurement (or estimation) of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ (or $\mathrm{HR}_{\text {max }}$ ) and then assigns an exercise level to correspond to some percentage of maximum.

| TABLE 21.7 | Relationship Between <br> Percentage Maximal Heart <br> Rate and Percentage VO $_{2 \text { max }}$ |
| :---: | :---: |
| Percentage $\mathbf{H R}_{\text {max }}$ | Percentage $\mathbf{V O}_{\text {2 max }}$ |$|$| 50 | 40 |
| :---: | :---: |
| 60 | 58 |
| 70 | 70 |
| 80 | 83 |
| 90 | 100 |
| 100 |  |

Establishing training intensity from measures of oxygen consumption provides a high degree of accuracy, but its use requires sophisticated monitoring that renders this method impractical for general use. An effective alternative relies on heart rate to classify exercise for relative intensity when individualizing training programs. Exercise heart rate is convenient because $\% \dot{\mathrm{VO}}_{2_{\text {max }}}$ and $\% \mathrm{HR}_{\text {max }}$ relate in a predictable way regardless of gender, race, fitness level, exercise mode, or age. Exercise training does not affect a particular individual s heart rate at a given $\% \dot{\mathrm{VO}}_{2_{\text {max }}}$, so there is little or no need to frequently test or adjust the exercise prescription relative to training-induced changes in aerobic capacity as long as exercise at the $\% \mathrm{HR}_{\text {max }}$ is maintained. ${ }^{192}$

Table 21.7 presents selected values for $\% \mathrm{~V}_{2 \text { max }}$ and corresponding $\% \mathrm{HR}_{\text {max }}$ obtained from several sources. ${ }^{4,127}$ The error in estimating $\% \mathrm{~V}_{2 \text { max }}$ from $\% \mathrm{HR}_{\text {max }}$, or vice versa, equals about $8 \%$. Thus, one need only monitor heart rate to estimate the relative exercise stress, or $\% \mathrm{~V}_{2 \text { max }}$, within the given error range. The relationship between $\% \mathrm{HR}_{\text {max }}$ and $\% \mathrm{~V}_{2 \text { max }}$ remains essentially the same for arm or leg exercises among healthy subjects, normal-weight and obese persons, cardiac patients, and persons with spinal cord injuries. ${ }^{48,83,132}$ Importantly, arm (upper-body) exercise produces lower $H R_{\text {max }}$ than leg exercises. One must consider this difference when formulating an individualized exercise prescription for different exercise modes (see p. 473).

## Train at a Percentage of $H R_{\text {max }}$

Aerobic capacity improves if exercise intensity regularly maintains heart rate between 55 and $70 \%$ of maximum. During lower-body exercise such as cycling, walking, or running, this heart rate increase equals about 40 to $55 \%$ of the $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$; for college-aged men and women, the training heart rate ranges from 120 to $140 \mathrm{~b} \cdot \mathrm{~min}^{-1}$.

An alternative and equally effective method to establish the training threshold, termed the Karvonen method, requires that subjects exercise at a heart rate equal to $60 \%$ of the difference between resting and maximum. ${ }^{94}$ With the Karvonen method, one computes training heart rate as follows:

$$
\mathrm{HR}_{\text {threshold }}=\mathrm{HR}_{\text {rest }}+0.60\left(\mathrm{HR}_{\max }-\mathrm{HR}_{\text {rest }}\right)
$$

This approach to determining heart rate training threshold creates a somewhat higher value than computing the threshold heart rate as $70 \%$ of $\mathrm{HR}_{\text {max }}$.

Clearly, achieving positive training adaptations does not require strenuous exercise. For most healthy persons, an exercise heart rate of $70 \%$ maximum represents moderate exercise with no discomfort. This training level, frequently referred to as moderate conversational exercise, achieves sufficient intensity to stimulate a training effect yet does not produce a level of discomfort (e.g., lactate accumulation and associated hyperpnea) that prevents talking during the workout. A previously sedentary person need not exercise above this threshold heart rate to improve physiologic capacity.

Figure 21.16 shows that as aerobic fitness improves, submaximal exercise heart rate decreases 10 to $20 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ for a given level oxygen consumption. To keep pace with physiologic improvement, the exercise level must increase periodically to achieve the desired exercise heart rate. A person begins training by walking, then walks more briskly; jogging then replaces walking for periods of the workout; and eventually continuous running elicits the desired exercise heart rate. In each progression, exercise remains at the same relative intensity. If exercise intensity progression does not adjust to training improvements, the exercise program essentially becomes a lowerintensity maintenance program for aerobic fitness.

## Is Strenuous Training More Effective?

Generally, the higher the training intensity above threshold, the greater the training improvement for $\dot{\mathrm{V}}_{2 \text { max }}$, particularly when the volume of exercise is controlled. ${ }^{63}$ Although minimal threshold intensity exists below which no meaningful training effect occurs, a ceiling may also exist above which no further gains accrue. More fit men and women generally require higher threshold levels to stimulate a training response than less fit persons. The ceiling for training intensity remains unknown, although about $85 \% \dot{\mathrm{~V}} \mathrm{O}_{2 \max }$ (corresponding to $90 \%$ $\mathrm{HR}_{\text {max }}$ ) probably represents an upper limit. Importantly, regardless of the exercise level selected, more does not necessarily produce greater (or faster) results. Excessive training intensity and abrupt increases in training volume increase risk for injury to bones, joints, and muscles. ${ }^{3,90}$ For men and women, the number of miles run per week represents the only variable consistently associated with running injuries. In preadolescent children, running excessive distances strains the articular cartilage, which could injure the bone s growth plate (epiphysis) and adversely affect normal growth and development.

## Determining the Training-Sensitive Zone

One can determine maximum exercise heart rate immediately after several minutes of all-out exercise. This exercise intensity requires considerable motivation and stress-a requirement inadvisable for adults without medical clearance, particularly those predisposed to coronary heart disease. Most individuals should use age-predicted maximum heart rates presented in Figure 21.17 because these tables are based on averages in population studies.


Figure 21.16 Improvement in exercise heart rate response with aerobic training in relation to oxygen consumption. A reduction in exercise heart rate with training usually reflects enhanced stroke volume.


Figure 21.17 Maximal heart rates and training-sensitive zone for aerobic training of men and women of different ages.

While individuals of a given age have varying $\mathrm{HR}_{\text {max }}$ values, the inaccuracy from individual variation ( $\pm 10 \mathrm{~b} \cdot$ $\min ^{-1}$ standard deviation for any age-predicted $\mathrm{HR}_{\max }$ ) has little influence in establishing effective training for healthy persons. Maximum heart rate has commonly been estimated as 220 minus age in years, with values independent of race or gender in children and adults. ${ }^{87,114,115}$

$$
\mathrm{HR}_{\max }=220-\operatorname{age}(\mathrm{y})
$$

Perhaps a Modification Is Required. Recent evidence from a longitudinal study of 132 persons measured an average of 7 times over 9 years indicates a bias in the above prediction of $\mathrm{HR}_{\text {max }}$. The bias overestimates this measure in men and women under the age of 40 years and it underestimates in those older than 40 years (Fig. 21.18). ${ }^{55}$ This prediction equation (with a standard deviation of 5 to 8 beats per minute), independent of sex, BMI, and resting heart rate is as follows:

$$
\mathrm{HR}_{\max }=206.9-0.67 \times \text { age }(\mathrm{y})
$$

For example, the above equation can estimate maximum heart rate for a 30-year-old man or woman:

$$
\begin{aligned}
\mathrm{HR}_{\max } & =206.9-(0.67 \times 30) \\
& =206.9-20.1 \\
& =187 \mathrm{~b} \cdot \mathrm{~min}^{-1}
\end{aligned}
$$

This prediction agrees closely with other research in the area. ${ }^{114,202}$ Chapter 32 continues the discussion of the affects of age on maximum heart rate.

These prediction formulas associate with a plus/minus error and should be used with caution. Each formula represents
a convenient rule of thumb, but it does not determine a specific person $s$ maximum heart rate. For example, within normal variation limits and using the 220-minus-age formula, the actual maximum heart rate of $95 \%( \pm 2$ standard deviations) of 40 -year-old men and women ranges between 160 and $200 \mathrm{~b} \cdot \mathrm{~min}^{-1}$. Figure 21.17 also depicts the training-sensitive zone related to age.

A 40-year-old woman or man who wants to train at moderate intensity but still achieve the threshold level would select a training heart rate equal to $70 \%$ of age-predicted $\mathrm{HR}_{\text {max }}$. Using the 220 -minus-age formula results in a target exercise heart rate of $126 \mathrm{~b} \cdot \mathrm{~min}^{-1}(0.70 \times 180)$. To increase training to $85 \%$ of maximum, exercise intensity must increase to produce a heart rate of $153 \mathrm{~b} \cdot \min ^{-1}(0.85 \times 180)$.

## Running Versus Swimming and Other Forms of

 Upper-Body Exercise. Estimation of $\mathrm{HR}_{\max }$ requires an adjustment when swimming or performing other upper-body exercises. Maximum heart rate during these exercise modes averages about $13 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ lower for trained and untrained men and women than while running. ${ }^{48,57,129}$ This difference probably results from less feed-forward stimulation from the motor cortex to the medulla during swimming, in addition to less feedback stimulation from the smaller, active upper-body muscle mass. In swimming, the horizontal body position and cooling effect of the water may also contribute to a lower $\mathrm{HR}_{\text {max }}$.Establishing the appropriate exercise intensity for swimming and upper-body exercise requires subtracting 13 b $\min ^{-1}$ from the age-predicted $\mathrm{HR}_{\max }$ in Figure 21.17. A 30 -year-old person who chooses to swim at $70 \% \mathrm{HR}_{\max }$ should select a swimming speed that produces a heart rate of


- 220 - Age
$\square 206.9-0.67 \times$ Age

Figure 21.18
Modified maximum heart rate versus age prediction compared with the commonly used equation of 220 age. (From Gellish RL, et al. Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc 2007;39:822.)
$124 \mathrm{~b} \cdot \min ^{-1}(0.70 \times[190-13])$. This would more accurately represent the proper threshold heart rate for swimming to induce a training effect. Without this heart rate adjustment, a prescription of upper-body exercise based on $\% \mathrm{HR}_{\text {max }}$ in leg exercise overestimates the appropriate threshold training heart rate.

## Is Less Intense Training Effective?

The often-cited recommendation of $70 \% \mathrm{HR}_{\text {max }}$ as a training threshold for aerobic improvement represents a general guideline for effective yet comfortable exercise. The lower limit may depend on the participants initial exercise capacity and current state of training. In addition, older and less fit, as well as sedentary, overweight men and women have training thresholds closer to $60 \% \mathrm{HR}_{\max }$ (about $45 \% \dot{\mathrm{~V}}_{2 \max }$. Twenty to 30 minutes of continuous exercise at $70 \% \mathrm{HR}_{\max }$ stimulates a training effect; exercise at the lower intensity of $60 \% \mathrm{HR}_{\text {max }}$ for 45 minutes also proves beneficial. Generally, longer exercise duration offsets lower exercise intensity in terms of benefits.

## Train at a Perception of Effort

The rating of perceived exertion (RPE) can be used in addition to oxygen consumption, heart rate, and blood lactate to indicate exercise intensity. ${ }^{15,173}$ With this psychophysiologic approach, the exerciser rates on a numerical scale perceived feelings relative to exertion level. Monitoring and adjusting RPE during exercise provides an effective way to prescribe exercise from an individuals perception of effort that coincides with objective measures of physiologic/metabolic strain ( $\% \mathrm{HR}_{\text {max }}, \% \mathrm{VO}_{2 \text { max }}$, blood lactate concentration).

Exercise that corresponds to higher levels of energy expenditure and physiologic strain produces higher RPE ratings. For example, an RPE of 13 or 14 (exercise that feels somewhat hard; Fig. 21.19) coincides with about $70 \% \mathrm{HR}_{\max }$ during cycle ergometer and treadmill exercise; an RPE between 11 and 12 corresponds to exercise at the lactate threshold for trained and untrained individuals. The RPE establishes an exercise prescription for exercise intensities that correspond to blood lactate concentrations of 2.5 mM ( $\mathrm{RPE} \sim 15$ ) and $4.0 \mathrm{mM}(\mathrm{RPE} \sim 18)$ during a 30-minute treadmill run where subjects self-regulated exercise intensity. ${ }^{200}$ Individuals learn quickly to exercise at a specific RPE. In similar fashion, a simple talk test that asks whether comfortable speech is possible produces exercise intensities within accepted guidelines for exercise prescription for treadmill and cycle ergometer exercise. ${ }^{153}$

## Train at the Lactate Threshold

Exercising at or slightly above the lactate threshold provides yet another effective aerobic training method. The higher exercise levels produce the greatest benefits, particularly for fit individuals. ${ }^{113,220}$ Figure 21.20 illustrates how to


Figure 21.19 The Borg scale (and accompanying estimates of relative exercise intensity) for obtaining the RPE during exercise. (Modified from Borg GA. Psychological basis of physical exertion. Med Sci Sports Exerc 1982;14:377.)
determine the appropriate activity level by plotting intensity (e.g., running speed) in relation to blood lactate level. In this example, the running speed to produce a blood lactate concentration at the $4-\mathrm{mM}$ level (OBLA) represented the recommended training intensity. Many coaches use the $4-\mathrm{mM}$ blood lactate level as the optimal aerobic training intensity, yet no convincing evidence exists to justify this particular blood lactate


Figure 21.20 Blood lactate concentration in relation to running speed for one subject. At a lactate level of 4.0 mM , the corresponding running speed was approximately $13 \mathrm{~km} \cdot \mathrm{~h}^{-1}$. This speed establishes the subjects initial training intensity.
level as ideal. Regardless of the specific blood lactate level chosen for endurance training, the blood lactate exercise intensity relationship should be evaluated periodically, with exercise intensity adjusted as fitness improves. If regular blood lactate measurement proves impractical, the exercise heart rate at the initial lactate determination remains a convenient and relatively stable marker to set an appropriate predetermined exercise intensity. During incremental exercise, no systematic training-induced change occurs in the heart rate blood lactate relationship. ${ }^{46}$

The RPE provides an effective tool to estimate blood lactate threshold when establishing training intensity for continuous exercise. However, a change in the blood lactate concentration RPE relationship does occur with repeated exercise bouts. The relationship remains altered from a single exercise bout, even after 3.5 hours of recovery. ${ }^{221}$ This limits RPE to gauge exercise intensity for a specific blood lactate concentration if repeated bouts of exercise occur during the same training session (e.g., during interval training; see p. 480).

One important distinction between $\% \mathrm{HR}_{\text {max }}$ and lactate threshold for setting training intensity lies in the physiologic dynamics each method reflects. The $\% \mathrm{HR}_{\text {max }}$ method establishes a level of exercise stress to overload the central circulation (e.g., stroke volume, cardiac output), whereas the capability of the peripheral vasculature and active muscles to sustain steady-rate aerobic metabolism dictates exercise intensity adjustments based on lactate threshold.

## Training Duration

No threshold duration per workout exists for optimal aerobic improvement. If a threshold exists, it likely depends on the interaction of total work accomplished (duration or training volume), exercise intensity, training frequency, and initial fitness level. For previously sedentary adults, a dose response relationship may exist. ${ }^{25}$ A 3- to 5 -minute daily exercise period produces some improvements in poorly conditioned people, but 20- to 30 -minute sessions achieve more optimal results if intensity achieves at least the minimum threshold.

As for training volume, more time devoted to workouts does not necessarily translate to greater improvements, particularly among active individuals. For collegiate swimmers, one group trained for 1.5 hours daily while another group performed two 1.5 -hour exercise sessions each day. ${ }^{33}$ Even when one group exercised at twice the daily volume, no differences in swimming power, endurance, or performance time improvements emerged between groups.

## Training Frequency

Do 2- and 5-day-a-week training produce different effects if exercise duration and intensity remain constant for each training session? Unfortunately, the precise answer remains elusive. Some investigators report training frequency influences cardiovascular improvements, while others maintain this factor contributes considerably less than either exercise intensity
or duration. ${ }^{159}$ Studies using interval training show that training 2 days a week produced $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ changes similar to training 5 days weekly. ${ }^{47}$ In other studies that maintained a constant total exercise volume, no differences emerged in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ improvement between training frequencies of 2 and 4 or 3 and 5 days a week. ${ }^{191}$ As with training duration, morefrequent training produces beneficial effects when training occurs at a lower intensity.

While the extra time invested to increase training frequency may not prove profitable for improving $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, the extra quantity of exercise (e.g., 3 vs. 6 days per week) often represents a considerable caloric expenditure with concomitant improvements in well-being and health. To produce meaningful weight loss through exercise, each exercise session should last at least 60 minutes at sufficient intensity to expend 300 kCal or more. Training only 1 day a week generally does not meaningfully change anaerobic or aerobic capacity, body composition, or body weight. ${ }^{5}$

Typical aerobic training programs take place 3 days a week, usually with a single rest day separating workout days. One could reasonably ask whether training on consecutive days would produce equally effective results. In an experiment concerned with this question, nearly identical improvements in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ occurred regardless of sequencing of the 3-days-per-week training schedule. ${ }^{136}$ Thus, the stimulus for aerobic training probably links closely to exercise intensity and total work accomplished, not to the sequencing of training days.

## Exercise Mode

Maintaining constancy for exercise intensity, duration, and frequency produces a similar training response independent of training mode-provided exercise involves relatively large muscle groups. Bicycling, walking, running, rowing, swimming, in-line skating, rope skipping, bench-stepping, stair climbing, and simulated arm leg climbing all provide excellent overload for the aerobic system. ${ }^{20,121,216}$ Based on the specificity concept, the magnitude of training improvement varies considerably depending on training and testing mode. Individuals trained on a bicycle show greater improvement when tested on a bicycle than on a treadmill. ${ }^{150}$ Likewise, individuals who train by swimming or arm cranking show the greatest improvement when measured during upper-body exercise. ${ }^{57}$

## AMERICAN COLLEGE OF SPORTS MEDICINE AND AMERICAN HEART ASSOCIATION UPDATED FITNESS GUIDELINES AND RECOMMENDATIONS

The American College of Sports Medicine (ACSM) and American Heart Association (AHA) have jointly published guidelines for a well-rounded training program for adults aged 18 to 65 years to update and clarify previous recommendations on the types and amounts of physical activity needed by

## TABLE 21.8 Physical Activity Recommendations by the American College of Sports Medicine and the American Heart Association for Healthy Adults Aged 18 to 65 Years

1. To promote and maintain good health, adults aged 18 to 65 yr should maintain a physically active lifestyle.
2. They should perform moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic activity for a minimum of 20 min on 3 days each week.
3. Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation. For example, a person can meet the recommendation by walking briskly for 30 min twice during the week and then jogging for 20 min on 2 other days.
4. These moderate- or vigorous-intensity activities are in addition to the light-intensity activities frequently performed during daily life (e.g., self-care, washing dishes, using light tools at a desk) or activities of very short duration (e.g., taking out trash, walking to parking lot at store or office).
5. Moderate-intensity aerobic activity, which is generally equivalent to a brisk walk and noticeably accelerates the heart rate, can be accumulated toward the $30-\mathrm{min}$ minimum by performing bouts each lasting 10 or more minutes.
6. Vigorous-intensity activity is exemplified by jogging and causes rapid breathing and a substantial increase in heart rate.
7. In addition, at least twice each week adults will benefit by performing activities using the major muscles of the body that maintain or increase muscular strength and endurance.
8. Because of the dose-response relation between physical activity and health, persons who wish to further improve their personal fitness, reduce their risk for chronic diseases and disabilities, or prevent unhealthy weight gain will likely benefit by exceeding the minimum recommended amount of physical activity.

From Haskell WL, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423.
health adults to improve and maintain health (Table 21.8). ${ }^{6,73}$ For example, a combined program of aerobic training and resistance training increases muscular strength and aerobic power, decreases body fat, and increases basal metabolic rate. In contrast, singular-focus programs of either resistance only or aerobic training only produce singularly larger but more limited overall effects. ${ }^{40,160}$ For older adults (Table 21.9), emphasis is also placed on exercises to increase joint flexibility and improve balance so as to reduce the risk of injury from slips and falls. ${ }^{143}$

INTEGRATIVE QUESTION
Explain what factors account for differences in responsiveness of individuals to the same exercise-training program.

## HOW LONG BEFORE IMPROVEMENTS OCCUR?

Improvements in aerobic fitness occur within several weeks. Figure 21.21 shows absolute and percentage improvements in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ for subjects who trained 6 days a week for 10 weeks. Training consisted of stationary cycling for 30 minutes 3 days a week combined with running for up to 40 minutes on alternate days. The continuous week-to-week improvement in aerobic capacity indicates that training improvement in previously sedentary persons occurs rapidly and steadily. Adaptive responses eventually level off as subjects approach their genetically predisposed maximums. The exact time for this leveling off remains unknown, particularly for highintensity training. The data presented in Figure 21.15 indicate
that each physiologic and metabolic system responds in a unique and different way.

The data in Table 21.10 complement those in Figure 21.21; they reveal the rapidity of maximum cardiovascular adaptations to aerobic exercise training. Five young adult men and five women trained daily for 10 consecutive days. Exercise consisted of 1 hour of cycling- 10 minutes at $65 \% \mathrm{~V}_{\text {2peak }}$, 25 minutes at $75 \% \quad \mathrm{VO}_{2 \text { peak }}$ and the last 25 minutes of repeat five 3-minute intervals at $95 \% \dot{\mathrm{~V}}_{2 \text { peak }}$ followed by a 2-minute recovery. This relatively brief 10-day training period induced a $10 \%$ increase in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { peak }}$ and a $12 \%$ increase in cardiac output, $15 \%$ increase in stroke volume, and a slight decrease in peak exercise heart rate. Resting plasma volume increased nearly $9 \%$ during the 10 days of training and correlated with the increases in exercise cardiac output and stroke volume. This means that cardiovascular adaptations occur with short-term exercise training in young men and women. The stroke volume increases during exercise reflect the combined effects of increased left ventricular end-diastolic dimension (preload in accordance with the Frank-Starling mechanism) and increased systolic ejection.

## Trainability and Genes

A strenuous exercise program enhances a person s level of fitness regardless of genetic background. However, the limits for developing fitness capacity appear to link closely to natural endowment. Of two individuals in the same exercise program, one might show 10 times more improvement than the other. A genotype dependency exists for much of one s sensitivity in responding to maximal aerobic and anaerobic power training, including adaptations of most muscle enzymes. ${ }^{17,39,67}$ Stated differently, identical twins in a pair

TABLE 21.9 Physical Activity Recommendations by the American College of Sports Medicine and the American Heart Association for Older Adults ( $>65$ years)

1. To promote and maintain good health, older adults should maintain a physically active lifestyle.
2. They should perform moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic activity for a minimum of 20 min on 3 days each week. Moderate-intensity aerobic activity involves a moderate level of effort relative to an individual s aerobic fitness. On a 10 -point scale, where sitting is 0 and all-out effort is 10, moderate-intensity activity is a 5 or 6 and produces noticeable increases in heart rate and breathing. On the same scale, vigorousintensity activity is a 7 or 8 and produces large increases in heart rate and breathing. For example, given the heterogeneity of fitness levels in older adults, for some older adults a moderate-intensity walk is a slow walk, and for others it is a brisk walk.
3. Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation. These moderate- or vigorous-intensity activities are in addition to the light-intensity activities frequently performed during daily life (e.g., self-care, washing dishes) or moderate-intensity activities lasting 10 min or less (e.g., taking out trash, walking to parking lot at store or office).
4. In addition, at least twice each week older adults should perform muscle strengthening activities using the major muscles of the body that maintain or increase muscular strength and endurance. It is recommended that 8 to 10 exercises be performed on at least two nonconsecutive days per week using the major muscle groups. To maximize strength development, a resistance (weight) should be used that allows 10 to 15 repetitions for each exercise. The level of effort for muscle-strengthening activities should be moderate to high.
5. Because of the dose response relationship between physical activities and health, older persons who wish to further improve their personal fitness, reduce their risk for chronic diseases and disabilities, or prevent unhealthy weight gain will likely benefit by exceeding the minimum recommended amount of physical activity.
6. To maintain the flexibility necessary for regular physical activity and daily life, older adults should perform activities that maintain or increase flexibility on at least 2 days each week for at least 10 min each day.
7. To reduce risk of injury from falls, community-dwelling older adults with substantial risk of falls should perform exercises that maintain or improve balance.
8. Older adults with one or more medical conditions for which physical activity is therapeutic should perform physical activity in a manner that effectives and safely treats the condition(s).
9. Older adults should have a plan for obtaining sufficient physical activity that addresses each recommended type of activity. Those with chronic conditions for which activity is therapeutic should have a single plan that integrates prevention and treatment. For older adults who are not active at recommended levels, plans should include a gradual (or stepwise) approach to increase physical activity over time. Many months of activity at less-than-recommended levels is appropriate for some older adults (e.g., those with low fitness) as they increase activity in a stepwise manner. Older adults should also be encouraged to self-monitor their physical activity on a regular basis and to reevaluate plans as their abilities improve or as their health status changes.

From Nelson ME et al. Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2006;39:1435.

| TABLE 21.10 $\begin{array}{ll}\text { Max } \\ & \text { Erg } \\ & \text { Da }\end{array}$ | logic Resp ises Before Training | Peak Cycle Consecutive |
| :---: | :---: | :---: |
| Variable | Pretraining | Posttraining |
| $\dot{\mathrm{V}} \mathrm{O}_{2 \text { peak }}, \mathrm{L} \cdot \mathrm{min}^{-1}$ | $2.54 \pm 0.29$ | $2.80 \pm 0.32^{a}$ |
| Cardiac output, $\mathrm{L} \cdot \mathrm{min}^{-1}$ | $18.3 \pm 1.3$ | $20.5 \pm 1.7^{a}$ |
| Heart rate, b $\cdot \mathrm{min}^{-1}$ | $189 \pm 2$ | $184 \pm 2^{a}$ |
| Stroke volume, mL | $97 \pm 7$ | $112 \pm 9^{a}$ |
| $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff, $\mathrm{mL} \cdot \mathrm{dL}^{-1}$ | $13.6 \pm 0.8$ | $13.4 \pm 0.6$ |
| Plasma volume (rest), mL | $2896 \pm 175$ | $3152 \pm 220^{a}$ |
| From Mier CM, et al. Cardiovascular adaptations to 10 days of cycle exercise. J Appl Physiol 1997; 83:1900. ${ }^{a}$ Statistically significant at the .05 level from pretraining value. |  |  |

generally show a training response of similar magnitude. Figure 21.22 ( A and B ) indicates a clear similarity in the response of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ (both $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ and $\%$ improvement) among 10 pairs of male identical twins who participated in the same 20 -week aerobic exercise training program. If one twin showed high responsiveness to training, a high likelihood
existed that the other twin would also be a responder; similarly, the brother of a nonresponder to exercise training generally showed little improvement. Presence of the muscle-specific creatine kinase gene provides one example of the possible contribution of genetic makeup to individual differences in responsiveness of $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ to endurance training. ${ }^{171,172}$


Figure 21.21 Continuous improvements in $\mathrm{VO}_{2 \text { max }}$ during 10 weeks of high-intensity aerobic training. (From Hickson RC, et al. Linear increases in aerobic power induced by a program of endurance exercise. J Appl Physiol 1977;42:373.)

## MAINTENANCE OF AEROBIC FITNESS GAINS

An important question concerns optimal exercise frequency, duration, and intensity to maintain aerobic improvements with training. In one study, healthy young adults increased $\dot{\mathrm{V}}{ }_{2 \text { max }} 25 \%$ with 10 weeks of interval training by bicycling and running for 40 minutes, 6 days a week. ${ }^{78}$ They then joined one of two groups that continued to exercise an additional 15 weeks at the same intensity and duration but at reduced frequency to either 4 or 2 days a week. Both groups maintained their gains in aerobic capacity despite up to two-thirds reduction in training frequency.

A similar study evaluated reduced training duration on maintenance of improved aerobic fitness. ${ }^{79}$ Upon completion of the same protocol outlined previously for the initial 10 weeks of training, subjects continued to maintain intensity and frequency of training for an additional 15 weeks, but at reduced training duration from the original 40 -minute sessions to either 26 or 13 minutes per day. They maintained almost all $\dot{\mathrm{V}}{ }_{2 \text { max }}$ and performance increases despite a twothirds reduction in training duration. Importantly, if training intensity decreased and frequency and duration remained constant, even a one-third reduction in exercise intensity reduced the $\dot{\mathrm{V}}_{2 \text { max }} \cdot{ }^{80}$

Aerobic capacity improvement involves somewhat different training requirements than its maintenance. With intensity held constant, the frequency and duration of exercise required to maintain a certain level of aerobic fitness remain considerably lower than that required to induce improvement. In contrast, a small decline in exercise intensity reduces $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$. This indicates that exercise intensity plays a principal role in maintaining the increase in aerobic capacity achieved through training.


Figure 21.22 Responsiveness of $\mathrm{VO}_{2 \max }\left(\mathrm{~A}, \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1} ; \mathbf{B}, \%\right.$ improvement) of 10 pairs of identical twins to a 20 -week program of aerobic exercise training. $r$, Pearson product-moment correlation coefficient. Each of the 10 colored data points represents a twin pair. (From Bouchard C. Heredity, fitness, and health. In: Bouchard C, et al., eds. Physical activity, fitness, and health, Champaign, IL: Human Kinetics, 1990.)

## Components Other Than $\stackrel{\vee}{V}_{2 \text { max }}$

Fitness components other than $\dot{\mathrm{V}}{ }_{2 \text { max }}$ more readily suffer adverse effects of reduced exercise training volume. Welltrained endurance athletes who normally trained 6 to 10 hours weekly reduced weekly training to one 35 -minute session over a 4-week period. ${ }^{125} \dot{\mathrm{~V}}_{2 \text { max }}$ remained constant during this period of reduced training volume. However, endurance capacity at $75 \% \dot{\mathrm{VO}}_{2 \text { max }}$ decreased; this performance decrement related to reduced preexercise glycogen stores and a diminished level of fat oxidation during exercise. A single measure such as $\dot{V} O_{2 \max }$ cannot adequately evaluate all of the factors that affect exercise training and detraining adaptations.

## Tapering for Peak Performance

Little improvement occurs in the aerobic systems during the competitive season. At best, athletes strive to prevent physiologic and performance deterioration as the season progresses. Before major competition, athletes often taper training intensity and/or volume, believing such adjustments reduce physiologic and psychologic stress of daily training and optimize exercise performance. The taper period and exact alterations in training vary by sport. A 1 - to 3 -week taper exponentially reduces training volume by 40 to $60 \%$, while maintaining training intensity provides the most efficient strategy to maximize performance gains. ${ }^{16,209}$

From a physiologic perspective, a 4- to 7-day taper should provide sufficient time for maximum muscle and liver glycogen replenishment, optimal nutritional support and restoration, alleviation of residual muscle soreness, and healing of minor injuries. In one study of competitive runners, a 1 -week taper period applied either no training (rest), lowintensity running ( 2 to 10 km daily at $60 \% \dot{\mathrm{VO}}_{2 \max }$ ), or highintensity running while reducing training volume (five $500-\mathrm{m}$ repeats on day 1 , decreasing one repeat each day). ${ }^{188}$ Measurements during the taper included blood volume, red blood cell mass, muscle glycogen content, muscle mitochondrial activity, and $1500-\mathrm{m}$ race performance. Compared with rest and low-intensity exercise taper conditions, highintensity exercise taper produced the most benefit. An optimal taper therefore should include progressive reductions in training volume while maintaining training intensity at a moderate-to-high level. With proper tapering, expected performance improvement usually ranges between 0.5 and $6.0 \%$. ${ }^{141}$ Tapering does not associate with substantial changes in exerciseinduced oxidative stress. ${ }^{215}$

## TRAINING METHODS

Performance improvements occur yearly in almost all athletic competitions. These advances generally relate to increased opportunities for participation: Individuals with natural endowment have opportunities to participate in different sports. Improved nutrition and health care, better equipment, and more systematic and scientific approaches to athletic training also contribute. The following sections present general guidelines for effective anaerobic and aerobic exercise training.

## Anaerobic Training

Figure 21.1 shows that the capacity to perform all-out exercise for up to 60 seconds largely depends on ATP generated by the immediate and short-term anaerobic systems for energy transfer.

## INTEGRATIVE QUESTION

In what specific ways would anaerobic exercise training improve performance in all-out physical activity?

## The Intramuscular High-Energy Phosphates

American football, weightlifting, and other brief sprint power sport activities rely almost exclusively on energy derived from the intramuscular high-energy phosphates ATP and PCr. Engaging specific muscles in repeated 5- to 10 -second maximum bursts of effort overloads energy transfer from this phosphagen pool. Consequently, only small amounts of lactate accumulate and recovery progresses rapidly. Exercise can begin again after a 30 -second rest period. The use of brief, all-out exercise bursts interspersed with recovery represents a highly specific application of interval training to anaerobic conditioning (see p. 480).

Physical activities to enhance ATP PCr energy transfer capacity must engage the sport-specific muscles at the movement speed and power output similar to performance of the sport itself. This strategy enhances metabolic capacity of specifically trained muscle fibers; it also facilitates recruitment and modulation of the neural firing sequence of appropriate motor units activated in the particular movement.

## Lactate-Generating Capacity

To improve energy transfer capacity by the short-term lactic acid energy system, training must overload this aspect of energy metabolism.

Training of the glycolytic short-term energy system demands extreme physiologic and psychologic effort. Blood lactate rises to near-peak levels with a 1 -minute maximum bout of exercise. The individual repeats the exercise bout after 3 to 5 minutes of recovery. Repetition of exercise causes lactate stacking, which produces a higher blood lactate level than just one all-out exhaustive effort. As with all training, one must exercise the specific muscle groups that require enhanced anaerobic function. A backstroke swimmer trains by swimming the backstroke (or use of an appropriate swimbench ergometer); a cyclist should bicycle; and basketball, hockey, or soccer players rapidly perform various movements and direction changes similar to the sport requirement.

As discussed in Chapter 7, recovery requires considerable time when exercise involves a large anaerobic component. For this reason, anaerobic power training of the short-term energy system should occur at the end of the conditioning session so fatigue does not hinder ability to perform subsequent aerobic training.

## Aerobic Training

Figure 21.23 indicates two important factors in formulating aerobic training:

1. Cardiovascular overload must be intense enough to sufficiently increase (overload) stroke volume and cardiac output.
2. Cardiovascular overload must occur from activation of sport-specific muscle groups to enhance local circulation and the muscle $s$ metabolic machinery.

In essence, proper endurance training overloads all components of oxygen transport and use. This consideration embodies the specificity principle of aerobic training. Simply stated, runners must run, cyclists must bicycle, rowers must row, and swimmers must swim.


Figure 21.23 The two major goals of aerobic training: Goal 1 , develop the capacity of the central circulation to deliver oxygen; Goal 2, enhance the capacity of the active musculature to supply and process oxygen.

Relatively brief bouts of repeated exercise, as well as continuous, long-duration efforts, enhance aerobic capacity, provided exercise reaches sufficient intensity to overload the aerobic system. Interval training, continuous training, and fartlek training represent three common methods to improve aerobic fitness.

## INTEGRATIVE QUESTION

What information would you need to effectively improve aerobic capacity for the specific physical job performance requirements for (1) firefighters, (2) police officers, and (3) oil field workers?

## Interval Training

With correct spacing of exercise and rest intervals, one can perform extraordinary amounts of intense physical activity, not normally possible if activity progressed continuously. Repeated exercise bouts (with brief rest periods or lowintensity exercise relief intervals) vary from a few seconds to several minutes or longer depending on the desired training outcome. ${ }^{76,103,105}$ As little as six sessions of brief near all-out effort interval training over a 2 -week period increases skeletal muscle oxidative capacity and endurance performance. ${ }^{58}$ The interval training prescription evolves from the following four considerations:

1. Intensity of exercise interval
2. Duration of exercise interval
3. Length of recovery (relief) interval
4. Number of repetitions of the exercise relief interval

Consider the following example of performing a large volume of intense exercise during an interval-training workout. Few people can maintain a 4-minute-mile pace for longer than 1 minute, let alone complete a mile in 4 minutes. Suppose running intervals were limited to only 10 seconds followed by a 30 -second recovery. This scenario makes it reasonably easy to maintain the exercise relief intervals and complete the mile in 4 minutes of actual running. This does not parallel a world-class performance but illustrates that a person can accomplish a considerable quantity of normally exhausting exercise given proper spacing of rest and exercise intervals. This strategy of intense training interspersed with rest intervals would apply to treadmill, stair climbing, and bicycle ergometer exercise routines performed in health clubs and training centers.

Rationale for Interval Training. Interval training has a sound basis in physiology and energy metabolism. In the example of a continuous 4-minute-mile run, anaerobic glycolysis generates a large portion of the energy requirement. Within a minute or two, the lactate level rises precipitously and the runner fatigues. For interval training, repeated 10 -second exercise bouts permit completion of intense exercise without

# TABLE 21.11 Guidelines for Determining Interval-Training Exercise Rates for Running and Swimming Different Distances 

Interval Training
Distances (yards)

| Run | Swim | Work Rate for Each Exercise Interval or Repeat |
| :---: | :---: | :---: |
| 55 | 15 | 1.5 feconds slower than best |
| 110 | 25 | 3.0 times from a running (or swimming) start |
| 220 | 55 | 5.0 for each distance |
| 440 | 110 | 1 to 4 seconds faster than the average 440-yard run or 110-yard swim times recorded during a mile run or 440 -yard swim |
| 6601320 | 165320 | 3 to 4 seconds slower than the average 440 -yard run or 100-yard swim times recorded during a mile run or 440-yard swim |

From Fox EL, Mathews DK. Interval training. Philadelphia: WB Saunders, 1974.
appreciable lactate buildup because intramuscular highenergy phosphates provide the primary energy source. Minimal fatigue develops during the predominantly alactic exercise interval and recovery progresses rapidly. The exercise interval can then begin following only a brief rest.

In interval training, exercise intensity must activate the particular energy systems that require improvement. TABLE 21.11 provides practical guidelines to determine the appropriate exercise and recovery intervals for running and swimming different distances. The following examples serve to illustrate:

- Exercise interval: Generally add 1.5 to 5.0 seconds to the exerciser s best time for training distances between 55 and 220 yards for running and 15 and 55 yards for swimming. ${ }^{47}$ If a person can run 60 yards from a running start in 8 seconds, the training time for each repeat equals $8+1.5$, or 9.5 seconds. For an interval-training distance of 110 yards, add 3 seconds, and for a distance of 220 yards, add 5 seconds to the best running times. This particular type of interval training applies to training the intramuscular ATP PCr energy system.
- Training distances of 440 yards running or 110 yards swimming: Determine the exercise rate by subtracting 1 to 4 seconds from the best 440 -yard part of a mile run or 110 -yard part of a 440 -yard swim. If a person runs a mile in 7 minutes (averaging 105 s per 440 yd ), the interval time for each 440 -yard repeat range is 104 seconds $(105-1)$ to 101 seconds (105-4). For training intervals beyond 440 yards, add 3 to 4 seconds for each 440-yard portion of the interval distance. In running an interval of 880 yards, the 7 -minute miler runs each interval at about 216 seconds [ $(105+3) \times 2=216]$.
- Relief interval: The relief interval is either passive (rest relief) or active (work relief). A ratio of exercise duration to recovery duration usually formulates
the duration of the relief interval. The ratio 1:3 generally applies to training the immediate energy system. Thus, for a sprinter who runs 10 -second intervals, the relief interval equals about 30 seconds $(3 \times 10 \mathrm{~s})$. For training the short-term glycolytic energy system, the relief interval averages twice the exercise interval, or a ratio of 1:2. These specific work relief ratios for anaerobic training should ensure sufficient restoration of intramuscular phosphates and/or sufficient lactate removal so the next exercise bout can continue with minimal fatigue.
- To train the long-term aerobic energy system, the exercise relief interval ratio usually is 1:1 or 1:1.5. During a 60 - to 90 -second high-intensity exercise interval, oxygen consumption increases rapidly to a high level but remains inadequate to meet exercise energy requirements. The recommended relief interval causes the succeeding exercise interval to begin before complete recovery (before return to baseline oxygen consumption). This ensures that cardiovascular and aerobic metabolic stress reach near peak levels with repeated but relatively short exercise intervals. The duration of the rest interval takes on less importance with longer periods of intermittent exercise because sufficient time exists for the body to adjust metabolic and circulatory parameters during exercise.


## INTEGRATIVE QUESTION

A coach insists that a single exercise mode improves aerobic capacity for all physical activities requiring a high level of aerobic fitness. Give your opinion regarding the potential effectiveness of single-mode exercise to produce generalized cross-training effects.


Figure 21.24 Peak power output and total power output during four successive maximum 30-second efforts (A), $\mathrm{VO}_{2 \max }$ (B), maximal enzyme activity for phosphofructokinase (PFK) and hexokinase (HEX) (C), and maximal enzyme activity for malate dehydrogenase (MDH), succinate dehydrogenase (SDH), and citrate synthase (CS) (D) before (yellow bars) and after (red bars) 7 weeks of sprint interval training. (From MacDougall JD, et al. Muscle performance and enzymatic adaptations to sprint interval training. J Appl Physiol 1998;84:2138.)

Sprint-Type Interval Training Affects Anaerobic and Aerobic Physiologic Systems. Figure 21.24 shows that relatively brief but intense sprint-type interval training increases parameters of both anaerobic and aerobic metabolic capacity. The 7 -week training program for 12 young adult men consisted of 30 seconds of maximum sprint effort (Wingate protocol) interspersed with 2 to 4 minutes of recovery performed three times a week. Week 1 began with four exercise intervals with 4 minutes recovery per interval and progressed to 10 exercise intervals with a 2.5 -minute recovery per exercise bout by week 7. Despite this relatively brief training stimulus in which exercise duration reached only 5 minutes per session during week 7, improvements occurred in $\dot{\mathrm{V}}{ }_{2 \text { max }}$, short-term power output, and maximal activity of key marker enzymes in the aerobic and anaerobic energy pathways. Healthy elderly persons also show positive clinical and cardiovascular adaptations to interval training. ${ }^{2}$

## Continuous Training

Continuous or long, slow, distance (LSD) training involves steady-paced, prolonged exercise at either moderate or high aerobic intensity, usually 60 to $80 \% \dot{\mathrm{~V}}_{2 \text { max }}$. The exact pace can vary, but it must minimally meet a threshold intensity to ensure aerobic physiologic adaptations. Previously, we outlined the method to establish the training-sensitive zone that uses $\mathrm{HR}_{\max }$ (pp. 471 474). Continuous training that exceeds one hour has become popular among fitness enthusiasts, including competitive endurance athletes such as triathletes and cross-country skiers. Many elite distance runners train twice daily and run 100 to 150 miles weekly to prepare for competition.

Continuous exercise training (because of its submaximal nature) progresses in relative comfort. This contrasts with the potential hazards of high-intensity interval training for
coronary-prone individuals and the high level of motivation required for such strenuous exercise. Continuous training ideally suits novices who wish to accumulate a large caloric expenditure for weight loss. When applied to athletic training, continuous training truly represents overdistance training, with most athletes training two to five times the actual distances of competitive events.

Continuous training allows endurance athletes to exercise at nearly the same intensity as actual competition. Specific motor unit recruitment depends on exercise intensity, so continuous training may best apply to endurance athletes who desire adaptations at the cellular level. In contrast, interval training often places disproportionate stress on the fasttwitch motor units, not slow-twitch units predominantly recruited in endurance competition.

## Fartlek Training

Fartlek, a Swedish word meaning speed play, represents a training method introduced to the United States in the 1940s. This relatively unscientific blending of interval and continuous training has particular application to exercise out-of-doors over natural terrain. The system uses alternate running at fast and slow speeds over level and hilly terrain.

In contrast to the precise exercise-interval training prescription, fartlek training does not require systematic manipulation of exercise and relief intervals. Instead, the performer determines the training schema based on how it feels at the time, similar to gauging exercise intensity based on one s rating of perceived exertion (RPE). When properly applied, this method overloads one or all of the energy systems. Fartlek training provides ideal general conditioning and off-season training strategies, although it lacks the systematic and quantified approaches of interval and continuous training. It also adds freedom and variety to workouts.

Insufficient evidence prevents proclaiming superiority of any specific training method to improve aerobic capacity and associated physiologic variables. ${ }^{138}$ Each form of training produces success. One can probably use the various training methods interchangeably, particularly to modify training and achieve a more psychologically pleasing exercise or training regimen.

## OVERTRAINING: TOO MUCH OF A GOOD THING

Ten to $20 \%$ of athletes experience overtraining or staleness. The overtrained condition (syndrome) represents more than just short-term inability to train hard or a slight dip in competition-level performance. Athletes can fail to endure and adapt to training so that normal exercise performance deteriorates, and they encounter increasing difficulty fully recovering from a workout. ${ }^{22,194,212}$ This takes on crucial importance for elite athletes where performance decrements of 1 to $3 \%$ can cause a gold medalist to fail to qualify for competition. Overtraining also relates to increased incidence of infections, persistent muscle soreness, and general malaise and loss of interest in sustaining high-level training. Injuries occur more frequently in the overtrained state. ${ }^{213}$

Two clinical forms of overtraining have been described:

1. The less common sympathetic form (basedowian for thyroid hyperfunction patterns), characterized by increased sympathetic activity during rest; generally typified by hyperexcitability, restlessness, and impaired exercise performance. This form of overtraining may reflect excessive psychologic/emotional stress that accompanies the interaction among training, competition, and responsibilities of normal living. ${ }^{108}$
2. The more common parasympathetic form (addisonoid for adrenal insufficiency patterns) characterized by predominance of vagal activity during rest/ and exercise. More properly termed overreaching in the early stages (within as few as 10 days), the syndrome qualitatively is similar in symptoms to the full-blown parasympathetic overtraining syndrome but of shorter duration. Excessive and protracted exercise overload with inadequate recovery and rest leads to overreaching. Initially, maintaining exercise performance requires greater effort; this eventually leads to performance deterioration in training and competition. Short-term rest intervention of a few days up to several weeks usually restores full function. Untreated overreaching eventually leads to the overtraining syndrome.

Parasympathetic overtraining syndrome involves chronic fatigue during exercise workouts and recovery periods. Associated symptoms include sustained poor exercise performance, altered sleep patterns and appetite, frequent infections, persistent feelings of fatigue, altered immune and reproductive functions, acute and chronic alterations in systemic inflammatory responses, mood disturbances (anger, depression, anxiety), and general malaise and loss of interest in high-level training.

## fyi

Definitions of Terms Related to the Overtraining Syndrome ${ }^{175}$

- Overload: A planned, systematic, and progressive increase in training to improve performance.
- Overreaching: Unplanned, excessive overload with inadequate rest. Poor performance is observed in training and competition. Successful recovery should result from short-term (i.e., a few days up to 1 or 2 weeks) interventions.
- Overtraining syndrome: Untreated overreaching that produces long-term decreased performance and impaired ability to train. Other associated problems may require medical attention.

Figure 21.25 illustrates possible interactive factors that initiate the parasympathetic-type overtraining syndrome. Interactions among chronic neuromuscular, neuroendocrine, psychologic, immunologic, and metabolic overload during long-term, high-volume training (with insufficient recuperation) eventually alter physiologic function and the stress

Selected Mechanisms Underlying Genesis of Overtraining Syndrome in Endurance Exercise


Figure $\mathbf{2 1 . 2 5}$ Schematic overview of the genesis of the overtraining syndrome in endurance sports requiring prolonged highvolume training. (Modified from Lehmann M, et al. Autonomic imbalance hypothesis and overtraining syndrome. Med Sci Sports Exerc 1998;30:1140.)

TABLE 21.12 The Overtraining Syndrome: Symptoms of Staleness

- Unexplained and persistently poor performance and high fatigue ratings
- Prolonged recovery from typical training sessions or competitive events
- Disturbed mood states characterized by general fatigue, apathy, depression, irritability, and loss of competitive drive
- Persistent feelings of soreness and stiffness in muscles and joints
- Elevated resting pulse and increased susceptibility to upper respiratory infections (altered immune function) and gastrointestinal disturbances
- Insomnia
- Loss of appetite, weight loss, and inability to maintain proper body weight for competition
- Overuse injuries
response to produce the overtrained state..$^{68,123,174}$ Preexisting medical conditions, poor diet (e.g., inadequate carbohydrate or dehydration), environmental stress (e.g., heat, humidity, altitude), and psychosocial pressures (e.g., monotonous training, frequent competition, personal conflicts) often exacerbate training demands and increase the risk of developing the overtraining syndrome.

Significant effects of overtraining include the following:

1. Functional impairments in the hypothalamo pituitary gonadal and adrenal axes and sympathetic neuroendocrine system reflected by depressed urinary excretion of norepinephrine and a desensitization of the $\beta_{2}$-adrenergic system. ${ }^{50,108,207}$
2. Exercise-induced increases in adrenocorticotropic hormone and growth hormone and decreases in cortisol and insulin levels. ${ }^{212}$

In some ways, the syndrome reflects the body s attempt to provide the athlete with an appropriate recuperative period from intense training and competition. Despite the highly individualized specific symptoms of overtraining, those outlined in Table 21.12 are most common. No simple method diagnoses overtraining in its earliest stages. ${ }^{52,71}$ The best indications include deterioration in physical performance, alterations in mood, a relatively high cortisol/cortisone ratio, and possibly decreased nocturnal heart rate variability. ${ }^{7,154,187}$ Conditions that cause some athletes to thrive in training initiate an overtraining response in others. Generally, rest can relieve the symptoms; if not, they will persist, so complete recovery often requires weeks or months. No reliable method can determine the point of complete recovery from the overtraining syndrome, but most athletes know when they can successfully return to competition.

Coaches must allow adequate recuperation during the most intense training cycles or when an athlete attempts to regain peak form following a protracted layoff. Nutrition becomes particularly important during intense training; special emphasis placed on glycogen replenishment (sufficient recovery time plus high levels of dietary carbohydrate) and rehy-
dration reduce symptoms but nutrition alone cannot prevent the syndrome s development. ${ }^{1,165,190}$

## EXERCISING DURING PREGNANCY

Estimates indicate that $40 \%$ or more of women in the United States exercise during pregnancy. ${ }^{74,227}$ Figure 21.26 illustrates the prevalence and pattern of exercise during pregnancy among pregnant and nonpregnant women during the years 1994, 1996, 1998, and 2000 combined. Nonpregnant women were more likely than pregnant women to meet the moderate or vigorous physical activity recommendations. For both groups, walking was the most common activity ( $52 \%$ for pregnant and $45 \%$ for nonpregnant). Pregnant women who engaged in either moderate or vigorous physical activity were generally younger, non-Hispanic white, unmarried, more educated, nonsmokers, and had higher incomes than less physically active counterparts.

## Exercise Effects on the Mother

Maternal cardiovascular dynamics follow normal response patterns; moderate exercise offers no greater physiologic stress to the mother other than the additional weight gain and possible encumbrance of fetal tissue. Pregnant women showed similar capacity as postpartum women to perform 40 minutes of cycling at 70 to $75 \% \mathrm{~V}_{2}{ }_{2 \max }$. The physiologic responses to this weight-supported exercise remained largely independent of gestation. ${ }^{117}$ Pregnancy does not compromise the absolute value for aerobic capacity $\left(\mathrm{L} \cdot \min ^{-1}\right){ }^{118}$ The increase in maternal body mass and changes in coordination and balance as pregnancy progresses adversely affect exercise economy; this adds to exercise effort with weight-bearing exercise. Pregnancy, particularly in the last trimester, also increases pulmonary ventilation at a given submaximal exercise level. ${ }^{117}$ The direct stimulating effects of progesterone and increased chemoreceptor sensitivity to carbon dioxide contribute to maternal exercise hyperventilation. ${ }^{226}$ Regular, moderate exercise during the second and third trimesters reduces submaximal ventilatory demands and RPE. ${ }^{147}$ This training adaptation increases the mother s ventilatory reserve and possibly inhibits exertional dyspnea. Table 21.13 summarizes the important maternal metabolic and cardiorespiratory adaptations during pregnancy.

## Exercise Effects on the Fetus

Performing exercise during pregnancy requires adherence to prudent guidelines and recommendations. ${ }^{4}$ Epidemiologic evidence indicates that exercise during pregnancy does not increase risk of fetal deaths or low birth weights, and may significantly reduce the risk of preterm births. ${ }^{91,184}$ In fact, a moderate program of weight-bearing exercise or recreational activity early in pregnancy through term enhances fetoplacental growth and reduces preeclampsia risk. ${ }^{29,177}$ A study of middle-class women evaluated the effects of daily low-tomoderate exercise $\left(<1000 \mathrm{kCal} \cdot \mathrm{wk}^{-1}\right)$, more intense exercise $\left(>1000 \mathrm{kCal} \cdot \mathrm{wk}^{-1}\right)$, or no exercise on timely delivery


Figure 21.26 Common physical activities among pregnant and nonpregnant women (1994, 1996, 1998, and 2000 data combined). (From Petersen AM, et al. Correlates of physical activity among pregnant women in the United States. Med Sci Sports Exerc 2005;37:1748.)

TABLE 21.13 Important Metabolic and Cardiorespiratory Adaptations During Pregnancy

- Blood volume increases 40 to $50 \%$; hemodilution reduces hemoglobin concentration
- Increase in blood volume dilates the left ventricle
- Slight increase in oxygen consumption during rest and submaximal, weight-supported exercise such as stationary cycling
- Substantial increase in oxygen consumption during weightbearing exercise such as walking and running
- Increased heart rate during rest and submaximal exercise
- No change in $\dot{\mathrm{V}}{ }_{2 \text { max }}\left(\mathrm{L} \cdot \mathrm{min}^{-1}\right)$
- Increased ventilatory response-largely progesterone induced-during rest and submaximal exercise
- Possible magnified hypoglycemic response during exercise, especially late in pregnancy
- Possible depressed sympathetic nervous system response to exercise in late gestation

Modified from Wolfe LA, et al. Maternal exercise, fetal well-being and pregnancy outcome. Exerc Sport Sci Rev 1994;22:145.
and the safety and potential benefits of regular exercise during pregnancy. ${ }^{74}$ No association emerged between low-to-moderate exercise and gestation length. A positive finding indicated that higher volume weekly exercise lowered rather than raised the risk of preterm birth; among births after the projected term, women who performed more intense exercise delivered faster than nonexercisers.

Potential exercise risks of intense maternal exercise that could alter fetal growth and development include:

- Reduced placental blood flow and accompanying fetal hypoxia
- Fetal hyperthermia
- Reduced fetal glucose supply

Any factor that might temporarily compromise fetal blood supply raises concern in counseling pregnant women about exercise.

Neonates born to exercising mothers exhibit a neurobehavioral profile as early as the fifth day after birth, earlier than neonates from more sedentary counterparts. ${ }^{28}$ Exercising mothers either ran, performed aerobics, swam, or used stairclimbing exercises at least three times weekly for more than 20 minutes at $55 \%$ of aerobic capacity or above. The women in the control group led active lives that did not include regular, sustained exercise. Figure 21.27 shows data for five behavioral clusters of the Brazelton Neonatal Assessment Scales for the offspring of 34 women who exercised regularly and 31 sedentary women. No significant differences emerged between neonates born to exercising women and sedentary controls for clusters of factors to assess motor organization, autonomic stability, and range of state behaviors. Neonates born to exercising women scored higher in orientation behavior and ability to regulate state (i.e., more alert and interested in the surroundings and less demanding of their mothers). Although the inset table indicates that axial length and head circumference remained similar between groups, the offspring of the exercising women were lighter and leaner than offspring


Figure 21.27 Behavioral constellation scores of neonates in exercise and nonexercise control groups on Brazelton Neonatal Behavioral Assessment Scales. Numbers preceding each set of vertical bars represent an optimum score for each constellation; asterisks indicate statistical significance at the . 01 level. Insert table presents neonatal morphometric values. (From Clapp JF III, et al. Neonatal behavioral profile of the offspring of women who continue to exercise regularly throughout pregnancy. Am J Obstet Gynecol 1999;180:91.
from the control group. The findings support the concept that continuing regular exercise throughout pregnancy modifies neonatal behavior by positively affecting early neurodevelopment.

## INTEGRATIVE QUESTION

What weight control advantage during pregnancy would a daily walking program offer compared with stationary cycling if each program remained at the same initial exercise level (i.e., constant walking speed or cycling power output), frequency, and duration?

## Current Opinion Regarding Physical Activity and Pregnancy

Despite examples of extreme physical activity for welltrained women without apparent negative affect on maternal
or fetal health, ${ }^{9,92,124}$ more conservative, prudent recommendations apply during a normal pregnancy. Thirty to 40 minutes of moderate aerobic exercise for a previously active, healthy, low-risk woman during an uncomplicated pregnancy does not compromise fetal oxygen supply or acid base status, induce heart rate signs of fetal distress, or produce other adverse effects to mother or fetus. ${ }^{36,117,195}$ Performed on a regular basis, such exercise maintains cardiovascular fitness and promotes a training effect. ${ }^{53,156,161,162}$ Hormonal action via the sympathetic nervous system during strenuous exercise probably diverts some blood from the uterus and visceral organs for preferential distribution to active muscles. This could pose a hazard to a fetus with restricted placental blood flow. The accompanying In a Practical Sense on page 488 outlines guidelines for formulating an exercise prescription during pregnancy. This prudent approach dictates that a pregnant woman (in consultation with her health care provider) should exercise in moderation, especially if the pregnancy is at all compromised. In addition, exercise late in pregnancy can magnify the normal maternal hypoglycemic response by increasing glucose consumption by maternal skeletal muscle; in the extreme, this response could adversely affect fetal glucose supply. ${ }^{14,27}$

Pregnant women should avoid supine exercise, contact sports, high-altitude exertion, hot tub immersion, and scuba diving. A decrease in uterine blood flow or elevation in maternal core temperature with extended-duration exercise during environmental heat stress could compromise heat dissipation from the fetus through the placenta. ${ }^{130}$ Hyperthermia negatively affects fetal development (e.g., increased risk of neural tube defect), particularly in the first trimester, ${ }^{134}$ so women should exercise during warm weather in the cool part of the day for shorter intervals while maintaining regular fluid intake. Within this framework, aquatic exercise serves as an ideal form of maternal exercise.

Current fitness level and previous physical activity patterns should guide a womans exercise behavior throughout an uncomplicated pregnancy and postpartum. Regular aerobic exercise during pregnancy plays an important role to maintain functional capacity and general well-being. It also optimizes overall weight gain during the later stages of pregnancy ${ }^{27}$ and may reduce risk for cesarean delivery in women who have never borne children. ${ }^{23}$ Controversy remains about whether (1) extremes of maternal exercise benefit either mother or fetus or (2) whether exercise during pregnancy benefits labor, delivery, birth weight, and general outcome. ${ }^{13,157}$ Beginning regular exercise 6 to 8 weeks postpartum produces no deleterious effect on volume or composition of lactation and improves aerobic fitness without impairing immune function. ${ }^{36,116,120}$ Any fitness and strength declines in the early postpartum period relative to prepregnancy performance generally return by 27 weeks after delivery. ${ }^{210}$ Combining moderate exercise with a reduced energy intake of about 500 kCal a day allows overweight lactating women to safely lose 0.5 kg per week without adversely affecting infant growth. ${ }^{119}$

## IN A PRACTICAL SENSE

## Exercise Prescription During Pregnancy

Pregnancy alters normal physiology, necessitating some modification in exercise prescription. Pregnant women should consult their physician before initiating an exercise program (or modifying an existing program) to rule out possible complications. This pertains particularly to women of low fitness status and little exercise experience prior to pregnancy.
Exercise during pregnancy should heighten awareness about heat dissipation, adequate caloric and nutrient intake, and knowing when to reduce exercise intensity. For a normal, uncomplicated pregnancy, light-to-moderate exercise does not negatively affect fetal development; the benefits of properly prescribed regular exercise during pregnancy generally outweigh potential risks.

## EXERCISE GUIDELINES

Exercise mode: Avoid exercise in the supine position, particularly after the first trimester. Supine exercise impairs venous return (mass of the fetus compresses inferior vena cava), which could affect cardiac output and uterine blood flow. Non weight-bearing exercise (e.g., cycling, swimming) minimizes the effect of gravity and the added weight associated with fetal development. Low-impact, weight-bearing exercise in moderation should not pose a risk.

Exercise frequency: Exercise 3 days a week, emphasizing continuous, steady-rate effort. Reduce the intensity of more frequent exercise.
Exercise duration: Exercise 30 to 40 minutes, depending on how the person feels.
Exercise intensity: Pregnancy alters the relationship between heart rate and oxygen consumption, making it difficult to establish guidelines from heart rate. An effective alternative establishes exercise intensity based on RPE, which should range between 11 ( fairly light ) to 13 ( somewhat hard ).
Rate of progression: Perform exercise on a regular basis; moderate aerobic exercise maintains cardiovascular fitness and often produces a small training effect. Most women should not strive to induce training effects, but rather maintain cardiorespiratory fitness, muscle mass, and physician-recommended weight gain. The combined effects of pregnancy per se and regular exercise often produce improved fitness after delivery.

## WHEN TO STOP EXERCISE AND SEEK MEDICAL ADVICE

Discontinue exercise immediately under the following conditions:

- Any signs of vaginal bleeding
- Any gush of fluid from the vagina (premature rupture of membranes)
- Sudden swelling of ankles, hands, or face
- Persistent, severe headaches and/or disturbances in vision; unexplained lightheadedness or dizziness
- Elevated pulse rate or blood pressure that does not rapidly return to normal following exercise
- Excessive fatigue, palpitations, or chest pain
- Persistent uterine contractions (more than 6 to 8 per h)
- Unexplained or unusual abdominal pain
- Insufficient weight gain ( $<1.0 \mathrm{~kg}$ per month during the last two trimesters)

Contraindications to exercise during pregnancy:

- Pregnancy-induced hypertension
- History of two or more spontaneous abortions
- Preterm rupture of membranes
- Preterm labor during the prior or current pregnancy
- Incompetent cervix
- Excessive alcohol intake
- Persistent second to third trimester bleeding
- History of premature labor
- Intrauterine growth retardation
- Anemia
- Type 1 diabetes
- Significant obesity
- Multiple pregnancy
- Smoking

From Exercise during pregnancy: Current comment from the American College of Sports Medicine, August 2000. www.Americanpregnancyhealth/ exerciseguidelines.html

## Summary

1. Physical activities generally classify by the specific energy transfer system predominantly activated. An effective exercise program trains the appropriate energy system(s) to improve a desired physiologic function or performance goal.
2. Physical conditioning based on sound principles optimizes improvements. The four primary training principles include overload, specificity, individual differences, and reversibility.
3. Exercise training initiates cellular adaptations and gross physiologic changes that enhance functional capacity and exercise performance.
4. Anaerobic training increases resting levels of intramuscular anaerobic substrates and key glycolytic
enzymes. Adaptations usually accompany concomitant increases in maximal exercise performance.
5. Aerobic training adaptations increase mitochondrial size and number, quantity of aerobic enzymes, muscle capillarization, and fat and carbohydrate oxidation. These improvements contribute to enhanced aerobic ATP production.
6. A linear relationship exists between heart rate and oxygen consumption from light to moderately intense exercise in trained and untrained individuals. Improved stroke volume with aerobic training shifts this line to the right to decrease heart rate at any submaximal exercise level.
7. Aerobic training induces functional and dimensional changes in the cardiovascular system to decrease resting and submaximal exercise heart rate, enhance
stroke volume and cardiac output, and expand the $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference.
8. Cardiac hypertrophy represents a fundamental biologic adaptation to increased myocardial workload imposed by exercise training. Cardiac enlargement with endurance training increases left ventricular volume and enhances stroke volume.
9. Structural and dimensional changes in the left ventricle vary with exercise training modes. Regular exercise does not harm normal cardiac function.
10. Exercise intensity is the most crucial factor that affects the magnitude of training improvements; other factors include initial fitness level, frequency, exercise duration, and training mode.
11. Training intensity can be applied on either an absolute basis for exercise load or relative to a person $s$ physiologic response. The most practical approach sets exercise intensity to a percentage of $\mathrm{HR}_{\text {max }}$. Training levels between 60 and $90 \% \mathrm{HR}_{\max }$ induce meaningful changes in aerobic fitness.
12. Training duration and intensity interact to affect the training response. Generally, 30-minute exercise sessions are practical and effective. Extending duration compensates for reduced exercise intensity.
13. Two to 3 days a week represents the minimum frequency for aerobic training. Optimal training frequency remains undetermined.
14. Similar aerobic improvements occur when intensity, duration, and frequency remain constant, regardless of whether exercise mode when training involves large muscle groups, and the evaluation process remains mode specific.
15. Training frequency and duration to maintain improved aerobic fitness are lower than those required
to improve it. Even small decreases in exercise intensity reduce $\dot{\mathrm{V}}_{2 \text { max }}$.
16. Interval, continuous, and fartlek training improve the capacity of the different energy transfer systems. Interval training most effectively improves the immediate and short-term anaerobic energy systems.
17. Aerobic training must overload both cardiovascular function and metabolic capacity of specific muscles. Peripheral adaptations in trained muscle profoundly enhance endurance performance.
18. Prolonged and intense endurance training can precipitate the syndrome of overtraining or staleness, with associated alterations in neuroendocrine and immune functions. The syndrome includes chronic fatigue, poor exercise performance, frequent infections, and general loss of interest in training. Symptoms generally persist until the athlete relinquishes training, possibly for several days to months.
19. At least $40 \%$ of American women exercise during pregnancy, with walking the most common form of exercise ( $42 \%$ ) followed by swimming ( $12 \%$ ) and aerobics (12\%).
20. The most serious potential exercise risks during pregnancy include reduced placental blood flow and accompanying fetal hypoxia, fetal hyperthermia, and reduced fetal glucose supply.
21. For previously active, healthy women, moderate aerobic exercise does not compromise fetal oxygen supply.

1, References are available online at http://thepoint.lww.com/mkk7e.

## CHAPTER 22



## Muscular Strength: Training Muscles to Become Stronger

## CHAPTER OBJECTIVES

> Describe the following five methods to assess muscular strength: (1) cable tensiometry, (2) dynamometry, (3) one-repetition maximum (1-RM), (4) computer-assisted isokinetic dynamometry
> Outline a procedure to assess 1-RM for trained and untrained individuals
> Describe how to ensure test standardization and fairness to evaluate muscular strength
> Compare absolute and relative upper- and lowerbody muscular strength in men and women
> Describe allometric scaling to equalize individuals when comparing physical and exercise performance characteristics

- Define concentric, eccentric, and isometric muscle actions and give examples of each
> Discuss the advisability of resistance training for children and adolescents
> Summarize the main research findings on optimal number of sets and repetitions, and frequency and relative intensity of progressive-resistance training
> Outline the model for strength-training periodization
> Discuss specificity of the strength-training response related to sports and occupational tasks
> Differentiate between resistance training goals of competitive athletes and untrained middle-aged and elderly persons
> Respond to the question: Which is better for strength improvementprogressive resistance weight training, isometric training, or isokinetic training?
> Describe advantages and disadvantages of plyometric training for power athletes
- Describe how psychologic factors and muscular factors influence maximum strength capacity and training responsiveness
- List physiologic adaptations with chronic resistance training
> Summarize current opinion concerning resistance trainings effect on muscle fiber type and number
> Outline a circuit resistance training program for middle-aged men and women to improve muscular strength and aerobic fitness
- Discuss whether specific resistance training can shape a muscles appearance
> Review (1) the type of exercise most frequently associated with delayed-onset muscle soreness (DOMS), (2) the best way to minimize DOMS when initiating training, and (3) significant cellular alterations with DOMS
> Explain core strength development and its role in physical performance


## Part 1 STRENGTH MEASUREMENT AND RESISTANCE TRAINING

Weightlifting in America in the early 1840s became a spectator sport practiced by strongmen who showcased their prowess in traveling carnivals and sideshows. As pointed out in the texts Introduction: A View of the Past, the military evaluated the strength of conscripts during the Civil War; strength measurements also provided the basis for routine fitness assessments in the prototype college and university physical education programs. An 1897 meeting of College Gymnasium Directors (Dr. D. A. Sargent, committee chair from Harvard University) established strength contests for college undergraduates to determine overall body strength and the colleges strongest man. Measures included back, leg, arm, and chest strength evaluated with several of the devices depicted in Figure 9 of the Introduction (see p. xlvii). Harvard, Columbia, Amherst, University of Minnesota, and Dickinson were the first five colleges to rank in the 18981899 competitions.

By the mid-1900s, physical culture specialists, circus performers, bodybuilders, competitive weightlifters, field event athletes, and wrestlers trained predominantly using weightlifting exercises. Most other athletes refrained from lifting weights for fear such training would slow them and increase muscle size to the point where they would lose joint flexibility and become musclebound. Subsequent research in the late 1950s and early 1960s dispelled this myth that muscle-strengthening exercises reduced speed or range of joint motion. Instead, the opposite usually occurred; elite weightlifters, bodybuilders, and muscle men had exceptional joint flexibility without limitations in general limb movement speed. For untrained healthy individuals, heavy-resistance exercises increased speed and power of muscular effort without impairing subsequent sports performance.

In the sections that follow, we explore the rationale that underlies resistance training and physiologic adaptations when training muscles to become larger and stronger. The discussion centers on different methods to measure muscular strength, gender differences in strength, and resistance-training programs to increase muscle strength (including a discussion of core strength) and power.


Left. Early 1890s pose of strongman Eugene Sandow (Frederick Mueller), billed by showman Florenz Ziegfeld as The Most Perfect Man. Sandow helped to design a physical fitness training program for the British military, inspiring a future generation of bodybuilders. Right. John Grimek, member of the United States 1936 Olympic weightlifting team, two-time Mr. America (1940, 1941), 1948 Mr. Universe, and undefeated in bodybuilding competition. Recognized as the best-built human of the first half of the 20th century.


Late 1890s strength equipment advertised for home gym use. By the mid-1850s, rowing machines and strengthening devices became commonplace, eventually leading to studies of their effectiveness in American colleges (Harvard and Amherst) in the 1890s.

## MEASUREMENT OF MUSCLE STRENGTH

One of the following four methods commonly assesses muscle strength, or, more precisely, maximum force or tension output generated by a single muscle or related muscle groups:

1. Tensiometry
2. Dynamometry
3. One-repetition maximum
4. Computer-assisted force and power output determinations

## Cable Tensiometry

Figure 22.1A shows a cable tensiometer for measuring knee extension muscle force. Increasing the force on the cable depresses the riser over which the cable passes. This deflects the pointer and indicates the subjects strength score. The instrument measures muscle force in a static (isometric) muscle action that elicits little or no change in the muscles external length. The tensiometer (lightweight, portable, and easy to use) provides the advantage of versatility for recording force measurements at virtually all angles about a specific joints range of motion (ROM). Standardized cable-tension strength-test batteries can assess static force capacity of all major muscle groups.

## Dynamometry

Figure 22.1B and C illustrate hand-grip and leg and back-lift dynamometers for static strength measurement based on the compression principle. An external force applied to the dynamometer compresses a steel spring and moves a pointer. The force required to move the pointer a given distance determines the external force applied to the dynamometer.

## One-Repetition Maximum

A dynamic procedure for measuring muscular strength applies the one-repetition maximum (1-RM) method. 1-RM refers to the maximum amount of weight lifted one time using proper form during a standard weightlifting exercise. To assess 1-RM for any muscle group, the tester makes a reasonable guess at an initial weight close to, but below, the persons maximum lifting capacity. Weight is progressively added to the exercise device on subsequent attempts until the person reaches maximum lift capacity. The weight increments usually range between 1 and 5 kg depending on the muscle group evaluated. Rest intervals of 1 to 5 minutes usually provide sufficient recuperation before attempting a lift at the next heavier weight.

## Estimate the 1-RM

Impracticality and/or potential risk in performing 1-RM with preadolescents, the elderly, hypertensives, cardiac patients, and other special populations requires an estimate 1-RM from submaximal effort. We present equations below for untrained and resistance-trained young adults. Different equations are necessary because resistance training alters the relationship between a submaximal performance (7- to $10-\mathrm{RM}$ ) and maximal lift capacity (1-RM). Generally, the weight that one can lift for 7- to 10-RM represents about $68 \%$ of the $1-\mathrm{RM}$ score for the untrained person and $79 \%$ of the new 1-RM after training. ${ }^{30}$

## Untrained:

$$
1-\mathrm{RM}(\mathrm{~kg})=1.554 \times 7 \text { - to } 10-\mathrm{RM} \text { weight }(\mathrm{kg})-5.181
$$

## Trained:

$$
1-\mathrm{RM}(\mathrm{~kg})=1.172 \times 7-\text { to } 10-\mathrm{RM} \text { weight }(\mathrm{kg})+7.704
$$

For example, estimate 1-RM bench press score for a trained person whose $10-\mathrm{RM}$ bench press equals 70 kg as follows:

$$
\begin{aligned}
1-\mathrm{RM}(\mathrm{~kg}) & =1.172 \times 70 \mathrm{~kg}+7.704 \\
& =89.7 \mathrm{~kg}
\end{aligned}
$$

## Computer-Assisted, Electromechanical, and Isokinetic Methods

Microprocessor technology rapidly quantifies forces, torques, accelerations, and velocities of body segments in numerous movement patterns. Force platforms measure the


Figure 22.1 Measurement of static strength with (A) cable tensiometer, (B) hand-grip dynamometer, and (C) back leg lift dynamometer.
external application of muscle force by a limb, as in jumping. Other electromechanical devices assess forces generated during all phases of an exercise movement (e.g., cycling) or primarily arm (supine bench press) or leg (leg press) movements.

An electromechanical accommodating resistance instrument, termed an isokinetic dynamometer, contains a speed-controlling mechanism that accelerates to a preset, constant velocity with force application. Once attaining this speed, the isokinetic loading mechanism adjusts automatically to provide a counterforce to variations in force generated by muscle as movement continues throughout the strength curve. Thus, maximum force (or any percentage of maximum effort) generates throughout the full ROM at a preestablished velocity of limb movement. This allows training (and measurement) under a continuum from high-velocity (low-force) to low-velocity (high-force) conditions. A microprocessor within the dynamometer continuously monitors the immediate level of applied force. An electronic integrator in series with a monitor displays the average or peak force generated during any interval for almost instantaneous feedback about performance (e.g., force, torque, work).

The interface of microprocessor technology with mechanical devices provides the sport and exercise scientist with valuable data to evaluate, test, train, and rehabilitate individuals. The argument in support of isokinetic strength measurement maintains that muscle strength dynamics involve considerably more than just the final outcome of 1 RM. For example, two individuals with identical 1-RM scores could exhibit dissimilar force curves throughout the movement. Individual differences in force dynamics (e.g., time to peak tension) throughout the full ROM may reflect an entirely different underlying neuromuscular physiology that 1-RM does not assess. Figure 22.2 illustrates the differences between conventional 1-RM knee extension (top: highest force score during five lifts represents only total weight lifted) and a microprocessor-controlled, isokinetic resistance device that can produce a force curve throughout the ROM (bottom: force related to movement duration). In this example with an early-generation isokinetic device, note that peak torque occurred in the early phase of movement at the most advantageous angle in the ROM; the lowest torque occurred at full knee extension. Table 22.1 lists measurement units for various expressions of muscular performance during linear and angular movements.


Figure 22.2 Top. Conventional 1-RM testing. The heaviest weight lifted constitutes the $1-\mathrm{RM}$. If $150 \mathrm{~kg}(100 \%)$ is the maximum lifted, then 150 kg equals the 1-RM. Bottom. Force curve obtained during an isokinetic test performed at an angular velocity of $30 \cdot \mathrm{~s}^{-1}$ over a 3 -second interval. Peak torque in this example equals $342 \mathrm{~N}-\mathrm{m}$. Average torque is the force-time integral, or impulse divided by time. Impulse equals $602 \mathrm{~N}-\mathrm{m} \cdot \mathrm{s}^{-1}$, and average torque equals $200.7 \mathrm{~N}-\mathrm{m}$ ( $602 \mathrm{~N}-\mathrm{m} \div 3$ ). Work equals the product of average torque $\times$ distance moved ( 90 , or 1.57 radians). Using the data for average torque and distance, work equals $174 \mathrm{~N}-\mathrm{m} \times 157$ radians $=273 \mathrm{~N}-\mathrm{m}$, or 273 joules (J). Power is work per unit time, or $273 \mathrm{~J} \div 3.0 \mathrm{~s}=91 \mathrm{~W}$.

## INTEGRATIVE QUESTION

Explain why many resistance-trained athletes have their spotters during a free-weight bench press apply external force (to make the lift more difficult) in the early phase of the lift and provide assistance toward its completion.

## Resistance-Training Equipment Categories

Resistance training typically uses one of four types of exercise equipment to manipulate movement speed and/or resistance throughout the ROM.

1. Free weights and barbells, common weightlifting equipment that does not control for or measure speed of movement of the resistance through the range of ROM
2. a. Isokinetic equipment that provides constant speed and variable resistance
b. Isokinetic, hydraulic equipment that provides constant speed and variable resistance, where the individual controls movement speed
3. Cam devices and concentric eccentric apparatus where movement speed varies and resistance remains constant

Another possible type of machine, not currently available, would optimize muscle force with true constant speed and constant resistance.

## Strength-Testing Considerations

Seven important considerations exist for muscle strength testing regardless of measurement method:

1. Standardize instructions prior to testing.
2. Ensure uniformity in duration and intensity of the warm-up.

TABLE 22.1 International System (SI) of Units for Expressing Muscular Strength and Power During Linear and Angular Motions ${ }^{a}$

|  | Linear Motion |  | Angular Motion |
| :--- | :--- | :--- | :--- |
| Quantity | Unit | Quantity | Unit |
| Force | Newton, N | Torque, $T$ | Newton meter, $\mathrm{N}-\mathrm{m}$ |
| Velocity | Meters per second, $\mathrm{m} \cdot \mathrm{s}^{-1}$ | Velocity, $v$ | Radians per second, rad $\cdot \mathrm{s}^{-1}$ |
| Mass | Kilogram, kg | Moment of inertia, $I$ or $J$ | Kilogram meters squared, $\mathrm{kg}-\mathrm{m}^{2}$ |
| Acceleration | Meters per second squared, $\mathrm{m} \cdot \mathrm{s}^{-2}$ | Acceleration, $a$ | Radians per second squared, $\mathrm{rad} \cdot \mathrm{s}^{-2}$ |
| Displacement | Meter, m | Displacement, $\theta$ | Radian, rad |
| Time | Second, s | Time, $t$ | Second, s |

${ }^{a}$ Appendix A, available online at http://thepoint.lww.com/mkk7e, provides additional information about SI units, including interconversions.
3. Provide adequate practice prior to testing to minimize learning that could compromise initial results.
4. Ensure consistency among subjects in the angle of limb measurement and/or body position on the test device.
5. Predetermine a minimum number of trials (repetitions) to establish a criterion strength score. For example, if administering five repetitions of a test, what score represents the individuals strength score? Is the highest score best, or should one use the average? In most cases, an average of several trials provides a more representative (reliable) strength or power score than a single measure.
6. Select test measures with high test score reproducibility. This crucial but often overlooked aspect of testing evaluates the variability of the subjects responses on repeated efforts. Lack of test score consistency (unreliability) can mask an individuals representative performance on the measure (or change in performance when evaluating strength improvement).
7. Recognize individual differences in body size and composition when evaluating strength scores among individuals and groups.

For example, consider the fairness of comparing absolute muscular strength of a $120-\mathrm{kg}$ football lineman with the strength of a $62-\mathrm{kg}$ distance runner. No clear-cut answer resolves this dilemma; in the section on Allometric Scaling on page 498, we present alternatives for comparing strength scores relative to body size.

## fyi <br> Exercise Equipment to Overload Skeletal Muscle

| Category | Speed | Resistance | Equipment <br> Example |
| :--- | :--- | :--- | :--- |
| (I) | Variable | Variable | Barbells (resistance <br> varies through ROM <br> even though absolute <br> weight remains <br> constant) |
| (II) | Constant Variable | Hydraulic (person <br> controls speed) |  |
| (III) | Variable | Constant | Computer-regulated <br> (movement speed <br> controlled by <br> computer) <br> CAM-adjusted <br> equipment and <br> concentric eccentric <br> apparatus |
| (IV) | Constant | Constant | None available |

## Strength Related to Muscle Cross-Sectional Area

Human skeletal muscle regardless of gender generates a maximum of between 16 and 30 newtons ( N ) of force per square centimeter of muscle cross section. In the body, force-output capacity varies depending on the arrangement of the bony levers and muscle architecture (see Chapter 18). Applying the value of 30 N as a representative force capacity per $\mathrm{cm}^{2}$ of muscle tissue indicates that a muscle with a cross-sectional area of $5.0 \mathrm{~cm}^{2}$ develops maximal force of 150 N . If all of the bodys muscles became maximally activated simultaneously (with force applied in the same direction), the resulting force would equal 168 kN . This estimation assumes a muscle total cross section of $0.56 \mathrm{~m}^{2}$.

Figure 22.4A compares the absolute arm flexor strength of men and women related to the flexor muscles total crosssectional area (MCSA). Clearly, individuals with the largest MCSA generate the greatest absolute force. The near-linear relation between strength and muscle size indicates little difference in arm flexor strength for the same size muscle in men and women. Figure 22.4B further demonstrates this point when expressing the strength of the men and women per unit area of MCSA. In addition, women and men matched for absolute muscular strength show similar fatigability of the elbow flexor muscles during sustained low-level isometric contraction. ${ }^{109}$

## Absolute Muscle Strength

Comparisons of muscular strength on an absolute score basis (i.e., total force in lb or kg ) indicate that men possess considerably greater strength than women for all muscle groups tested. Women score about $50 \%$ lower than men for upperbody strength and about $30 \%$ lower for leg strength. This gender disparity exists independent of the measuring device and generally coincides with gender-related difference in muscle mass distribution. Exceptions usually emerge for strengthtrained female track-and-field athletes and bodybuilders who have strength-trained for years.

## Gender Differences in Weightlifting Championships

A unique set of data exists on gender differences in weightlifting competitions in which men and women of identical body mass participated in the same weightlifting categories. Figure 22.5 displays the percentage differences in maximum weight lifted in the combined snatch and clean-and-jerk lifts during national championship competitions. These comparisons do not equate or adjust performance scores on the basis of the well-documented gender difference in body composition. The six body weight categories range from 52 to 82.5 kg . The lighter-weight categories usually produce the smallest gender difference, with the effect most pronounced in the heavier lifters. Women of 75- and


Figure 22.4 A. Variability of upper-arm flexion strength of men and women related to the flexor muscles total crosssectional area. B. Strength per unit muscle cross-sectional area in males and females aged 12 to 20 years. (From Ikai M, Fukunaga T. Calculation of muscle strength per unit crosssectional area of human muscle by means of ultrasonic measurements. Arbeitsphysiologie 1968;26:26.)
$82.5-\mathrm{kg}$ body mass lift only about $60 \%$ of the maximal weight lifted by similar-weight male counterparts. This represents a more pronounced gender difference than other comparisons that matched male and female competitors for body composition, not just body mass. In such comparisons, it is impossible to determine what role, if any, anabolic steroid use impacted the gender differences in various expressions of muscular strength.


Figure 22.5 Difference in maximum weight lifted between men and women in the same body mass categories during a national weightlifting competition. The inset shows the absolute weight lifted for each body mass category.

## 12 <br> INTEGRATIVE QUESTION <br> What performance would you expect in maximum weightlifting tests comparing (1) an averagesized man and average-sized woman, (2) a man and woman of equivalent training history and identical body mass, and (3) a man and woman of equivalent training history and identical fat-free body mass?

## Relative Muscle Strength

Relative strength comparisons among individuals involve creating a comparative ratio score by dividing a strength measurement (e.g., weight lifted) by a reference measurement such as body mass, FFM, MCSA, or limb volume or girth. In general, strength ratio scores based on body mass or FFM considerably reduce (if not eliminate) the large absolute strength differences between genders. ${ }^{40}$

Consider the following example. A male who weighs 95 kg bench presses 114 kg ; a $60-\mathrm{kg}$ woman bench presses only 70 kg ( $62 \%$ of the mans lift). Who is stronger? In absolute terms, we
would conclude the male, by $61.3 \%$. However, the bench press score divided by body mass yields a much different conclusion. For the male, the strength ratio ( 114 kg 95 kg ) equals 1.20 ; the ratio for the woman is $1.17(70 \mathrm{~kg} 60 \mathrm{~kg})$, which reduces the percentage difference in bench press strength to only $2.5 \%$ ! This alternative result would support the argument that no differences exist in muscle quality between men and women; rather, the observed gender difference in absolute muscle strength would reflect differences in muscle quantity (crosssectional area). Men and women generally do not differ significantly in either upper- or lower-body strength when comparisons are made applying ratios with FFM (or MCSA) as the divisor.

We must emphasize that this traditional ratio adjustment may not equalize women and men on the basis of the underlying physiology. As with aerobic capacity (discussed in Chapter 11), a fair way to evaluate a potential gender difference in a criterion trait such as muscular strength or aerobic capacity either (1) compares men and women who do not differ in body size variables such as body mass or FFM and who exhibit similar training status or (2) adjusts for these variables through appropriate statistical control. These solutions preclude the need to create a ratio score because men and women in essence become equalized for body size and/or body composition. With this approach, researchers assessed five measures of muscular strength for men and women, using 1-RM concentric (shortening) muscle actions for the bench press and squat and isokinetic dynamometry to assess maximum force during knee flexion and extension and seated shoulder press. Figure 22.6 shows that matching men and women for body mass produced larger gender differences in the sedentary group ( $44.0 \%$ for the shoulders and $25.1 \%$ for knee flexion) than in the trained group ( $33.0 \%$ for the bench press and $10.7 \%$ for knee flexion). The percentage differences decreased (but were not eliminated) for both groups by matching subjects for FFM. The shoulder press (39.4\%) and bench press (31.2\%) produced the largest gender differences in the sedentary group, while the corresponding differences for the trained group were $30.6 \%$ (shoulder press) and $35.4 \%$ (bench press).

These results differ from prior studies that used the traditional ratio score approach to express the strength of women and men. Without doubt, ratio scoring supports the argument that few gender differences exist in muscle quality, at least reflected by force output capacity. In contrast, matching men and women for body size, body composition, and training status before testing yields higher upper- and lower-body strength scores for men. ${ }^{187}$ In a latter study of 2061 male and 1301 female military personnel, mean lift capacity averaged $51 \%$ greater in men despite a regression, ratio, or exponential mathematical adjustment in the strength score based on interindividual differences in FFM.

## INTEGRATIVE QUESTION

> Based on gender-related differences in physical fitness components, devise a physical test that (1) minimizes and (2) maximizes performance differences between men and women.


Figure 22.6 Men and women matched for body mass (top) and fat-free body mass (bottom) for five measures of muscle strength. Above the zero line indicates the percentage by which values for men exceed values for women. (Data courtesy of Keller B. The influence of body size variables on gender differences in strength and maximum aerobic capacity. Unpublished doctoral dissertation, University of Massachusetts, Amherst, 1989.)
between maximal grip strength and body mass in collegeaged men (purple) and women (green). The top graphs illustrate the simple relationship between body mass and grip strength without adjustment for body size. A positive relationship emerges ( $r=0.51$ for males and $r=0.33$ for females). The middle graphs depict the relationship with grip strength indexed to body mass (i.e., strength divided by body mass in kg ). The bottom graphs illustrate the relationship between strength and allometric scaling of body mass. The resulting correlations between strength and body mass with the appropriate allometric scaling fall essentially to zero ( $r=0.013$ for males and 0.030 for females). This satisfies one of the basic tenets of allometrythe correlation between the scaled variable (muscular strength) and the scaling factor (body mass) must equal zero. The inset table (C) presents percentile norms for the grip strength adjusted to allometric-scaled body mass exponent (grip strength per $\mathrm{kg}^{0.51}$ ) for college-aged men and women.

## INTEGRATIVE QUESTION

You have a list of the names of young adults with their corresponding body weights. Justify your selection of just two people to complete these tasks: One must push a vehicle stuck in the mud while the other must move hand-over-hand on a rope strung across a ravine. Hint: Consider absolute and relative strength requirements of each task and association between body mass and absolute and relative muscular strength.

## TRAINING MUSCLES TO BECOME STRONGER

A muscle strengthens when trained near its current maximal force-generating capacity. Standard weightlifting equipment, pulleys or springs, immovable bars, resistance bands, or a variety of isokinetic and hydraulic devices provide effective muscle overload. Importantly, overload intensity (level of tension placed on muscle), not the type of exercise that applies the overload, generally governs strength improvements. Certain exercise methods lend themselves to precise and systematic overload applications. Progressive-resistance weight training, isometric training, and isokinetic training represent three common exercise systems to train muscles to become stronger. These systems rely on the types of muscle actions illustrated in Figure 22.8A C.

## Different Muscle Actions

Neural stimulation of a muscle causes the contractile elements of its fibers to shorten along the longitudinal axis. The terms isometric and static describe muscle activation without observable change in muscle fiber length. A dynamic muscle action produces movement of a skeletal body part such as an

c

| Percentile rank | Grip Strength Male $\overline{\mathrm{X}}=5.46, \mathrm{SD}=0.79)$ | $\begin{gathered} \mathrm{kg} \cdot \mathrm{~kg} \mathrm{BW}-0.51) \\ \text { Female } \\ (\overline{\mathrm{X}}=3.84, \mathrm{SD}=0.59) \end{gathered}$ |
| :---: | :---: | :---: |
| 90 | 6.47 | 4.60 |
| 80 | 6.12 | 4.35 |
| 70 | 5.87 | 4.15 |
| 60 | 5.66 | 4.00 |
| 50 | 5.46 | 3.85 |
| 40 | 5.26 | 3.70 |
| 30 | 5.05 | 3.55 |
| 20 | 4.80 | 3.35 |
| 10 | 4.45 | 3.10 |



Figure 22.7 Relationship between body mass and different expressions of muscular strength. A. Total weight lifted in two events as a function of body mass of Olympic weightlifters (1980 Olympic games). Each point represents the body mass of the top six male weightlifters in each of the following weight categories: Fly, flyweight; Ban, bantamweight; Fea, featherweight; LW, lightweight; Mid, middleweight; LHW, light-heavyweight; MW, middle-heavyweight; 1st HW, 1st heavyweight; 2nd HW, 2nd heavyweight; and Super, superheavyweight. (Modified from data of Lathan and cited by Titel K, Wutscherk H. In: Komi PV, ed. Strength and power in sport. Oxford: Blackwell Scientific Publications, 1993.) B. Maximal absolute grip strength, relative grip strength, and strength scaled allometrically to body mass of 100 men and 105 women of college age. C. Percentile norms for grip strength scaled to body mass. (Data courtesy of Dr. Paul Vanderburgh, University of Dayton).


Figure 22.8 Muscle force generated during (A) concentric (shortening), (B) eccentric (lengthening), and (C) isometric (static) muscle actions.
upper or lower limb or the trunk. Concentric and eccentric actions represent the two types of dynamic muscle actions.

Concentric action occurs when the muscle shortens and joint movement occurs as tension develops. Figure 22.8A illustrates a concentric action when raising a dumbbell from the extended to the flexed elbow position.
Eccentric action occurs when external resistance exceeds muscle force and the muscle lengthens while developing tension (Fig. 22.8B). The weight slowly lowers against the force of gravity. The muscle fibers (more specifically the sarcomeres) of the upper-arm muscles lengthen in an eccentric action to prevent the weight from crashing to the surface. In weight lifting, muscles frequently act eccentrically as the weight slowly returns to the starting position to begin the next concentric (shortening) action. Eccentric muscle action during this recovery phase adds to the total work and effectiveness of the exercise repetition.
Isometric action occurs when a muscle generates force and attempts to shorten but cannot overcome the external resistance (Fig. 22.8C). From a physics standpoint, this type of muscle action does not produce external work. An isometric (static) action can generate considerable force despite the lack of noticeable lengthening or shortening of muscle sarcomeres and subsequent joint movement.

The term isotonic, derived from the Greek word isotonos (iso meaning the same or equal, tonos meaning tension or strain), commonly refers to concentric and eccentric
muscle actions because movement occurs. This term lacks precision when applied to most dynamic muscle actions that involve movement; the muscles effective force-generating capacity continually varies as the joint angle changes throughout the ROM.

## Resistance Training

The most popular form of resistance training involves lifting and lowering an external weight. Through appropriate and progressive manipulation of training volume, intensity, and frequency to optimize dose response, this method selectively strengthens specific muscles to overcome a fixed initial or changing resistance. ${ }^{137,209}$ This resistance typically takes the form of a barbell, dumbbell, or weight plates on a pulley- or cam-type machine. As with cardiovascular training, muscular strength improvements vary inversely on a continuum with initial training status. Generally, improvements average $40 \%$ for the untrained, $20 \%$ in the moderately trained, $15 \%$ in the trained, $10 \%$ in the advanced, and $2 \%$ in elite athletes who achieve a high level of competitive success. ${ }^{4}$

## Progressive Resistance Exercise

Progressive resistance exercise (PRE) provides a practical application of the overload principle and forms the basis of most resistance-training programs. Physical therapists in a rehabilitation hospital in the late 1940s and early 1950s devised weight-training regimens to improve the strength of previously injured limbs of soldiers returning from WWII (see Focus on Research, p. 501). The procedure involved three

## FOCUS ON RESEARCH

## Develop Strength by Increasing Load, Not Repetitions

DeLorme TL. Restoration of muscle power by heavyresistance exercises. J Bone Joint Surg 1945;27:645.

- The accepted principle for muscle rehabilitation from injury prior to DeLormes classic research involved lowresistance, high-repetition exercises called endurancebuilding exercises. Examples include stationary cycling, stair climbing, and repetitively lifting light sandbags or weights with the aid of pulleys. The prevailing approach to restoring atrophied, weak, or neglected muscles relied on developing muscular endurance, not muscular strength and power. DeLorme challenged conventional wisdom by advocating heavy-resistance exercise. He reasoned that proportionality existed between the load resisting the muscle action and the rate and extent of muscle hypertrophy. DeLorme predicted that an inactive or injured persons strength would return to normal levels faster with heavier resistance exercise than lighter resistance exercise.

Based on observations of 300 patients, most of whom required lower-extremity rehabilitation, DeLorme developed a new training system named progressive resistance exercise (PRE). Within the PRE system, he introduced the concepts of one-repetition maximum (1-RM) strength and $10-\mathrm{RM}$ strength for (1) setting initial overload and adjusting increasing resistance, (2) establishing maximal sets and repetitions, and (3) applying the concept of muscle-training specificity. For muscle rehabilitation, DeLorme recommended that patients accumulate 70 to 100 repetitions of an exercise using 7 to 10 sets with a maximum of 10 repetitions per set. Initially, workouts began with a weight considerably lighter than the maximum weight lifted for 10 repetitions ( $10-\mathrm{RM}$ ) so subjects could complete $10-\mathrm{RM}$ in the final set. When the person achieved $10-\mathrm{RM}$, total repetitions equaled 70 to 100. For example, if $10-\mathrm{RM}$ for the first week equaled 20 pounds, then beginning the first set with 2.5 pounds and increasing 1.5 pounds after each 10 -repetition set accumulated 80 repetitions when performing the final 20-pound 10-RM.

DeLorme advocated exercising once daily, 5 days weekly, with workouts not exceeding 30 minutes. The patient performed one maximal lift (1-RM) only once each week. DeLorme believed that a person should exercise smoothly, rhythmically, and without haste, but not so slowly that the mere holding of the weight would tire the
patient. Sudden motions should be avoided, and a momentary pause at the end of each repetition was advocated. Weekly 1-RM measurement provided the basis for progressively adjusting the load to maintain the $10-\mathrm{RM}$ training level. The figure illustrates strength improvement in one patient undergoing rehabilitation from a femur fracture. After 36 days, note the $8 \%$ gain in thigh girth ( 1.8 in) and the 40 -pound ( $200 \%$ ) increase in quadriceps muscle strength.

The DeLorme paper represented the first in the modern strength-training literature to advocate the concept of training specificity. DeLorme argued that power-building and endurance exercises were two entirely different types, each one producing its own results, and each being incapable of producing the results obtained by the other. More than 65 years of subsequent research has validated the specificity concept for strength improvement, including almost every claim made by DeLorme about PREs beneficial effects.


Time course of 1-RM (yellow line) and changes in thigh girth (red line) for a representative subject during 35 days of progressive resistance exercise.
sets of exercises, each set consisting of 10 repetitions done consecutively without resting. The first set required one-half the maximum weight that could be lifted 10 times, or $1 / 2$ $10-\mathrm{RM}$; the second set used $3 / 410-\mathrm{RM}$, and the final $10-\mathrm{RM}$ required maximum weight. As patients trained, the muscles of the exercised limbs became stronger, so the 10-RM resistance increased periodically to maintain continued strength improvements. Similar improvements occurred even when reversing the exercise intensity progression so patients performed the 10RM as the first set.

Variations of PRE. The following summarizes 13 general findings from research studies on the optimal number of sets and repetitions, including frequency and relative intensity of PRE training for optimal strength improvement:

1. Eight- to $12-\mathrm{RM}$ proves effective in novice training, whereas 1 - to 12 -RM effectively loads for intermediate training. This can then increase to heavy loading using 1 - to $6-\mathrm{RM}$.
2. Rest 3 minutes between sets of an exercise at moderate movement velocity ( 1 to 2 s concentric; 1 to 2 s eccentric).
3. For PRE at a specific RM load, increase load 2 to $10 \%$ when the individual performs 1 to 2 repetitions above the current workload.
4. Performing one exercise set induces only slightly less strength improvement in recreational weight lifters than performing two or three sets. ${ }^{38,95}$ For those who desire to maximize muscle strength and size gains, higher volume, multiple-set paradigms emphasizing 6- to $12-\mathrm{RM}$ at moderate velocity with 1- to 2-minute rests between sets prove most effective.
5. Single-set programs generally produce most of the health and fitness benefits of multiple-set programs. These lower volume programs also produce greater compliance and reduce financial cost and time commitment.
6. Novices and intermediates should train 2 to 3 days a week, whereas the advanced can train 3 to 4 days a week. Such a generalization is not without a potential downside. High training frequency extends the transient activation of inflammatory signaling cascades, concomitant with persistent suppression of key mediators of anabolic responses, which could blunt the training response. ${ }^{45}$
7. Training twice every second day produces overall superior results compared with daily training. ${ }^{92}$ This may occur from the effects of low muscle glycogen content (with training twice every second day) on enhanced transcription of genes involved in training adaptations. ${ }^{229}$
8. If training includes multiple exercises, 4 or 5 days per week may produce less improvement than training 2 or 3 times per week because near-daily training of the same muscles impairs muscle recuperation
between training sessions. Inadequate recovery retards progress in neuromuscular and structural adaptations and strength development.
9. A fast rate of moving a given resistance generates more strength improvement than moving at a slower rate. Neither free weights (barbells, weight plates, dumbbells) nor an array of exercise machines shows inherent superiority for developing muscle strength.
10. Exercise should sequence to optimize workout quality by engaging large before small muscle groups, multiple-joint exercises before single-joint exercises, and higher intensity exercise before lower intensity exercise.
11. Combined resistance-training concentric and eccentric muscle actions augment effectiveness; include both single-joint and multiple-joint exercises to potentiate a muscles strength and fiber size. ${ }^{121,222,230,246}$
12. Overload training that includes eccentric muscle actions preserves strength gains better during a maintenance phase than concentric-only training. ${ }^{47}$
13. Power training should apply the strategy to improve muscular strength plus include lighter loads ( 30 to $60 \%$ of 1-RM) performed at fast contraction velocity. Use 2- to 3-minute rest periods between sets. Emphasize multiple-joint exercises that activate large muscle groups.

Table 22.2 summarizes the major recommendations of the American College of Sports Medicine position stand on progression in resistance training for healthy adults.

Periodization. In 1972, Russian scientist Leonid Matveyev introduced the concept of strength-training periodization; ${ }^{163}$ it has since become incorporated into the training regimens of novice and champion athletes involved in resistance training. ${ }^{32,120,137,139,208}$ Conceptually, periodization varies training intensity and volume to ensure that peak performance coincides with major competition. It also proves effective for achieving recreational and rehabilitative goals. Periodization subdivides a specific resistance-training period such as 1 year (macrocycle) into smaller periods or phases (mesocycles), with each mesocycle again separated into weekly microcycles. In essence, the training model progressively decreases training volume and increases intensity as duration of the program progresses to maximize gains in muscular strength and power. Fractionating the macrocycle into components allows manipulation of training intensity, volume, frequency, sets, repetitions, and rest periods (to prevent overtraining). It also provides a way to alter workout variety. Periodization variation can reduce negative overtraining or staleness effects so athletes achieve peak performance at competition. Figure 22.9 (top) depicts the generalized design for periodization and a typical macrocycles four distinct phases. As competition approaches, training volume


[^38]

Figure 22.9 Top. Periodization subdivides a macrocycle into distinct phases or mesocycles. These in turn separate into weekly microcycles. The general plan provides modifications, but mesocycles typically include four parts: (1) preparation phase, (2) first transition phase, (3) competition phase, and (4) a second transition or active recovery phase. Bottom. Example of periodization for an elite athlete (gymnast) preparing for competition. Competitions took place throughout the yearly training program so periodization focused on achieving peak performance at the end of each macrocycle. Periodization places training into context for intensity, duration, and frequency of strength power workouts. The major purpose of this focus attempts to avoid overtraining (staleness), minimize injury potential, and reduce training monotony, while progressing toward peak competition performance (filled circles).
gradually decreases while training intensity concurrently increases.

Preparation phase emphasizes modest strength development with high-volume ( 35 sets, 812 reps), low-intensity workouts ( 50 to 80\% 1-RM plus flexibility and aerobic and anaerobic training).
First transition phase emphasizes strength development with workouts of moderate volume (3 5 sets, 56 reps) and moderate intensity ( 80 to

90\% 1-RM plus flexibility and interval aerobic training).
Competition phase lets the participant peak for competition. Selective strength development is emphasized with low-volume, high-intensity workouts (3 5 sets, 24 reps at 90 to $95 \%$ 1-RM plus short periods of interval training that emphasize sportspecific exercises).
Second transition phase (active recovery) emphasizes recreational activities and low-intensity workouts
that incorporate different exercise modes. For the next competition, the athlete repeats the periodization cycle.

Periodization structures an inverse relation between training volume and training intensity through the competition phase; it then decreases both aspects during the second transition or recuperation period. Note the increase in time devoted to technique training as competition approaches, with training volume at the periodization cycles lowest point. The bottom part of Figure 22.9 shows how training volume and intensity interact within a mesocycle for an athlete in a specific sport.

Sport-specific training principles usually apply in periodization to design a training regimen based on a sports distinct strength, power, and endurance requirements. A detailed analysis of metabolic and technical requirements of the sport also frames the training paradigm. The concept of periodization makes intuitive sense, yet limited data exist for the superiority of this training approach. Periodized resistance training has produced greater improvements in upper- and lower-body muscular strength and sport-specific motor performance than a traditional resistance-training program in collegiate women tennis players. ${ }^{107}$

Researchers have studied shorter mesocycles to determine what combination of factors optimizes performance improvements. One study that equated training volume and intensity among three approaches to periodization (linear periodization, undulating periodization, and a nonperiodized time interval) found each training method equally effective. ${ }^{17}$ The training groups made similar gains in muscular strength ( $25 \%$ squat, $13.1 \%$ bench press) and muscular power ( $7.6 \%$ vertical jump). Without equating training volume and intensity, it is impossible to evaluate differences in training effects reported previously. ${ }^{276}$

A critical review of the few studies of periodized strength training concluded that this approach produced greater improvements in muscular strength, body mass, FFM, and percentage body fat than nonperiodized multiset and single-set training programs. ${ }^{75}$ Research must evaluate how periodization interacts with fitness status, age, gender, and specific sports (motor) performance. Studies must equate participants on various fitness parameters and then manipulate different training protocols, accounting for factors that affect training response. Program evaluation must consider the following four factors:

1. Biomechanical and motor control sequences in the targeted sport skill
2. Changes in segmental and whole-body composition
3. Biochemical and ultrastructural tissue adaptations
4. Transfer of newly acquired strength to subsequent sport performance measures

INTEGRATIVE QUESTION
Discuss the statement There is no one best system of resistance training.

## Resistance Training Guidelines for Sedentary Adults, the Elderly, and Cardiac Patients: Benefits in Health and Disease

Currently, the American College of Sports Medicine (www. acsm.org), American Heart Association (www.americanheart. org/), Centers for Disease Control and Prevention (www.cdc. gov/), American Association of Cardiovascular and Pulmonary Rehabilitation (www.aacvpr.org/), and the U.S. Surgeon Generals Office ( www.surgeongeneral.gov/) consider regular resistance exercise an important component of a comprehensive, health-related physical fitness program. ${ }^{3,10,76,201,255}$ Resistance training goals for competitive athletes focus on optimizing muscular strength, power, and hypertrophy (highintensity with $1-\mathrm{RM}$ to $6-\mathrm{RM}$ training loads). In contrast, goals for most middle-aged and older adults focus on maintenance (and possible increase) of muscle and bone mass and muscular strength and muscular endurance to enhance the overall health and physical-fitness profile. ${ }^{39,110,146,148}$ Adequate muscular strength in midlife maintains a margin of safety above the necessary threshold to prevent injury in later life. ${ }^{28}$ Among 45- to 68-year-old men, hand-grip strength accurately predicted functional limitations and disability 25 years later (Fig. 22.10). Men in the lowest one-third for grip strength showed the greatest risk; those in the middle one-third showed intermediate risk; and men in the top one-third experienced the least disability risk at the 25 -year follow-up. The resistancetraining program recommended for middle-aged and older men and women classifies as moderate intensity. In contrast to the multiple-set, heavy-resistance approach of younger athletes, the program uses single sets of diverse exercises performed between 8 - and $15-\mathrm{RM}$ a minimum of twice weekly. Table 22.3 presents guidelines from different groups and health organizations for prudent resistance training of older men and women and cardiac patients.

## Does Resistance Training Plus Aerobic Training Equal Less Strength Improvement?

Debate concerns whether concurrent resistance and aerobic training yields less muscular strength and power improvement than training for strength only. ${ }^{22,84,138,169}$ This has caused many strength and power athletes and bodybuilders to refrain from including endurance activities in the belief they diminish strength improvements. Advocates for abstaining from aerobic training when attempting to optimize gains in muscle size and strength maintain that the added energy (and perhaps protein) demands of intense endurance training limit a muscles growth and metabolic responsiveness to resistance training. Some data support this position. For example, different modes of exercise induce antagonistic molecular level, intracellular signaling mechanisms that could exert a negative impact on the muscles adaptive response to resistance training. ${ }^{179}$ For example, endurance exercise training may inhibit signaling to the muscles protein-synthesis machinery, which would definitely be counterproductive to the goals of resistance training. ${ }^{27,130,280}$


Grip strength tertiles $\square$ Highest $\square$ Middle $\square$ Lowest
Figure 22.10 Relationship between grip strength assessed in 3218 healthy middle-aged 45- to 68-year-old men and functional limitations and difficulties 25 years later. (From Rantanen T, et al. Midlife hand grip strength as a predictor of old age disability. JAMA 1999;281:558.)

A short-term bout of high-intensity endurance exercise also inhibits performance in subsequent muscular strength activities. ${ }^{152}$ Further research must determine whether this acute effect on maximal force output limits ability to overload skeletal muscle optimally to a degree that impairs strength development with concurrent strength and endurance training. If it does, then a 20 to 30 -minute recovery between aerobic and strength-training components might enhance the quality of subsequent strength workout. These considerations should not deter those who desire a well-rounded conditioning program that offers specific fitness and health benefits from incorporating both training modes. ${ }^{64,110}$

## Resistance Training for Children

Many textbooks in exercise physiology do not focus on the benefits and possible risks of resistance training for
preadolescents, largely because of limited data on the topic. Obvious concern arises regarding the potential for injury from excessive musculoskeletal loading (epiphyseal fractures, ruptured intervertebral disks, lower back bony disruptions, acute low back trauma). A childs hormonal profile also lacks full developmentparticularly the tissue-building hormone testosterone (refer to Chapter 20). One might question whether resistance training in children could even induce significant strength improvements.

Supervised resistance training using concentric-only muscle actions with relatively high repetitions and low resistance improves muscular strength of children and adolescents without adverse effect on bone, muscle, or connective tissue. ${ }^{69,197,274}$ More than likely, learning and enhanced neuromuscular activation rather than substantial increases in muscle size account for childrens relatively rapid strength

TABLE 22.3 Strength-Training Guidelines for Sedentary Adults, Elderly Persons, and Cardiac Patients

| Guideline | Sets | Repetitions ${ }^{\text {a }}$ | Number of Exercises | Frequency (Days/Week) |
| :---: | :---: | :---: | :---: | :---: |
| Healthy sedentary adults |  |  |  |  |
| 1990 ACSM Position Stand ${ }^{\text {b }}$ | 1 | 812 | $810^{c}$ | 2 |
| 1995 ACSM Guidelines ${ }^{\text {d }}$ | 1 | 812 | 810 | 2 |
| 1996 Surgeon Generals Report ${ }^{e}$ | 12 | 812 | 810 | 2 |
| Elderly persons |  |  |  |  |
| Pollock et al, ${ }^{f} 1994$ | 1 | 1015 | 810 | 2 |
| Cardiac patients |  |  |  |  |
| 1995 AHA Exercise Standards ${ }^{g}$ | 1 | 1015 | 810 | 23 |
| 1995 AACVPR Guidelines ${ }^{h}$ | 1 | 1015 | 810 | 23 |

From ACSM, American College of Sports Medicine; AHA, American Heart Association; AACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation.
${ }^{a}$ For healthy persons under age 50, weight should be sufficient to induce volitional fatigue with the number of repetitions listed. For older persons, lighter loads may be used.
${ }^{b}$ American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. Med Sci Sports Exerc 1990;22:265.
${ }^{c}$ Minimum one exercise per major muscle group (e.g., chest press, shoulder press, triceps extension, biceps curl, pull-down [upper back], lower back extension, abdominal crunch/curl-up, quadriceps extension, leg curls [hamstrings], calf-raise).
${ }^{d}$ American College of Sports Medicine. Guidelines for exercise testing and prescription. 5th ed. Baltimore: Williams \& Wilkins, 1995; also included lowrisk diseased populations.
${ }^{e}$ U.S. Department of Health and Human Services. Physical activity and health: a report of the surgeon general. Atlanta: US Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996.
${ }^{f}$ Pollock ML, et al. Exercise training and prescription for the elderly. South Med J 1994;87:S88.
${ }^{g}$ Fletcher GF, et al. Exercise standards: a statement for health care professionals from the American Heart Association. Circulation 1995;91:580.
${ }^{h}$ American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for Cardiac Rehabilitation Programs. 2nd ed. Champaign, IL: Human
Kinetics, 1995.

## IN A PRACTICAL SENSE

The Lower Back

In the developed world, musculoskeletal disorders are the most frequent causes of physical disability. As the aging global population increases, the prevalence of many musculoskeletal disorders will increase in both the developed and developing parts of the world with the likely result being an increase in the number of people with chronic disabling disorders. This will have a definite negative impact on healthcare provision and the economies of countries in the coming years.
The burden of musculoskeletal conditions at the start of the new millennium; WHO Technical Report Series 919 (World Health Organization, Geneva) 2003. 218 pages.

According to the Bone and Joint Decade Monitor Project and the World Health Organization (WHO) (www.ota.org/downloads/ bjdExecSum.pdf), the total costs in the United States related to musculoskeletal conditions exceeds $\$ 250$ billion yearly. Of this amount, direct costs account for $\$ 88.7$ billion. Thirty-eight percent was spent on hospital admissions, $21 \%$ on nursing home admissions, $17 \%$ on physician visits, and $5 \%$ on administrative costs. Indirect costs account for 58\% of the total ( $\$ 126.2$ billion), which include lost wages through morbidity or premature mortality. Musculoskeletal diseases include approximately 150 different diseases and syndromes typically associated with pain or inflammation. Back injuries account for one-fourth of all work-related injuries and one-third of all compensation costs, which, according to the Bureau of Labor Statistics (www.bls.gov/), cost the government
about $\$ 90$ billion yearly in related health costs. Most cases result from on-the-job injuries, particularly men in lumber and building retailing (highest risk) and construction (most cases); major-risk industries for women include nursing and personal care centers (highest risk) and hospitals (most cases). Grocery stores and agricultural crop production rank among the top 10 occupations for lower back injury for men and women. Estimates indicate that at least 32 million adult Americans frequently experience lower back pain, the primary cause for workplace disability. ${ }^{145}$ Workplace disability from injuries to the lower back region also occurs in common tasks like refuse collection and other manual handling and lifting tasks. ${ }^{\text {59,63,132 }}$

Muscular weakness, particularly in the abdominal and lower lumbar back regions, lumbar spine instability, and poor joint flexibility in the back and legs represent primary external factors related to low back pain syndrome. ${ }^{228}$

Prevention of and rehabilitation from chronic low back strain commonly use muscle-strengthening and joint-flexibility exercises. ${ }^{23,70,171,212,263}$ Continuing normal activities of daily living (within limits dictated by pain tolerance) yields more rapid recovery from acute back pain than bed rest. Maintaining normal physical activity facilitates greater recovery than specific back-mobilizing exercises performed after pain onset. ${ }^{161}$ Prudent use of resistance-type training isolates and strengthens the abdomen and lower lumbar

## IN A PRACTICAL SENSE

extensor muscles that support and protect the spine through its full range of motion. Patients with low back pain who strengthen the lumbar extensors with the pelvis stabilized experience less pain, fewer chronic symptoms, and improved muscular strength and endurance and range of motion. ${ }^{37}$

Weak Link Testing, or WLT, is a relatively new Norwegian methodology to assess low back/hip instability using a sling support system that features closed kinetic chain movements combined with manual vibration added to the slings (www.redcord.com). In the example illustrated below, the initial body position isolates the gluteus medius muscle whose function stabilizes hip flexion/ extension and inward and outward rotational movements. Golfers with poor initial hip rotation during the downward phase of the swing often exhibit poor hip and spinal rotation, primarily from weak (or deactivated) gluteus medius muscle action. Reactivating this key muscle with closed kinetic chain movements combined with vibration may help to alleviate the inefficient slide phase during the golf swing to restore effective hip rotation. Biomechanical analysis of the golf swing has provided insight into the rudiments of golf mechanics and injury incidence and disability in amateur and professional golfers. ${ }^{68,82,150,265,288}$

(Sling and rope photos courtesy of Frank Katch, Santa Barbara, CA, and Oyvind Pedersen, Redcord Clinic, Santa Barbara, Santa Barbara, CA.)

Improper performance of a typical resistance-exercise movement (with a relatively heavy load and the hips thrust forward with arched back) creates considerable compressive force on the lower spine. For example, pressing and curling exercises with back hyperextension create unusually high shearing stress on the lumbar vertebrae, often triggering low back pain accompanied by muscle instability in this region. ${ }^{14,97,102}$ Compressive forces with heavy lifting also can hasten damage to the disks that cushion the vertebrae. Performing half squats with barbell loads from 0.8 to 1.6 times body mass produces compressive loads on the L3 L4

## Continued

segment of the spine equivalent to 6 to 10 times body mass. ${ }^{36,43} \mathrm{~A}$ person who weighs 90 kg and squats with 144 kg can create peak compressive forces in excess of $1367 \mathrm{~kg}(13,334 \mathrm{~N})$ ! A sudden amplification of compressive force can precipitate anterior disk prolapse; a lower-intensity but sustained compressive force that produces fatigue can increase posterior bulging of the lamellas in the posterior annulus. ${ }^{6}$ In national-level male and female powerlifters, average compressive loads on L4 L5 reached 1757 kg $(17,192 \mathrm{~N}) .{ }^{173}$ At the practical level, during sports training with resistance methods (i.e., functional training with free weights), one should not sacrifice proper execution of an exercise to lift a heavier load or squeeze out additional repetitions. The extra weight lifted through improper technique does not facilitate muscle strengthening; instead, improper body alignment or unwarranted muscle substitution during force production can trigger debilitating injury where surgery unfortunately becomes the option of choice. This fact of life should encourage proper strengthening of そore abdominal and lower back muscles (with lower back and hip exercises, as those depicted on pages 509 510, to avoid either prolonged reliance on pain-relieving drugs or potentially debilitating surgical alternatives. Wearing a relatively stiff weightlifting belt during heavy lifts (squats, dead lifts, clean-and-jerk maneuvers) reduces intraabdominal pressure compared with lifting without a belt. ${ }^{42,81,93,144}$ The belt reduces potentially injurious compressive forces on spinal disks during near-maximal lifting, including most Olympic and powerlifting events and associated training. In one study, nine experienced weightlifters lifted barbells up to $75 \%$ body weight under three conditions: (1) while inhaling and wearing a belt, (2) inhaling and not wearing a belt, and (3) exhaling and wearing a belt. ${ }^{133}$ Measurements included intraabdominal pressure, trunk muscle EMG, ground reaction forces, and kinematics. The belt reduced compression forces by about 10\%, but only when inhaling before lifting. The authors concluded that wearing a tight and stiff-back belt while inhaling before lifting reduces spinal loading during the lift.

A person who normally trains wearing a belt should generally refrain from lifting without one. Further recommendations include performing at least some submaximal resistance training without a belt to strengthen the deep abdominal and pelvic stabilizing muscles. This also develops the proper pattern of muscle recruitment to generate high intraabdominal pressures when not wearing a belt. Wearing a back belt to increase intraabdominal pressure to ameliorate low back injuries in the workplace does not provide a clear-cut biomechanical advantage. ${ }^{198}$ A 2-year prospective study of nearly 14,000 material-handling employees in 30 states evaluated the effectiveness of using back belts to reduce back injury workers compensation claims and reports of low back pain. ${ }^{270}$ Neither frequent back belt use (usually once a day, once or twice a week) nor a store policy that required the use of these belts reduced injury or reports of low back pain. Researchers continue to probe for answers about the etiology of low back pain syndrome and how to minimize its severity and reduce its occurrence. ${ }^{125,214,221,275}$ Studies have focused on numerous contributing factors that include intradisk pressure; ${ }^{174}$ facet loads and disk fiber strains; ${ }^{223}$ lumbar disk height and cross-sectional area; ${ }^{182}$ compressive follower loads; ${ }^{196}$ spinal joint force distribution; ${ }^{41}$ ligament strain, disk shear, and facet impingement; ${ }^{78}$ and prediction models to estimate spinal compression and shear forces. ${ }^{88,128}$

The following 12 exercises provide general strengthening of the abdomen, pelvic region, and lower back, and improve hamstring and lower back flexibility for individuals with no apparent lower back and spinal injuries. Symptomatic individuals (including athletes) require specific back exercises. ${ }^{204,219}$

## IN A PRACTICAL SENSE

Continued
I. Lower back stretches (hold each exercise for 30 to 60 s)

1. Knees-to-chest stretch: Lie supine and pull the knees into the chest while keeping the lower back flat on the surface.

2. Cross-leg stretch: Cross the legs and pull one 90 -flexed knee toward the chest.

3. Hamstring stretch: Wrap a strap over the foot, keeping lower back flat; pull leg upward toward the head.

4. Allah stretch: Sit, buttocks on bilateral heels; move hands as far as possible forward along the surface.


## II. Abdominal exercises

5. Bent-knee sit-up: Keep hands low on neck (or across chest) with the head positioned over the shoulders. Roll up slowly, engaging one row of the abdominals at a time. Raise shoulders 4 to 6 inches off the surface.

6. Dying bug: Flex the pelvis to flatten lower back against the surface. Over one side bring an extended arm and flexed knee together. On opposing side, extend arm straight overhead and leg straight backward. Maintain pelvic flexion while exchanging opposing arms and legs in this position.


## IN A PRACTICAL SENSE

Continued

## III. Prone lumbar extension exercises

7. Dry-land swimming: Lying prone with pelvic flexion, alternately lift opposite arm and leg.

8. Both legs up: Lie prone with pelvic flexion, and lift both legs simultaneously while keeping the head on the floor.

9. Upper-body up: Lying prone with pelvic flexion and arms outstretched or behind the back, lift upper torso while keeping legs on the floor.

10. Pointer (bird dog): Start with hands and knees on the floor. Flex pelvis into a counter position. Exchange by pointing opposite arm and leg while keeping torso level.


## IV. Supine pelvic-flexion exercises

11. Leg pointer: Lie supine on the floor and flex pelvis with lower abdominals to flatten the lower back into the surface. Extend one arm upward and one leg outward while keeping quadriceps level.

12. Prone cobra push-up: Keep pelvis on the floor while pressing up with arms to produce lower back extension.


| TABLE 22.4 | Guidelines for Resistance-Exercise Training and Progression <br> in Children and Adolescents |
| :--- | :--- |
| Age (Y) | Considerations |
| 7 or younger | Introduce child to basic exercises with little or no weight; develop the concept of a training session; teach exercise <br> techniques; progress from body weight calisthenics, partner exercises, and lightly resisted exercises; keep volume <br> low. |
| 10 | Gradually increase the number of exercises; practice exercise technique in all lifts; start gradual progressive <br> loading of exercises; keep exercises simple; gradually increase training volume; carefully monitor toleration to the <br> exercise stress. <br> Teach all basic exercise techniques; continue progressive loading of each exercise; emphasize exercise techniques; <br> introduce more advanced exercises with little or no resistance. |
| 1413 | Progress to more advanced youth programs in resistance exercise; add sport-specific components; emphasize <br> exercise techniques; increase volume. |
| Move child to entry-level adult programs after all background knowledge has been mastered and a basic level of |  |
| training experience has been gained. |  |

From Kraemer WJ, Fleck SJ. Strength training for young athletes. Champaign, IL: Human Kinetics, 1993.
Note: If a child of any age begins a program without previous experience, start the child at lower levels and move to more advanced levels as exercise toleration, skill, amount of training time, and understanding permit.
improvements. ${ }^{193}$ The guidelines in Table 22.4 provide prudent recommendations for initiating resistance exercise training for children and adolescents.

## Isometric Strength Training

Research in Germany during the mid-1950s showed that isometric strength increased about 5\% weekly by performing a daily single, maximum isometric muscle action of only 1 -second duration, or a 6 -second action at two-thirds maximum. ${ }^{104}$ Repeating this action 5 to 10 times daily produced greater gains in isometric strength.

## Isometric Exercise Limitations

Isometric exercise provides muscle overload and improves strength yet offers limited benefits for functional sports training. Without movement, one cannot readily evaluate the overload level and/or training progress. Also, a high degree of specificity affects isometric strength development. A muscle trained isometrically clearly improves strength primarily when the muscle acts isometrically, particularly at the training joint angle and body position. This means that isometric training to develop strengths for a particular movement probably necessitates training at many specific angles through the ROM. This becomes time consuming, particularly given the availability of conventional dynamic weight training and isokinetic and other functional resistance training methodologies.

## Isometric Exercise Benefits

The isometric method benefits muscle testing and rehabilitation. Isometric techniques can detect specific muscle
weakness at a particular angle in the ROM, thus forming a basis for optimizing muscle overload at an appropriate joint angle.

## Which Are Better: Static or Dynamic Methods?

Static and dynamic resistance training methods each increase muscle strengths. An individuals specific needs determine the optimal resistance training method governed by the specificity of the training response. ${ }^{177,287}$

## Specificity of Training Response

An isometrically trained muscle shows greatest strength improvement when measured isometrically; similarly, a dynamically trained muscle tests best when evaluated in resistance activities that require movement. Isometric strength developed at or near one joint angle does not readily transfer to other angles or body positions that must rely on the same muscles. ${ }^{272}$ In dynamic exercise, muscles trained through movement over a limited ROM show the greatest strength improvement when measured in that ROM. ${ }^{20,86}$ Even body position specificity exists; muscular strength of ankle plantar and dorsiflexors developed in the standing position with concentric and eccentric muscle actions showed no transfer with the same muscles evaluated in the supine position. ${ }^{202}$ Resistance training specificity makes sense because strength improvement blends adaptations in two factors:

1. The muscle fiber and connective tissue harness itself
2. Neural organization and excitability of motor units that power discrete patterns of voluntary movement ${ }^{155,181,203,233}$

Likewise, a muscles maximal force output depends on neural factors that effectively recruit and synchronize firing of motor units, not just local factors such as muscle fiber type and cross-sectional area. ${ }^{48,129,226}$

A 3-month study of young adult men and women emphasized the highly specific nature of resistance-training adaptations. ${ }^{65}$ One group trained the adductor pollicis muscle isometrically with 10 daily actions of 5 -seconds duration at a frequency of 1 per minute. The other group trained the same muscle dynamically with 10 daily 10 -repetition bouts of weight movement at one-third maximal strength. The untrained muscle served as the control. To eliminate any training influence from psychologic factors and central nervous system adaptations, a supermaximal electrical stimulation applied to the motor nerve evaluated the force capacity of the trained muscle. The results were clearbeth training groups improved maximal force capacity and peak rate of force development. The improvement in maximal force for the isometrically trained group nearly doubled the improvement for the dynamically trained group. Conversely, improvement in speed of force development averaged about $70 \%$ greater in the group trained with dynamic muscle actions. Such findings provide strong evidence that resistance training per se does not induce all-inclusive (general) adaptations in muscle structure and function. Rather, a muscles contractile properties (maximal force, velocity of shortening, rate of tension development) improve in a manner highly specific to the muscle action in training. Both static and dynamic training methods produce strength increases, yet no one system rates consistently superior to the other in how best to assess muscle function. The crucial consideration concerns the intended purpose of the newly acquired strength.

Practical Implications. The complex interaction between nervous and muscular systems helps explain why leg muscles strengthened in squats or deep knee bends fail to show equivalent improved force capability in other leg movements such as jumping or leg extension. ${ }^{183}$ Low relationships emerge between dynamic measures of leg extension force at any speed and vertical jumping height. A muscle group strengthened and enlarged by dynamic resistance training does not demonstrate equal improvement in force capacity when measured isometrically or isokinetically. ${ }^{226}$ Consequently, strengthening muscles for a specific athletic or occupational activity (e.g., golf, tennis, rowing, swimming, football, firefighting, package handling) demands more than just identifying and overloading the muscles in the movement. It requires neuromuscular training specifically in the important movements that necessitate improved strength. A more appropriate name for this type of training is functional strength training or functional resistance movement training. ${ }^{7,9,46,237}$ Increasing leg muscle strength through general weightlifting will not necessarily improve performance in a variety of subsequent leg movements. ${ }^{168}$ Newly acquired strength seldom transfers fully to other types of strength movements, even those that activate the same trained muscles. A standard program of weight training for leg extension increased leg extension strength by $227 \%$.

Evaluating leg extension peak torque of the same leg with an isokinetic dynamometer detected only a 10 to $17 \%$ improvement! ${ }^{59,77}$ To improve a specific physical performance through resistance training, one must train the muscle(s) in movements that mimic the movement requiring force capacity improvement, with focus on force, velocity, and power requirements rather than simply an isolated joint or muscle.

## Physical Testing in the Occupational Setting: The Role of Specificity

A comprehensive review outlines the development of physical tests and professionally and legally defensible validation strategies for preemployment occupational testing requiring diverse physical abilities or specific fitness characteristics. ${ }^{122}$ The high specificity of components of physical performance and physiologic function (e.g., muscular strength and power, joint flexibility, aerobic fitness) combined with the specific nature of the training response casts serious doubt that broad constructs of physical fitness exist to any important extent. Clearly, no single measure of overall muscular strength or aerobic fitness exists. Instead, an individual expresses an array of muscular strengths and powers and aerobic fitnesses. These expressions of muscle function and exercise performance often relate poorly to each other if at all. Likewise, testing a person for aerobic fitness produces different fitness scores depending on the activity. For example, it would be undesirable to administer the 12-minute run test (a test that purports to assess aerobic capacity; refer to Chapter 21) in the occupational setting to infer aerobic capacity for firefighting or lumbering (both requiring considerable upper-body aerobic function), or measuring static-grip or leg strength with tests to assess diverse dynamic strengths and powers required in these occupations.

Measurements applied in the occupational setting should closely resemble the actual requirements of the job (i.e., functional tests), not only for specific tasks but also in a manner that reflects the intensity, duration, and pace (i.e., physiologic demands) of the job. If such content testing remains impractical, one must substantiate alternative testing based on carefully conducted validation studies.

## INTEGRATIVE QUESTION

Advise a candidate for a firefighters job about the most effective way to train for a physical test that requires 7 minutes of a series of job-related tasks (e.g., stair climb with equipment, hose drag, ladder raise, forcible entry with sledge hammer, simulated rescue dummy drag).

## Isokinetic Resistance Training

Isokinetic resistance training combines the positive features of isometric exercise and dynamic weightlifting. It provides
muscle overload at a preset constant speed while the muscle mobilizes its force-generating capacity throughout the full ROM. ${ }^{213}$ Any effort during the exercise movement encounters an opposing force to that applied to the mechanical device; this represents accommodating-resistance exercise. Theoretically, isokinetic-type training activates the largest number of motor units to overload muscles consistentlyeven at the relatively weaker joint anglesas the bone muscle lever mechanics produce variations in force capacity throughout the ROM. Maintaining a constant movement speed remains a negative aspect of isokinetic resistance training because functional exercises rarely approximate a fixed speed of movement.

## Isokinetics Versus Standard Weightlifting

An important distinction exists between a muscle overloaded isokinetically and one overloaded with a standard weightlifting exercise. Figure 22.11 shows that the force capacity of a muscle (or muscle group) varies with the bony lever configuration (joint angle) as the joint moves through its ROM. During weight training, the external weight lifted usually remains fixed at the greatest load that allows completion of the movement for the desired number of repetitions. Resistance cannot exceed the maximum force generated at the weakest point in the ROM. If it did not, then one could not complete the movement. The term sticking point describes this area in the ROM.


Figure 22.11 Muscle force-generating capacity varies with joint angle in flexion and extension throughout the ROM.

The fact that muscles do not generate the same absolute maximum force through all movement phases represents a major limitation of weightlifting. To help alleviate this problem, manufacturers have devised variable-resistance training equipment that adjusts resistance with the generalized lever characteristics of a particular joint movement. This equipment still represents a classic mode of weightlifting except the relative resistance offered to the muscle theoretically remains fairly constant with respect to muscle capacity at a particular shortening velocity throughout the ROM. With an isokinetically loaded muscle, the desired movement speed occurs almost instantaneously with maximum force application, and the muscle generates peak power output throughout the ROM at a controlled shortening velocity.

## Isokinetic Exercise and Training Experiments

Experiments with isokinetic exercise have explored the force velocity patterns in various movements related to muscle fiber type composition. Figure 22.12 shows the progressive decline in peak torque output with increasing angular velocity of knee extensor muscles in two groups who differed in sports training and predominant muscle fiber type. For movement at $180 \cdot \mathrm{~s}^{1}$, maximal torque decrement averaged about $55 \%$ of maximal isometric ( $0 \cdot \mathrm{~s}^{1}$ ) force. The two curves in Figure 22.12 differ in peak torque depending on the groups muscle fiber composition. Peak force at zero velocity (isometric force) remained similar for athletes with relatively high (power athletes) or low (endurance athletes) percentages of fast-twitch muscle fibers; this indicated activation of both fast- and slow-twitch motor units in maximal isometric knee extension. As movement velocity increased, individuals with


## $\square$ Power athletes $>60 \%$ FT $\square$ Endurance athletes $<50 \%$ FT

Figure 22.12 Peak torque (per unit body mass) related to angular velocity of joint movement in two groups of athletes with different predominance of muscle-fiber type. The torque velocity curves were extrapolated (dashed line) to the approximated maximal velocity for knee extension. (From Thorstensson A. Muscle strength, fiber types, and enzyme activities in man. Acta Physiol Scand Suppl 1976:443.)
higher percentages of fast-twitch fibers exerted greater torque per unit body mass. This indicates the desirability of possessing a high percentage of fast-twitch fibers for power activities, where success largely depends on capacity to generate torque at rapid movement velocities.

## Fast- Versus Slow-Speed Isokinetic Training

Studies of strength and power improvement with isokinetic training at slow and fast limb speeds further support the specificity of exercise performance and training response. For example, strength and power gains from slow-speed isokinetic training relate specifically to the angular velocity of the movement in training. In contrast, exercising at fast speeds facilitates more general improvement; power output increased at fast and slow movement speeds, although measurement at the fast angular velocity in training improved the most. ${ }^{199}$ Muscle hypertrophy generally occurs from fast-speed training and mainly in the fast-contracting muscle fibers. ${ }^{50}$ Muscle fiber hypertrophy may account for the more general strength improvement with fast-speed training. Concentric muscle actions produce greater power increases and type II fiber hypertrophy from training than eccentric training at equivalent relative power levels. ${ }^{165}$

The attractiveness of isokinetic training allows muscular overload through a full ROM at many shortening velocities. Applications remain limited, however, because the most rapid speed of movement of the current isokinetic dynamometers approximates $400 \cdot \mathrm{~s}^{-1}$. Even this relatively fast movement speed does not approach limb speeds during sports activities. In baseball pitching, where upper-limb extension velocity exceeds $2000 \cdot \mathrm{~s}^{-1}$ in professional pitchers, even the relatively slow hip rotators move at $600 \cdot \mathrm{~s}^{-1}$ during a pitch. ${ }^{35}$ Also, the present generation of isokinetic dynamometers cannot simultaneously overload eccentric muscle actions that serve important functions in limb deceleration and braking control in normal movements.

## Plyometric Training

For sports that require powerful, propulsive movementsfootball, volleyball, sprinting, high jump, long jump, and basketballathletes apply a special form of exercise training termed plyometrics or explosive jump training. ${ }^{74,253,279}$ Plyometric exercise requires various jumps in place or rebound jumping (drop jumping from a preset height) to mobilize the inherent stretch recoil characteristics of skeletal muscle and its modulation via the stretch or myotatic reflex. Stated somewhat differently, plyometric exercise involves rapid stretching followed by shortening of a muscle group during a dynamic movement. Stretching produces a stretch reflex and elastic recoil within muscle. When combined with a vigorous muscle contraction, plyometric actions should greatly increase the force that overloads the muscles, thereby facilitating increases in strength and power. ${ }^{278}$ Plyometric exercises range in difficulty from calf jumps off the ground to multiple one-leg jumps to and from boxes ranging in height


## Bench throw $\square$ Bench press

Figure 22.13 Mean bar velocity in relation to total concentric bar movement for bench throw and traditional bench press performed rapidly. (Data from Newton RU, et al. Kinematics, kinetics, and muscle activation during explosive upper-body movements. J Appl Biomech 1996;12:31.)
from one foot to six feet. The basic principle for all jumping and plyometric exercises is to absorb the shock with the arms or legs and then immediately contract the muscles. For example, when doing a series of squat jumps, jump again as quickly into the air as possible after you land, while at the same time if possible, thrusting both heels up towards the buttocks. Quicker jumps provide greater overload to the muscles. In essence, fast plyometric exercise trains the nervous system to react quickly to activate muscles rapidly.

Plyometric maneuvers avoid the disadvantage of having to decelerate a mass in the latter part of the joint ROM during a fast movement; this provides for maximal power production. Figure 22.13 compares a traditional bench press movement to achieve maximal power output with a ballistic bench throw that attempts to maximize power output by projecting the barbell from the hands. The results were unequivocal. During a bench press, deceleration begins at about $60 \%$ of the bar position relative to the total concentric movement distance (purple line). In contrast, velocity during the bench throw (yellow line) continues to increase throughout the ROM and remains higher at all bar positions after movement begins. This translates into greater average force, average power, and peak power outputs. Achieving a faster average and peak velocity throughout the ROM produces greater power output and muscle activation (assessed by EMG) than the traditional weightlifting exercise movement. The throw condition produced greater muscle activity for the pectoralis major $(+19 \%)$, anterior deltoid $(+34 \%)$, triceps brachii $(+44 \%)$, and biceps brachii ( $+27 \%$ ).

Allowing the athlete to develop greater power at the end of the movement more closely simulates the projection phase of throwing an object (ball or implement), maximal effort jumping movements, or impact in striking movements. In this
form of training, called ballistic resistance training, the person moves the weight or projectile as fast as possible while trying to produce maximal force before releasing it. Sports performance examples include shot put, overhead soccer throw, javelin and discuss throws, push away from the pole vigorously in the pole vault, takeoff jump for a volleyball spike, positioning and jumping for a basketball rebound, multiple punches in boxing, and takeoff in the high jump.

Plyometric exercise overloads a muscle to provide forcible and rapid stretch (eccentric or stretch phase) immediately before the concentric or shortening phase of action. Recent reviews summarize that the stretch-shortening cycle, or SSC, represents an important concept that describes how skeletal muscles function efficiently in unrestricted human locomotor activities. When the muscle spindles of the gastrocnemius muscle suddenly become stretched, their sensory receptors fire with the impulses traveling through the dorsal root into the spinal cord (to activate the anterior motor neurons) and trigger the stretch reflex (see Chapter 19), the timing of which relies on the speed of movement. ${ }^{53,117,118,135}$ The sequence of stretching and shortening muscle fibers (as in the contact phase of running) serves a fundamental purposeto-enhance the final push-off phase. In many sports situations, the rapid lengthening phase in the SSC produces a more powerful subsequent movement from two main factors. ${ }^{52,116,151,154,176,206,249}$

1. Attainment of a higher active muscle state (greater potential energy) before the concentric, shortening action
2. Stretch-induced evoking of segmental reflexes that potentiate subsequent muscle activation

These two effects form the basis for the speed power benefits of this training mode. ${ }^{268,281}$ More than likely, improvement occurs from changes in the mechanical properties of the muscle-tendon complex rather than changes in muscle activation strategies. ${ }^{142}$ Figure 22.14 shows the sledge ergometer to (1) quantify force-generating capacity when affected by the stretch-shortening cycle, (2) train under such conditions, and (3) evaluate stretch reflex sensitivity and muscle stiffness under fatiguing exercise.

## Practical Application of Plyometrics

A plyometric drill uses body mass and gravity for the important rapid prestretch, or cocking, phase of the SCC to activate the muscles natural elastic recoil elements. ${ }^{54,114,186}$ Prior stretch augments the subsequent concentric muscle action in the opposite direction. Forcibly dropping the arms to the side before vertical jumping produces an eccentric prestretch of the quadriceps muscle group and exemplifies a natural plyometric movement. Lower-body plyometric drills include a standing jump, multiple jumps, repetitive jumping in place, depth jumps or drop jumping from a height of about 1 m , single- and dou-ble-leg jumps, and various modifications. Proponents believe that repetitive plyometric actions serve as neuromuscular training to enhance power output of specific muscles and sportspecific power performances as in jumping. ${ }^{100,143,170,285}$


Figure 22.14 The sledge ergometer for plyometric (stretch-shortening cycle) exercise, training, and research protocols. Illustration shows braking phase (and subsequent muscle stretch) just prior to maximal activation of leg and foot extensor muscles. (Modified from Strojnik V, Komi PV. Fatigue after submaximal intensive stretch-shortening cycle exercise. Med Sci Sports Exerc 2000;32:1314.)

Although testimonials tout the benefits of plyometric training, there is insufficient controlled evaluation of both benefits and possible orthopedic risks of such workouts. Concern for musculoskeletal injury stems partly from the estimation that drop jumping generates external skeletal loads equal to up to 10 times body mass. Research must quantify the appropriate role of plyometric drills in a complete strength power training program, particularly for children and older recreational athletes. A position paper from the National Strength and Conditioning Association (www.nscalift.org/) suggests that athletes first achieve lifts of 1.5 times body weight in the squat exercise before initiating highintensity plyometric training. ${ }^{278}$ This practical guideline requires validation. Figure 22.15 shows the rebound jumping technique in plyometric training along with four examples of plyometric exercise drills.

## Body Weight-Loaded Training

Body weight-loaded training using closed-kinetic chain exercise to enhance sports performance ${ }^{15,26,62,157,194}$ has gained popularity and research support, including such training in job-related functions ${ }^{156}$ and treatment of pelvic pain following pregnancy. ${ }^{239,240}$

In weight-supported exercises (Fig. 22.16), the distal segment bears the body weight or part of the body weight. This type of exercise activates both agonists and antagonists muscles about a joint, including other muscle groups along the kinetic chain. ${ }^{234}$ Such training is often considered more functional compared to exercises where the distal segment is non weight bearing as in conventional weightlifting (where agonists and synergists are activated). In addition, body weight-loaded exercise, as employed with the sling-system apparatus (Fig. 22.16), introduces the added component of instability, further challenging neuromuscular control of the trunk and back muscles. ${ }^{235,241,242,251,254}$ The role of adding such perturbation during relatively simple and/or complex
movements may play a key role in training the sophisticated signaling patterns involved in neuromuscular control of human movements. $15,26,62,71,162,194,250,252$

Recent studies using body weight supported movements in the sling and rope system during functional performance training for soccer, ${ }^{238}$ golf, ${ }^{218}$ handball, ${ }^{217}$ and softball ${ }^{219}$ show improvements in functional sport movements that range from 3 to $5 \%$ in velocity of limb movement, increased golf club head velocity and hence distance, and static and dynamic balance and shoulder stabilization. Future research should assess the effectiveness of the rope and sling methods versus conventional free weights, machines, and other resistance training modalities to improve functional strength and subsequent performance in sport and rehabilitative modalities. ${ }^{264}$

## Concept of the Core

The last 10 years have seen a resurgence of core trainingalso referred to as lumbar stabilization, core strengthening, dynamic stabilization, neutral spine control, trunk stabilization, abdominal strength, core pillar training, and corefunctional strength training.

The core concept does not simply refer to muscles that cross the midsection of the body and form the six-pack abdominals so commonly portrayed in magazine advertisements. Rather, consider the core as a four-sided muscular frame with abdominal muscles in front, paraspinals and gluteals in back, the diaphragm at the top, and the pelvic floor and hip girdle musculature framing the bottom. This region includes 29 pairs of muscles that hold the trunk steady, and balance and stabilize the bony structures of the spine, pelvis, thorax, and other kinetic chain structures activated during most movements. ${ }^{87}$ The totality of these spine-frame structures without adequate s trength and balance would become mechanically unstable. ${ }^{190,192,195}$ A properly functioning core provides appropriate distribution of forces, optimal control and efficiency of movements, adequate absorption of ground-im-

## Rebound Jumping Technique in Polymetric Training



Figure 22.15 A. Rebound jumping technique in plyometric training. B. Four examples of plyometric exercise drills: (1) Box jump. (2) Cone hop. (3) Hurdle hop. (4) Long jump from box. (Examples of plyometric jumps courtesy of Dr. Thomas D. Fahey, California State University at Chico, Chico, CA.)
pact forces, and an absence of excessive compressive, translation, and shearing forces on kinetic chain joints. ${ }^{127,172}$

## Window for Explosive Power Development

Figure 22.17 lists five components that contribute to the window of explosive power development. In this model,
each component makes important neuromuscular contributions to maximal power training. The window of adaptation opportunity shrinks for an athlete with already welldeveloped components and expands for components in need of considerable improvement. As an athlete approaches his or her high-velocity strength potential, that components contribution to overall maximal power development diminishes.


Figure 22.16 Example of a push-up exercise using the Norwegian sling-system apparatus; the individual performs the down and up phases of the push-up movement while countering instability of the dual suspended ropes for the arms and legs. The idea is to maintain stability and balance during the push-up, similar to a conventional push-up with the hands and/or feet supported on a solid surface. (Photo courtesy of Redcord, Kilsund, Norway.)


Figure 22.17 Five components that contribute to explosive power development. Adapted with permission from Dr. William J. Kraemer, Human Performance Laboratory, University of Connecticut. Storrrs, CT. (From Kraemer WJ, Newton RU. Training for muscular power. Phys Med Rehabil Clin 2000;11:341.)

Athletes must focus on training their least-developed components. Stated somewhat differently, maximal power performance improves more readily when targeting specific training routines to improve the weakest links because these have the largest adaptation window to develop explosive power.

## Summary

1. Tensiometry, dynamometry, 1-RM testing with weights, and computer-assisted force and workoutput determinations including isokinetic-type measurements provide the most common methods to measure muscular performance.
2. Human skeletal muscle generates a maximum force of about 30 N per $\mathrm{cm}^{2}$ of muscle cross section, regardless of gender. On an absolute basis, men generally exert greater maximal force than women.
3. The traditional method to evaluate gender differences in muscle strength creates a ratio score for strength (i.e., strength per unit body mass, FFM, limb volume, and girth). When considering measures of body size and/or composition in this manner, the large strength differences between men and women decrease considerably.
4. Allometric scaling offers another method to compare physiologic variables among individuals.
5. Optimal overload training to strengthen muscles involves three factors: (1) increasing resistance (load) to muscle action, (2) increasing speed of muscle action, or (3) combining increased load and speed.
6. An overload between 60 and $80 \%$ of a muscles force-generating capacity induces strength gains.
7. Three major strength-training systems include progressive resistance weight training, isometrics, and isokinetic training. Each produces strength gains highly specific to the type of training. Isokinetic training offers potential to generate maximum force throughout the full ROM at different angular velocities of limb movement.
8. Closely supervised resistance training programs that use relatively moderate concentric muscle actions improve childrens strength without adverse effects on bone, muscle, or connective tissue.
9. Periodization divides a distinct period or macrocycle of resistance training into smaller training mesocycles; these subdivide into weekly microcycles. Compartmentalization of training minimizes staleness and overtraining effects to maximize peak performance that coincides with competition.
10. Resistance training for competitive athletes optimizes muscular strength, power, and hypertrophy. Training goals for middle-aged and older adults aim to modestly improve muscular strength and endurance, maintain muscle and bone mass, and enhance overall health and fitness.
11. Concurrent training for muscular strength and aerobic capacity inhibits the magnitude of strength improvement compared with training only for muscular strength.
12. Plyometric training emphasizes the inherent stretch recoil characteristics of the neuromuscular system to facilitate muscle power development.
13. Specificity of physiologic and performance measures and their response to training casts doubt on the efficacy of general fitness measures to predict ability to perform specific tasks or occupations.
14. Functional movement training via body weight supported exercise offers a unique approach to sports training.
15. Core training remains an integral part of sports training and physical conditioning to improve muscular balance, muscular strength, and trunk stabilization.

## Part 2 STRUCTURAL AND FUNCTIONAL ADAPTATIONS TO RESISTANCE TRAINING

Muscle tissues exist in a dynamic state where proteins are alternately synthesized (net deposition of amino acids) and degraded (net release of amino acids). Figure 22.18 lists six factors that develop and maintain muscle mass. Without a doubt, genetic factors provide the governing frame of reference that modulates each of the other factors that increase muscle mass and strength. ${ }^{207}$ Muscular activity contributes little to tissue growth without appropriate nutrition, particularly amino acid availability, to provide essential building blocks. Similarly, specific hormones (e.g., testosterone, growth hormone, cortisol, and, most importantly, insulin and systemic and local insulin-like growth factors) and nervous system innervation help to pattern and reinforce the appropriate training response. Without tension overload, each of the other factors cannot effectively produce the desired training response.

## FACTORS THAT MODIFY THE EXPRESSION OF HUMAN STRENGTH

Figure 22.19 shows that factors broadly characterized as psychologic (neural) and muscular influence the expression of human strength. A resistance-training program modifies many components of these factors; other factors remain training resistant, probably determined by natural endowment or established early in life.

## Neural Adaptations with Resistance Training that Increase Muscular Strength

1. Greater efficiency in neural recruitment patterns
2. Increased motor neuron excitability
3. Increased central nervous system activation
4. Improved motor unit synchronization and increased firing rates
5. Lowering of neural inhibitory reflexes
6. Inhibition of Golgi tendon organs

## Psychologic Neural Factors

Adaptive alterations in nervous system function that elevate motor neuron output largely account for the rapid and large strength increases early in training, often without an increase in muscle size and cross-sectional area. ${ }^{1,211}$ Neural adaptations play a particularly important role in the dramatic muscular strength and power improvements of the elderly with resistance training. ${ }^{90}$ Figure 22.20 shows the generalized resistance training response for neural facilitation and muscle hypertrophy.

Research has considered the effects of exercise training on structural changes associated with the neuromuscular junction (NMJ). In one study with rats, endurance training

Figure 22.18 Interaction of six factors that develops and maintains muscle mass.


Figure 22.19 Relative roles of neural and muscular adaptations in strength improvement with resistance training. Note that neural adaptations predominate in the early phase of training (this phase encompasses the duration of most research studies). Hypertrophy-induced adaptations place the upper limit on longer term training improvements. This tempts many athletes to use anabolic steroids and/or human growth hormone (dashed line) to induce continual hypertrophy if training alone fails. (From Sale DG. Neural adaptation to resistance training. Med Sci Sports Exerc 1988;20:135.)
improved the ratio of nerve terminal area to muscle fiber size by reducing fiber diameter without altering nerve terminal size. ${ }^{266}$ In humans, high- and low-intensity training differentially affected the size of the NMJ. ${ }^{61}$ Less intense, prolonged workouts produced a more expansive NMJ area, whereas intense exercise produced greater dispersion of synapses.

A unique series of classic experiments illustrates the importance of psychologic factors in expressing muscular strength in humans. ${ }^{113}$ The researchers measured arm strength in college-aged men under (1) normal conditions, (2) immediately after a loud noise, (3) while the subject screamed loudly at the time of exertion, (4) under the influence of alcohol and amphetamines (pep pills), (5) and under hypnosis (told they possessed considerable strength and should not fear injury). Each of the alterations generally increased strength above normal levels; hypnosis, the most mental of all treatments, produced the greatest increments.

The investigators theorized that temporary modifications in central nervous system function accounted for strength improvements under the various experimental treatments. They argued that most persons normally operate at a level of neural inhibition, perhaps via protective reflex mechanisms that constrain the expression of strength capacity. Three factors,
muscle cross section, fiber type, and mechanical arrangement of bone and muscle, explain strength capacity. Neuromuscular inhibition can come from unpleasant past experiences with exercise, an overly protective home environment, or fear of injury. Regardless of the reason, the person usually cannot express maximum strength capacity. The excitement of intense competition or influence of disinhibitory drugs or hypnotic suggestion often induces a supermaximal performance from greatly reduced neural inhibition and optimal motor neuron recruitment.

Highly trained athletes often create an almost selfhypnotic state by intensely concentrating, or psyching, before competition. It sometimes takes years of training to perfect the block out of extraneous stimuli (e.g., crowd noise) so the muscle action relates directly to the performance. This practice has been perfected in powerlifting competition where success depends on precise, coordinated movements with maximal muscle tension output. Enhanced arousal level and accompanying neural disinhibition (or facilitation) fully activate muscle groups. Increased neurologic arousal also may account for unexplainable feats of strength and power during highly charged emergency and rescue situations (e.g., a relatively small person lifting an extremely heavy object off an injured person).


Figure 22.20 Generalized response curve for gains in muscle strength with resistance training from neural (orange) or muscular (yellow) factors. During a typical 8-week training period, neural factors account for approximately $90 \%$ of the strength gained over the first 2 weeks. In the subsequent 2 weeks, between 40 and $50 \%$ of the strength improvement still relates to nervous system adaptation. Thereafter, muscle fiber adaptations become progressively more important to strength improvement. Experiments of this type generally evaluate neural factors from integrated EMG recordings of the muscle groups trained.

## Muscular Factors

Psychologic disinhibition and learning factors greatly modify muscle strength in the early phase of training. Ultimately, anatomic and physiologic factors within the joint muscle unit determine strength capacity. Table 22.5 lists the physiologic and performance changes associated with long-term resistance training. Most of these components adapt to training, with some modifications occurring within several weeks. Resistance trainings effects on muscle fibers generally relate to adaptations in the contractile structures; these usually accompany substantial increases in muscular force and power through a given ROM.

## Muscle Hypertrophy

An increase in muscular tension (force) with exercise training provides the primary stimulus to initiate the process of skeletal muscle growth or hypertrophy. Changes in muscle size become detectable after only three weeks of training, and the remodeling of muscle architecture precedes gains in muscle

TABLE 22.5 Physiologic Adaptations to Resistance Training

| System/Variable | Response |
| :--- | :--- |
| Muscle fibers |  |
| Number | Equivocal |
| Size | Increase |
| Type | Unknown |
| Strength | Increase |
| Capillary density | No change |
| In bodybuilders | Decrease |
| In power lifters |  |
| Mitochondria | Decrease |
| Volume | Decrease |
| Density | Decrease |
| Twitch contraction time |  |
| Enzymes | Increase |
| Creatine phosphokinase | Increase |
| Myokinase |  |
| Enzymes of glycolysis | Increase |
| Phosphofructokinase | No change |
| Lactate dehydrogenase |  |
| Aerobic metabolism enzymes | Increase |
| Carbohydrate | Not known |
| Triglyceride | Increase |
| Basal metabolism |  |
| Intramuscular fuel stores | Increase |
| Adenosine triphosphate | Increase |
| Phosphocreatine | Increase |
| Glycogen | Not known |
| Triglycerides |  |
| vo | Increase |
| Circuit resistance training | No change |
| Heavy resistance training |  |
| Connective tissue | Increase |
| Ligament strength | Increase |
| Tendon strength | No change |
| Collagen content of muscle | Decrease |
| Body composition | Increase |
| Percent body fat |  |
| Lean body mass |  |
| Bone |  |
| Mineral content and density |  |
| Cross-sectional area |  |

Modified from Fleck SJ, Kraemer WJ. Resistance training: physiological responses and adaptations (part 2 of 4). Phys Sportsmed 1988;16:108.
cross-sectional area. Two fundamental adaptations necessary for muscle hypertrophy (increased protein synthesis and satellite cell proliferation) are mobilized from the initial phases of resistance training. ${ }^{220,286}$ Mechanical stress on components of the muscular system triggers signaling proteins to activate genes that activate translation of messenger RNA and stimulate protein synthesis in excess of protein breakdown. Accelerated protein synthesis, particularly when combined with the effects of insulin and adequate amino acid availability, increases muscle size during resistance training. ${ }^{131}$ Muscle hypertrophy reflects a fundamental biologic adaptation to increased workload independent of gender and age.

As mentioned previously, improving muscular strength and power does not necessarily require muscle fiber hypertrophy because important neurologic factors initially affect the expression of human strength. The later, slower occurring strength improvements generally coincide with noticeable alterations in a muscles subcellular molecular architecture.

Overload training enlarges individual muscle fibers with subsequent muscle growth. The fast-twitch fibers of weightlifters average about $45 \%$ larger than fibers of healthy sedentary persons and endurance athletes. The hypertrophic process couples directly to increased mononuclear number and synthesis of cellular components, particularly protein filaments (myosin heavy chain and actin) that constitute the contractile elements. ${ }^{18,96}$ Resistance exercise creates more efficient translation of mRNA that mediates stimulation of myofibrillar protein synthesis. ${ }^{273}$ Muscle growth occurs from repeated muscle fiber injury (particularly with eccentric actions) followed by overcompensation of protein synthesis to produce a net anabolic effect. The cells myofibrils thicken and increase in number, and additional sarcomeres form from accelerated protein synthesis and corresponding decreased protein breakdown. Intramuscular ATP, PCr, and glycogen also increase considerably. These anaerobic energy stores contribute to the rapid energy transfer required in resistance training. Body-build characteristics also help to explain individual differences in responsiveness to resistance training. The greatest increases in muscle mass occur for individuals with the largest relative FFM (corrected for stature and body fat before training begins). ${ }^{261}$

Figure 22.21 shows the change in muscle fiber size that accompanies exercise-induced hypertrophy. Figure 22.21 A (left) compares exercised and nonexercised rat soleus muscle. The hypertrophied exercised muscle appears on the right. Figure 22.21 B represents a typical cross section of untrained and hypertrophied muscles. Hypertrophied muscle diameter averages $30 \%$ larger and the fibers contain $45 \%$ more nuclei, which increase relative to fiber size. These compensatory changes relate to marked increases in DNA synthesis and proliferation of connective tissue cells and small, mononucleated satellite cells located beneath the basement membrane adjacent to the muscle fibers. These satellite cells, rich among type II muscle fibers, facilitate growth, maintenance, and repair of damaged muscle tissue. ${ }^{91,98}$ Connective tissue cellular proliferation thickens and strengthens the muscles connective tissue harness to improve the structural and functional integrity of tendons and ligaments (cartilage lacks sufficient circulation to stimulate growth). ${ }^{136}$ Such adaptations protect joints and muscles from injury. These adaptations justify including resistance exercise in preventive and rehabilitative orthopedic programs (see Focus on Research, Chapter 18, p. 356).

Resistance-trained muscle fibers have increased total contractile protein and energy-generating compounds without the following components:

1. Parallel increases in capillarization
2. Total volume of mitochondria
3. Mitochondrial enzymes


Figure 22.21 A. Control (left) and hypertrophied (right) rat soleus muscle. B. Cross sections of control and hypertrophied muscles shown in A. The average diameter for 50 fibers of the hypertrophied muscle was 24 to $34 \%$ greater than for controls; the average number of nuclei in hypertrophied muscle averaged 40 to $52 \%$ greater than controls. (From Goldberg AL, et al. Mechanism of work-induced hypertrophy of skeletal muscle. Med Sci Sports 1975;3:185.)

The absence of these factors decreases the ratio of mitochondrial volume and/or enzyme concentration to myofibrillar (contractile protein) volume. This training response does not hinder performance in strength and power activities because of the anaerobic nature of such efforts. It does, however, impede endurance in prolonged exercise by reducing the fibers aerobic capacity per unit of muscle mass.

## Specificity of the Hypertrophic Response

One should not assume that a single resistance exercise creates uniform strength improvement or the hypertrophic response in the muscle(s) activated. ${ }^{8}$ For example, bicep curls performed at close to $1-\mathrm{RM}$ do not produce equal strength gains from the muscles origin to its insertion. If they did, then the maximal force-generating capacity of the muscle would show similar percentage improvements throughout its ROM. This does not occur. Similarly, electrical activity measured by surface or needle EMG or MRI to assess a muscles cross-sectional area does not produce a homogeneous response within the entire muscle during maximal activation. ${ }^{31,175,215}$ A single muscle compartmentalizes into distinct regions. This indicates that the muscles different
areas respond differentially to the imposed adaptive stress. In essence, skeletal muscle remodels its internal architecture, potentially reconfiguring external orientation and hence its shape. The overall lack of homogeneity in skeletal muscles response to overload, coupled with intramuscular differences in fiber type and composition, governs the training adaptation to specific resistance exercise.

## Significant Metabolic Adaptations Occur

Elite sport performance success requires optimization of muscle fiber distribution. The relatively fixed nature of muscle fiber type suggests an obvious genetic predisposition for exceptional performance. Considerable plasticity exists for metabolic potential because specific training enhances the anaerobic and aerobic energy transfer capacity of both fiber types.

The heightened oxidative capacity of fast-twitch fibers with endurance training brings them to a level nearly equal to the aerobic capacity of the slow-twitch fibers of untrained counterparts. Endurance training induces some conversion of type IIb fibers to the more aerobic type IIa fibers. ${ }^{283}$ The welldocumented increase in mitochondrial size and number, and corresponding increase in total quantity of citric acid cycle and electron transport enzymes, accompanies these fiber subdivision changes. Only the specifically trained muscle fibers adapt to regular exercise; this helps to explain why trained athletes who change to a sport that requires different muscle groups (or different portions of the same muscle) often feel untrained. Within this framework, swimmers or canoeists (with welltrained upper-body musculature) do not necessarily transfer upper-body fitness to a running sport that relies predominantly on a highly conditioned lower-body musculature.

Metabolic characteristics of specific fibers and fiber subdivisions undergo modification within 4 to 8 weeks of targeted resistance training. This occurs despite the lack of dramatic changes in inherent muscle fiber type. A decrease in the percentage of type IIx and corresponding increase in type IIa fibers denotes one of the more prominent and rapid training adaptations. ${ }^{5}$ Furthermore, the volume of the trained fast-twitch fibers increases. Figure 22.22 clearly illustrates this increase for the relative areas of the fast- and slow-twitch muscle fibers before and after training. Considerable hypertrophy, predominantly of the fast-twitch fibers, occurs in power and Olympic-type lifters who train diligently over many years with progressive resistance training. ${ }^{243,245}$ This makes sense within the framework of exercise specificity because near-maximal resistance exercise that requires high levels of anaerobic power primarily recruits fast-twitch motor units. Resistance training also improves glucose transport in normal and insulin-resistant skeletal muscle by enhancing activation of the insulin signaling cascade and increasing GLUT-4 protein concentration. These training-induced alterations improve the quality of the skeletal muscle and occur independent of increases in skeletal muscle mass. ${ }^{284}$

Table 22.6 summarizes changes in skeletal muscle with specific training modalities. Generally, physical activity recruits both fiber types; however, certain activities require


Posttraining average $\square$ Pretraining average
Figure 22.22 Individual changes for 14 men in the ratio of fast- to slow-twitch muscle fiber area after 8 weeks of resistance training. Orange circle on right indicates average pretraining FT:ST area ratio; yellow circle represents the posttraining average. (From Thorstensson A. Muscle strength, fiber types, and enzyme activities in man. Acta Physiol Scand Suppl 1976:443.)
activation of a much greater proportion of one fiber type than another.

## Muscle Cell Remodeling: Current Thinking

Skeletal muscles represent dynamic tissues whose cells do not remain as fixed populations throughout life. Rather, muscle fibers undergo regeneration and remodeling to diverse functional demands (e.g., resistance or endurance training) to alter their phenotypic profile. ${ }^{99}$ Activation of muscle via specific types and intensities of long-term use stimulates otherwise dormant myogenic stem cells (satellite cells) situated under a muscle fibers basement membrane to proliferate and differentiate to form new fibers. Fusion of satellite cell nuclei and incorporation into existing muscle fibers allow the fiber to synthesize more protein to form additional myofibril contractile elements. Although this process does not create new muscle fibers per se, it does contribute directly to muscular hypertrophy and may stimulate transformation of existing fibers from one type to another.

A variety of extracellular signal molecules, primarily peptide growth factors (e.g., insulin-like growth factor [IGF], fibroblast growth factors, transforming growth factors, and hepatocyte growth factor) govern satellite cell activity and possibly exercise-induced muscle fiber proliferation and differentiation. Figure 22.23 proposes a model for muscle cell remodeling that involves satellite cell incorporation into an existing muscle fiber. A specific set of genes (gene A in the figure) is expressed in the fibers preexisting nuclei. Chronic activation from physical activity stimulates satellite cell proliferation, with some cells differentiating and fusing with

TABLE 22.6 Effects of Specific Types or Training on Skeletal Muscle

| Muscle Factor | Slow-Twitch Fibers |  | Fast-Twitch Fibers |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Type of Training |  |  |  |
|  | Strength | Endurance | Strength | Endurance |
| Percentage composition | 0 or? | 0 or ? | 0 or ? | 0 or ? |
| Size | + | 0 or + | ++ | 0 |
| Contractile property | 0 | 0 | 0 | 0 |
| Oxidative capacity | 0 | ++ | 0 | + |
| Anaerobic capacity | ? or + | 0 | ? or + | 0 |
| Glycogen content | 0 | + + | 0 | + + |
| Fat oxidation | 0 | ++ | 0 | + |
| Capillary density | ? | + | ? | ? or + |
| Blood flow during exercise | ? | ? or + | ? | ? |

preexisting muscle fibers. The new muscle nuclei alter gene expression (gene B in the figure) in the adapting muscle.

Muscle fiber-type transformation may occur with specific exercise training. In one study, four athletes trained anaerobically for 11 weeks followed by 18 weeks of aerobic training. Anaerobic training increased the percentage of type IIc fibers (a previous subclassification) and decreased the percentage of type I fibers; the opposite occurred during the aerobic training phase. ${ }^{123}$ Similarly, 4 to 6 weeks of sprint training increased the percentage of fast-twitch fibers, with a commensurate decrease in slow-twitch fiber percentage. ${ }^{58}$ Increasing daily training duration also increases the fast- to slow-twitch shift in myosin heavy-chain phenotype in rat hind limb muscles. ${ }^{60}$ Specific training (and perhaps inactivity) may convert different physiologic characteristics of type I to type II fibers (and vice versa). ${ }^{24,243}$ Available evidence does not permit definitive statements concerning the fixed nature of a muscles fiber composition. The genetic code more than likely exerts the greatest influence on fiber-type distribution. The major direction of a muscles fiber composition probably becomes fixed before birth or during the first few years of life.

## Benefits Regardless of Gender or Age

Muscles and tendons, highly adaptable tissues, respond favorably to chronic changes in loading independent of age or gender. ${ }^{13,140,141,180,205}$ A study of five active, older, healthy men (average age 68 y ) demonstrates the remarkable plasticity of human skeletal muscle (Fig. 22.24). The men trained for 12 weeks using heavy-resistance isokinetic and free-weight exercises. Training increased muscle volume and cross-sectional area of the biceps brachii ( $13.9 \%$ ) and brachialis ( $26.0 \%$ ), while hypertrophy increased by $37.2 \%$ in the type II muscle fibers. Increases of $46.0 \%$ in peak torque and $28.6 \%$ in total work output accompanied cellular adaptations. Similarly, older men experience percentage improvements in these variables similar to younger counterparts in response to a
rapid, high-power periodized resistance-training program. ${ }^{184}$ Preserving muscle structure and function as one ages may provide a physical reserve capacity above the critical threshold required for independent living at old age. ${ }^{2,282}$

Equally impressive training responses occur for persons 80 years and older. One hundred nursing home residents (average age 87.1 y ) trained for 10 weeks with high-intensity resistance exercise. ${ }^{72}$ For the 63 women and 37 men who participated, muscle strength increased an average of $113 \%$. Strength increases also paralleled improved function, reflected by an $11.8 \%$ increase in normal gait velocity and $28.4 \%$ increase in stair-climbing speed; thigh muscle cross-sectional area increased by $2.7 \%$. Other studies also have verified the benefits of functional strength training to improve activities of daily living $(A D L)$, including countering the devastating medical consequences of slips and falls in the older elderly. ${ }^{33,224,243}$

## Muscle Hyperplasia: Are New Muscle Fibers Made?

A common question concerns whether training increases the number of muscle cells (hyperplasia). If this does occur, to what extent does it contribute to muscle enlargement in humans? Chronic overload of skeletal muscle in various animal species stimulates new muscle fiber development from satellite cells or by longitudinal splitting. ${ }^{11}$ Under conditions of (1) stress, (2) neuromuscular disease, and (3) muscle injury, the normally dormant satellite cells develop into new muscle fibers (see Fig. 22.23). With longitudinal splitting, a relatively large muscle fiber splits into two or more smaller, individual daughter cells through lateral budding. These fibers function more efficiently than the large single fiber from which they originated. ${ }^{12}$

Generalizing findings from research on animals to humans poses a problem. The massive cellular hypertrophy observed in humans with resistance training does not occur in many animal species. In cats, for example, muscle fiber proliferation (hyperplasia) often reflects the primary compensatory


Figure 22.23 A model for skeletal muscle adaptation that involves satellite cells. A specific set of genes (gene A) is expressed in the preexisting myonuclei. Upon stimulation from increased neuromuscular activity, the satellite cells proliferate, and some of them differentiate and fuse with the preexisting myofibers. These myonuclei may alter gene expression (gene B) in the adapting muscle because they undergo altered differentiation from increased neuromuscular activities. (From Yan Z. Skeletal muscle adaptation and cell cycle regulation. Exerc Sport Sci Rev 2000;1:24.)
adjustment to overload. Some evidence supporting hyperplasia in humans does exist. For example, autopsy data from young, healthy men who died accidentally show that muscle fiber counts of the larger and stronger leg (leg opposite the dominant hand) contained $10 \%$ more muscle fibers than the smaller leg. ${ }^{225}$ Cross-sectional studies of bodybuilders with relatively large limb circumferences and muscle masses failed to show they possessed above-normal size individual muscle fibers. ${ }^{159,160,244}$ Some of the bodybuilders may have inherited an initially large number of small muscle fibers (that
hypertrophied to normal size with resistance training), yet the findings suggest hyperplasia with certain modes of resistance training. Muscle fibers may adapt differently to the highvolume, high-intensity training practiced by bodybuilders than the typical low-repetition, heavy-load system favored by strength and power athletes. Even if other human studies replicate a training-induced hyperplasia (and even if the response reflects a positive adjustment), enlargement of existing individual muscle fibers represents the greatest contribution to increased muscle size from overload training.


Figure 22.24 Plasticity of aging muscle. Data from five men, 68 years of age, before (orange) and after (yellow) 12 weeks of heavy-resistance training. Top. Peak torque of elbow flexors. Middle. Plot of flexor cross-sectional area computed from MRI scans from proximal (right) to distal (left) end of muscle. Bottom. Average for type I and type II fiber areas. (From Roman WJ, et al. Adaptations in the elbow flexors of elderly males after heavy-resistance training. J Appl Physiol 1993;74:750.)

## Changes in Muscle Fiber Type with Resistance Training

Research has evaluated the effects of 8 weeks of resistance exercise on muscle fiber size and fiber composition for the leg extensor muscles of 14 men who performed three sets of 6RM leg squats three times weekly. ${ }^{247}$ Biopsy specimens from the vastus lateralis muscle before and after training showed no change with resistance training in percentage distribution of fast- and slow-twitch muscle fibers. This finding agreed with previous short-term resistance and endurance-type training studies and indicates that several months of resistance training in adults does not alter the basic fiber composition of skeletal muscle. It remains unclear whether specific training early in life or for prolonged durations practiced by elite athletes alters a muscle fibers inherent twitch (speed of shortening) characteristics. Some progressive fiber-type transformation may occur with longer duration, specific training (see Chapter 18). Current thinking posits that genetic factors largely determine ones predominant muscle fiber type distribution.

## COMPARATIVE TRAINING RESPONSES IN MEN AND WOMEN

In todays society, women participate successfully in all sports and physical activities. Women generally had not incorporated resistance training during workouts, to avoid developing overly enlarged muscles similar to men. This hesitation was unfortunate because specific strength acquisition enhances performance in tennis, golf, skiing, dance, gymnastics, and most other sports including physically demanding occupations such as firefighting and construction work. The question often arises whether muscular strength acquisition differs between men and women, and if so, what factors might be responsible?

## INTEGRATIVE QUESTION

If women respond to resistance training essentially the same way as men, explain the disparity between the upper-arm girth of male and female bodybuilders.

## Muscular Strength and Hypertrophy

The absolute amount of muscle hypertrophy with resistance training represents a primary gender difference. Computed axial tomography (CAT) scans for direct evaluation of muscle cross-sectional area show that men and women respond similarly in hypertrophic response to resistance training. Without doubt, men experience a greater absolute change in muscle size because of their larger initial muscle mass, but muscular enlargement on a percentage basis remains similar between genders. ${ }^{55,108,193,269}$ Comparisons between elite male and female bodybuilders also indicate substantial muscular hypertrophy in females with many years of resistance training. ${ }^{231,232}$

Gender-related differences in hormonal response to resistance exercise (e.g., increased testosterone and decreased cortisol for men) may determine any ultimate gender differences in muscle size and strength adaptations with prolonged training. This intriguing area requires longitudinal research for a richer description of gender differences in how skeletal muscle responds to resistance training.

## Does Muscle Strength Relate to Bone Density?

A positive relationship exists between muscular strength and bone mineral density. ${ }^{57,164}$ Men and women who participate in strength and power activities have as much or more bone mass than endurance athletes. ${ }^{210,216,262}$ The lumbar spine and proximal femur bone mass of elite teenage weightlifters ${ }^{49}$ and in adolescent boys and girls ${ }^{271}$ exceed representative values for fully mature bone of reference adults.

A linear relation exists between increases in bone mineral density (BMD) and total and exercise-specific weight lifted during a 1 -year strength-training program. ${ }^{56}$ Such findings have raised speculation about the possible positive relationship between muscular strength and bone mass. Laboratory experiments have documented greater maximum flexion and extension dynamic strength in postmenopausal women without osteoporosis than in osteoporetic counterparts. ${ }^{236}$ For female gymnasts, BMD correlated moderately with maximal muscle strength and serum progesterone. ${ }^{103}$ For adolescent female athletes, absolute knee extension strength moderately associated with total body, lumbar spine, femoral neck, and leg BMD. ${ }^{66}$ Figure 22.25 shows chest flexion and extension strength in normal and osteoporotic women. Women with normal BMD (measured by dualphoton absorptiometry in the lumbar spine and femur neck) exhibited $20 \%$ greater strength in 11 of 12 test comparisons for flexion; 4 of 12 comparisons for extension showed $13 \%$ higher strength values for women with normal bone density. Subsequent data complement these findings; they indicate that regional lean tissue mass (often an indication of muscular strength) accurately predicts bone mineral density. ${ }^{185}$ Differences in maximum dynamic strength among postmenopausal women may serve a clinically useful role in osteoporosis screening.

Women at risk for osteoporosis or with osteoporosis can attenuate their factor of risk (ratio of the load on bone to the bones failure load) for fracture in one of two ways ${ }^{178}$ :

1. Strengthen bone by increasing bone density
2. Avoid risky activities that increase bone load or spinal compression (e.g., heavy lifting activities)

## DETRAINING

Limited data document muscle strength decrements and associated factors with cessation of resistance training. Discontinuing training for 2 weeks caused male power lifters to lose $12 \%$ of their isokinetic eccentric muscle strength and

$\square$ Flexion $\square$ Extension
Figure 22.25 Comparison of chest press extension and flexion strength in age- and weight-matched postmenopausal women with normal and low bone mineral density (BMD). Women with low BMD scored significantly lower on each measure of muscular strength than a reference group. (From Stock JL, et al. Dynamic muscle strength is decreased in postmenopausal women with low bone density. J Bone Miner Res 1987;2:338; Janey C, et al. Maximum muscular strength differs in postmenopausal women with and without osteoporosis. Med Sci Sports Exerc 1987;19:S61.)
$6.4 \%$ of their type II muscle fiber area, without loss in type I fiber area. ${ }^{105}$ Abstaining for a short period of resistance training in previously sedentary men caused loss of strength gains within several weeks, most likely from reversal of train-ing-induced neuromuscular and hormonal adaptations. ${ }^{47}$ Reducing training frequency to only one or two weekly sessions provides sufficient stimulus to maintain traininginduced strength gains. ${ }^{85}$

## METABOLIC STRESS OF RESISTANCE TRAINING

High-intensity, variable-resistance strength training produces no improvement in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ or submaximal exercise heart rate and stroke volume. ${ }^{111}$ Lack of cardiovascular improvement with standard resistance training probably results from the relatively low whole body metabolic and circulatory demands and high anaerobic metabolic requirements of such training. This is reflected by the potent stimulation of glucose uptake and lactate release by the active muscle. ${ }^{67}$ Data from young men during maximal isometric and 8- to $10-\mathrm{RM}$ weightlifting exercises indicate that such activity elicits only light-to-moderate heart rate response (generally less than $130 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ ) and oxygen consumption ( 3 to 4 METs). ${ }^{166}$

Undoubtedly, resistance training places considerable localized stress on specific muscles. The brief activation period
and typically small muscle mass activated in such exercise creates lower heart rates and aerobic metabolic demands than dynamic big-muscle running, hiking, climbing, swimming, or cycling. A person may devote an hour or more to complete a strength-training workout, yet the total time devoted to exercising does not usually exceed 8 minutes per hour. Clearly, traditional resistance-training workouts should not constitute the major portion of a program designed for cardiovascular improvement and weight control.

## CIRCUIT RESISTANCE TRAINING

Modifying the traditional approach to resistance training increases the caloric cost of exercise to improve several important fitness aspects. Circuit resistance training (CRT) deemphasizes the brief intervals of heavy, local-muscle overload in standard resistance training. It provides more-general conditioning that improves body composition, muscular strength and endurance, and cardiovascular fitness. ${ }^{8,80}$ With CRT, a person lifts a weight between 40 and $55 \%$ of 1-RM as many times as possible with good form for 30 seconds. After a 15 -second rest, the participant moves to the next resistance exercise station and so on to complete the circuit, usually composed of 8 to 15 different exercises. A modification that produces similar CRT energy expenditure uses exercise-torest ratios of $1: 1$, with either 15 - or 30 -second exercise periods. ${ }^{19}$ The circuit repeated several times allows for 30 to 50 minutes of continuous exercise, not just the 6 to 8 minutes of the traditional resistance-training workout. As strength increases, a new 1-RM determined for each exercise provides the basis to increasing the resistance.

The CRT modification of standard resistance training offers an attractive alternative to those who desire a more general conditioning program. Medically supervised CRT programs effectively train coronary-prone, cardiac, and spinal cord injured patients for a well-rounded fitness program. CRT supplements off-season conditioning for sports that require high levels of strength, power, and muscular endurance.

## Specificity of Aerobic Improvement with CRT

Some research indicates that CRT produces nearly $50 \%$ less aerobic fitness improvement than bicycle or run training. ${ }^{79}$ Importantly, CRT usually involves substantial upper-body exercise, but assessment of aerobic benefits from this training relied on treadmill or bicycle tests that predominantly activate lower-body musculature. To compensate for this limitation, one study assessed CRT effects on aerobic capacity with treadmill running and arm-crank ergometry tests. ${ }^{94}$ Aerobic capacity increased about $8 \%$ with treadmill testing and $21 \%$ with arm-crank testing, thus confirming the training specificity principle. These findings take on added significance because they occurred without negative effects in a group of borderline hypertensives. The program also increased muscular strength, decreased blood pressure, and modestly improved body composition.

TABLE 22.7 Energy Expenditure for Different Modes of Resistance Exercise Compared with Walking ${ }^{a}$

| Mode | Sex | kJ $\cdot \mathbf{m i n}^{\mathbf{1}}$ | kCal $\cdot \mathbf{m i n}^{\mathbf{1}}$ |
| :--- | :---: | :---: | :---: |
| Nautilus, circuit | M | 29.7 | 7.1 |
|  | F | 24.3 | 5.8 |
| Nautilus, circuit | M | 22.6 | 5.4 |
| Universal, circuit | M | 33.1 | 7.9 |
|  | F | 28.5 | 6.8 |
| Isokinetic, slow | M | 40.2 | 9.6 |
| Isokinetic, fast | M | 41.4 | 9.9 |
| Isometric and |  |  |  |
| $\quad$free-weight | M | 25.1 | 6.0 |
| Hydra-Fitness, circuit | M | 37.7 | 9.0 |
| Walking on level | M | 22.6 | 5.4 |

Data from Katch FI, et al. Evaluation of acute cardiorespiratory responses to hydraulic resistance exercise. Med Sci Sports Exerc 1985;17:168.
${ }^{a}$ Based on a body weight of 68 kg .

## Energy Cost of Different Resistance-Exercise Methods

Table 22.7 displays energy expenditures for exercise performed using free weights, Nautilus (eccentric), Universal Gym (concentric/eccentric), Cybex (isokinetic), and HydraFitness (hydraulic-concentric). Energy expenditure for hydraulic exercises averaged $9.0 \mathrm{kCal} \cdot \min ^{-1}$; this averaged $35 \%$ higher than exercise with free weights, $29.4 \%$ higher than Nautilus exercise, and $11.5 \%$ more than CRT using Universal Gym equipment. The energy expenditure values for hydraulic exercise averaged about $6.4 \%$ less than slow- and fast-speed isokinetic circuit exercise. For comparison, the last line lists the energy expenditure for walking at a normal pace on a level surface.

## MUSCLE SORENESS AND STIFFNESS

Following an extended layoff from exercise, or performing unaccustomed exercise, most persons experience soreness and stiffness in the exercised joints and muscles. Temporary soreness may persist for several hours immediately after such unaccustomed exercise, whereas residual delayed-onset muscle soreness (DOMS) appears later and can last for 3 or 4 days. Any one of the following seven factors may produce DOMS:

1. Minute tears in muscle tissue or damage to its contractile components with accompanying release of creatine kinase (CK), myoglobin (Mb), and troponin I, the muscle-specific marker of muscle fiber damage
2. Osmotic pressure changes that produce fluid retention in the surrounding tissues
3. Muscle spasms
4. Overstretching and tearing of portions of the muscles connective tissue harness
5. Acute inflammation
6. Alteration in the cells mechanism for calcium regulation
7. Combination of the above factors

## Eccentric Actions Produce Muscle Soreness

The precise cause of muscle soreness remains unknown, although the degree of discomfort, muscle disturbance, and loss of strength depends largely on the intensity and duration of effort and type of exercise performed. ${ }^{89,107,112,119,200}$ The magnitude of active strain imposed on a muscle fiber (rather than absolute force) precipitates muscle damage and soreness. ${ }^{153}$ Eccentric muscle actions trigger the greatest postexercise discomfort, particularly magnified in older individuals. ${ }^{25,227,267}$ Existing muscle damage or soreness from previous exercise does not exacerbate subsequent muscle damage or impair the repair process. ${ }^{188}$

In one study, subjects rated muscle soreness immediately after exercise and 24,48 , and 72 hours later. Greater soreness occurred from exercise that involved repeated intense strain during active lengthening in eccentric actions than from concentric and isometric actions. Soreness did not relate to lactate buildup because high-intensity, level running (concentric actions) produced no residual soreness despite significant elevations in blood lactate. In contrast, downhill running (eccentric actions) caused moderate-to-severe DOMS without lactate elevation during exercise.

Table 22.8 highlights muscle soreness and CK activity following an exercise circuit of either concentric-only or
concentric and eccentric muscle actions. Group 1 performed three sets of eight exercises (concentric eccentric) at $60 \%$ of 1-RM on Universal Gym equipment: One set equaled 20 seconds of exercise followed by 40 seconds of rest; total exercise time was 24 minutes. Group 2 followed the same exercise protocol, but they exercised maximally for each repetition on resistance devices powered by hydraulic cylinders that produced concentric-only actions. Blood samples and ratings of perceived muscle soreness took place before exercise and 5, 10, and 25 hours after exercise. The major difference in soreness ratings between exercise groups occurred 25 hours postexercise; the concentric eccentric workout produced higher perceived ratings of soreness for the major muscle groups exercised. The magnitude of increase in serum CK remained the same between groups from 5 to 25 hours postexercise. Both exercise modes elevated serum CK, but the concentric-only muscle actions did not cause DOMS.

## Cell Damage

Running downhill at a 10 slope for 30 minutes produced considerable DOMS 42 hours after exercise. ${ }^{34}$ Corresponding increases also occurred in serum levels of Mb and the musclespecific enzyme CK, both common markers of muscle injury. Acute inflammation also augments greater mobilization of leukocytes and neutrophils. Subject testing also took place after 3, 6, and 9 weeks. Figure 22.26 shows the perceived

TABLE 22.8 Acute Effects of Concentric-Only and Concentric Eccentric Exercise on DOMS 25 Hours After Exercise ${ }^{a}$

| Site | Soreness Ratings |  | Site | Soreness Ratings |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | Concentric | Concentric Eccentric |  | Concentric | Concentric Eccentric |
|  | X | X |  | X | X |
| Chest | 2.3 | 5.1 | Forearm (front) | 1.7 | 3.4 |
| Back (upper) | 2.6 | 2.8 | Forearm (back) | 1.7 | 2.9 |
| Shoulders (front) | 2.2 | 3.6 | Back (lower) | 1.7 | 2.9 |
| Shoulders (back) | 1.9 | 3.6 | Buttocks | 1.8 | 2.5 |
| Biceps (mid) | 1.9 | 4.3 | Quadricep (mid) | 2.0 | 4.1 |
| Biceps (lower) | 1.8 | 3.5 | Quadricep (lower) | 2.1 | 3.8 |
| Triceps (mid) | 1.9 | 3.4 | Hamstrings (mid) | 2.1 | 3.5 |
| Triceps (lower) | 1.9 | 3.0 | Hamstrings (lower) | 2.1 | 3.0 |


| Sample Time | CK Activity (mU $\mathrm{mL}^{-1}$ ) |  |
| :---: | :---: | :---: |
|  | Concentric X | Concentric Eccentric X |
| Pre | 86.7 | 126.9 |
| 5 h post | 344.8 | 232.0 |
| 10 h post | 394.3 | 368.5 |
| 25 h post | 288.0 | 482.2 |

[^39]

Exercise bout $1 \square$ Exercise bout 2
Figure 22.26 Highest soreness rating before and 8, 16, and 48 hours after exercise bout 1 (yellow) and a subsequent exercise bout (bout 2, orange) performed either 3, 6, or 9 weeks later. CK and Mb showed similar results. (From Byrnes WC, et al. Delayed onset muscle soreness following repeated bouts of downhill running. J Appl Physiol 1985;59:710.)
soreness rating for the leg muscles related to elapsed postexercise time for the three study durations. For the 3- and 6 -week comparisons, differences between exercise bouts reached statistical significance, with diminished DOMS noted in the second trial (orange). Similar patterns emerged for perception of muscle soreness and CK and Mb levels. Interestingly, peak soreness ratings at 48 hours did not relate to absolute or relative CK or Mb changes. Individuals who reported the greatest DOMS did not necessarily have the highest CK and Mb values. The first bout of repetitive, high-force exercise probably disrupts the integrity of the sarcolemma to produce mitochondrial swelling and temporary ultrastructural muscle damage in a pool of stress-susceptible or degenerating muscle fibers. This response occurs with an increase in blood markers such as protein carbonyls that reflect oxidative stress. ${ }^{147}$

The early mechanical damage to the myocytes (reflected by increased CK release) 24 hours postexercise does coincide with acute inflammatory cell infiltration within the muscle. ${ }^{29}$ The subsequent decrease in muscle performance for several days following eccentric injury primarily stems from failure in excitation contraction coupling and increased myofibrillar proteolysis. ${ }^{15,277}$ The fast-twitch fibers with low oxidative capacities show particular vulnerability, with more extensive damage several days after exercise than in the immediate postexercise period. A single exercise bout protects against muscle soreness and decrements in muscle strength in subsequent exercise, with the effect lasting up to 6 weeks. Resistance to muscle damage in succeeding exercise may result from an eccentric exercise induced increase in muscle fiber sarcomeres connected in series. ${ }^{158}$ Such adaptations support the wisdom of initiating a training program with light exercise to protect against the muscle soreness that almost always follows an initial intense exercise bout that includes an eccentric component. ${ }^{78}$ Intense concentric exercise performed just prior to strenuous eccentric exercise does not magnify muscle damage. It may prepare the muscle to respond more effectively to the next eccentric exercise stress. Even prior lower-intensity exercise of specific muscles does not fully protect from DOMS with more intense exercise.

## Altered Sarcoplasmic Reticulum

Four factors produce major alterations in sarcoplasmic reticulum structure and function with unaccustomed exercise:

1. Changes in pH
2. Changes in intramuscular high-energy phosphates
3. Changes in ionic balance
4. Changes in temperature

These effects depress the rates of $\mathrm{Ca}^{2+}$ uptake and release and increase free $\mathrm{Ca}^{2+}$ concentration as the mineral rapidly moves into the cytosol of the damaged fibers. Intracellular $\mathrm{Ca}^{2+}$ overload contributes to the autolytic process within damaged muscle fibers that degrades the contractile and noncontractile structures. Topographical mapping techniques to investigate sensory and EMG outcomes of DOMS have
been investigated 24 h and 48 h following eccentric exercise in multiple locations of the quadriceps muscle. Greater DOMS occurred in the distal region of the quadriceps, indicating a greater tendency of this region to further injury following the eccentric exercise along with reduced force capacity. ${ }^{101}$

Vitamin E supplementation, and perhaps vitamin C and selenium, protects against cellular membrane disruption and enzyme loss following muscle damage from resistance exercise (see Chapter 2). ${ }^{83,167}$ Postexercise protein supplementation also may protect against muscle soreness in severely exercisestressed individuals. ${ }^{73}$ In contrast, supplementing daily with either fish oil (high in omega-3 and omega-6 fatty acids) or isoflavones (soy isolate) for 30 days prior to and during the week of testing to reduce the inflammatory response produced no benefit to DOMS (strength, pain ratings, limb girth, and blood measures related to muscle damage, inflammation, and
lipid peroxidation) compared with placebo treatment. ${ }^{149}$ Supplementation with 750 mg per day of phosphatidylserine for 10 days did not afford additional protection against DOMS and markers of muscle damage, inflammation, and oxidative stress that follow prolonged downhill running. ${ }^{134}$ Similarly, taking a protease supplement had no effect on the perception of pain associated with DOMS or the blood markers of muscle damage. ${ }^{21}$ At 48 h postexercise-induced DOMS, milk and milk-based protein carbohydrate supplementation attenuated decreases in isokinetic muscle performance and increases in CK and $\mathrm{Mb} .^{44}$

## Current DOMS Model

Figure 22.27 diagrams the probable steps in the development of DOMS and subsequent recuperation.


Figure 22.27 Proposed sequence for delayed-onset muscle soreness following unaccustomed exercise. Cellular adaptations to short-term exercise provide enhanced resistance to subsequent damage and pain.

## INTEGRATIVE QUESTION

Respond to the following: I run and work out with free weights regularly, yet every spring my muscles are sore a day or two after a few hours of yard work.

## Summary

1. The size and type of muscle fibers and the anatomic lever arrangement of bone and muscle (physiologic factors) largely govern the upper limit to human muscular strength.
2. Central nervous system influences activate the prime movers in a specific action to affect maximal force capacity.
3. Six factorsgenetic, exercise, nutritional, hormonal, environmental, and neuralinteract to regulate skeletal muscle mass and corresponding strength development with resistance training.
4. Three factors contribute to increased muscle strength with resistance training: (1) improved capacity for motor unit recruitment, (2) changes in motor neuron firing pattern efficiency, and (3) alterations within the muscle fibers contractile elements.
5. Muscular overload increases strength and selectively stimulates muscle fiber hypertrophy. Muscle hypertrophy includes increased protein synthesis with myofibrillar thickening, connective tissue cell proliferation, and an increase in the number of satellite cells around each fiber.
6. Muscle hypertrophy entails structural changes within the contractile apparatus of individual fibers, particularly fast-twitch fibers and increased anaerobic energy stores.
7. The genetic code exerts the greatest influence on muscle fiber-type distribution; a muscles fiber composition is largely fixed before birth or during the first few years of life.
8. Human muscle fibers adapt to increased functional demands via action of myogenic stem cells (satellite cells) that proliferate and differentiate to remodel the muscle.
9. Relatively brief periods of resistance training generate similar strength improvements (on a percentage basis) for women and men.
10. Muscle weakness in the abdominal and lower lumbar back regions (core), including poor flexibility in the lower back and legs, represent primary factors related to low back syndrome. Core musclestrengthening, flexibility, and balance exercises effectively protect against and rehabilitate this condition.
11. Women at risk for osteoporosis (or with the disease) reduce fracture risk by increasing bone density and avoiding activities that increase spinal compression and bone stress.
12. Conventional resistance training does not improve aerobic fitness. These workouts do not affect weight loss because of their relatively low caloric cost.
13. Circuit resistance training, by using lower resistance and higher repetitions, effectively combines the muscle-training benefits of resistance exercise with the cardiovascular, calorie-burning benefits of continuous dynamic exercise.
14. Eccentric muscle actions induce greater DOMS than concentric-only or isometric actions. Serum markers of muscle damage ( CK and Mb ) increase with each form of muscle action.
15. A single exercise bout protects against DOMS and muscle damage from subsequent exercise. The protection mechanism supports the wisdom of progressing gradually (lower intensity; minimize eccentric actions) when beginning an exercise program that requires application of considerable muscular force.
16. The body initiates a series of adaptive cellular events (basically an inflammation response) to unaccustomed exercise that produces DOMS.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

American College of Sports Medicine www.acsm.org
American Heart Association
www.americanheart.org/
Centers for Disease Control and Prevention www.cdc.gov/
American Association of Cardiovascular and Pulmonary
Rehabilitation www.aacvpr.org/
Office of the Surgeon General
www.surgeongeneral.gov/
The Global Economic and Healthcare Burden of
Musculoskeletal Disease www.ota.org/downloads/bjdExecSum.pdf
Bureau of Labor Statistics www.bls.gov/
National Strength and Conditioning Association www.nsca-lift.org/


## CHAPTER 23

## Special Aids to Exercise Training and Performances

## CHAPTER OBJECTIVES

> Define ergogenic aids and outline possible mechanisms for their purported effects
> Outline the procedure for formulating a randomized, double-blind, placebo-controlled research study and give the benefits of such a design
> List the categories of substances currently banned by the International Olympic Committee
> Give examples of substances and procedures with alleged ergogenic benefits
> Discuss the mode of action of anabolic steroids, their effectiveness, and risks when used by males and females
> Summarize ACSM s Position Stand on Use of Anabolic Steroids
> Give positive and negative findings from research on animals of the effect of $\beta_{2}$-adrenergic agonists
> Discuss the medical use of human growth hormone and potential dangers for healthy athletes
> Outline the general trend for endogenous dehydroepiandrosterone (DHEA) production during a lifetime
> Discuss the rationale for DHEA as an ergogenic aid and its potential risks

- Summarize the controversy about androstenedione as a benign nutritional supplement or a harmful drug
> Discuss the effects of oral supplements of amino acids, carbohydrate-protein, and carbohydrate on hormone secretion, resistance-training responsiveness, and exercise performance
> Summarize the research findings about ergogenic benefits and risks of amphetamines, caffeine, buffering solutions, chromium picolinate, L-carnitine, glutamine, and $\beta$-hydroxy- $\beta$ methylbutyrate
> Describe the typical time course for red blood cell reinfusion and the mechanism for ergogenic effects on endurance performance and $\mathrm{VO}_{2 \text { max }}$
> Discuss the medical use of erythropoietin and potential dangers for healthy athletes
- Define general warm-up and specific warm-up and the potential benefits of each
> Describe possible cardiovascular benefits of moderate warm-up prior to extreme physical effort
> Provide a rationale for breathing hyperoxic gas mixtures to enhance exercise performance; quantify its potential to increase tissue oxygen availability
> Outline the classic carbohydrate-loading procedure and modified-loading procedure to augment glycogen storage
> Describe the theoretical role for an ergogenic effect of creatine supplements, and indicate physical activities that benefit from supplementation
> Summarize the research and rationale for consuming medium-chain triacylglycerols to enhance endurance performance
- Discuss the effects of pyruvate supplementation on endurance and body fat loss

Considerable literature exists about ergogenic aids and athletic performance-ergogenic referring to the application of a nutritional, physical, mechanical, psychologic, or pharmacologic procedure or aid to improve physical work capacity or athletic performance. This literature includes studies of potential performance benefits of alcohol, amphetamines, ephedrine, hormones, carbohydrates, amino acids, fatty acids, additional red blood cells, caffeine, carnitine, creatine, phosphates, oxy-gen-rich breathing mixtures, massage, wheat-germ oil, vitamins, minerals, ionized air, music, hypnosis, and even marijuana and cocaine! Athletes routinely use only a few of these aids, and only a few evoke real controversy. Specific concern focuses on the use of anabolic steroids, human growth hormone, dehydroepiandrosterone (DHEA), and other exogenous hormones and prohormones, nutritional components, amphetamines, and blood doping. Warm-up and breathing hyperoxic gas are common procedures, so we include these in our discussion of the effectiveness and practicality of ergogenic aids for exercise training and performance.

We discuss nutritional requirements for macro- and micronutrients for active individuals in the specific chapters dealing with these nutrients. The increasing use of herbs of undocumented quality by fitness enthusiasts and athletes raises concern about efficacy and possible toxicity. In a Practical Sense on page 535 summarizes ingredients, purported benefits, and possible side effects of commonly used herbal compounds.

The indiscriminate use of ergogenic substances increases the likelihood of adverse side effects that range from benign physical discomfort to life-threatening episodes. Many of these compounds fail to conform to labeling requirements to correctly identify the strength of the product s ingredients and contaminents. ${ }^{111,140}$

## AN INCREASING CHALLENGE TO FAIR COMPETITION

Examples of ergogenic use by athletes date to antiquity. Physicians encouraged Roman and Greek athletes to eat raw meat before competing to enhance their animal competitiveness. In more modern times, trainers advised marathon
runners in the 1908 Olympics to drink alcohol (brandy) to improve performance, and in the early 1970s athletes were fed high-carbohydrate meals by personal nutritionists before competition to decrease muscle fatigue. Use of ergogenic aids, including illegal drugs, to improve exercise performance in almost all sports has been making headlines since the 1950s, and unfortunately illegal doping has continued into the 2008 Tour de France (Kazakhstan s Dmitri Fofonov, Italy s Riccardo Ricco, and Spain s duo Manuel Beltran and Moises Duenas) and six athletes in the 2008 Beijing Olympic Games (as of June 10, 2009).

Improvements in doping control for the 2004 Athens Olympics have apparently had a major impact on sports performance. Figure 23.1 shows the lack of improvement in new world records, mainly in track and field, as evidence that the drug-tainted past has temporarily been put on hold. Twentythree athletes were barred from the 2004 games and only one world record was tied ( 12.92 s in the $110-\mathrm{m}$ men s hurdles). Note particularly the decline in men s and women s performances in the shot put, discus, javelin, and long jump.

Unfortunately, highly celebrated and idolized but now disgraced Olympians were required by the International Olympic Committee (IOC) to return their medals for illegal doping during the 2000 Sydney Olympic Games. Track star Marion Jones, who won five medals (gold in the $100-\mathrm{m}, 200-\mathrm{m}$, and $1600-\mathrm{m}$ relay and bronze in the long jump and $40-\mathrm{m}$ relay), pleaded guilty to two counts of lying to investigators about her doping abuse and was sentenced to federal prison for 6 months, including two years probation and community service.

## Urine Testing: The Method of Choice

Testing of urine samples provides the primary method for drug detection. Chemicals are added to the urine sample, which is then heated and vaporized in testing. The vapor passes through an absorbent column and an electric or magnetic field (gas chromatography-mass spectrometry). The pattern made by the molecules deflected by the field is compared with patterns made by known chemicals.

## IN A PRACTICAL SENSE

## Commonly Used Herbal Compounds for Exercise and Training: User Beware

Aside from the influence of genetics and proper training, nutrition often exerts an important influence on athletic performance. In seeking the competitive edge, exercise enthusiasts and athletes fall prey to fad diets and unnecessary supplements whose potency, quality, and effectiveness lack scientific validation. Athletes often eat a suboptimal diet, particularly when attempting to reduce body weight while training strenuously. This leads to the use of a diverse array of nutritional supplements, including herbal compounds (used by $23 \%$ of U.S. adults), to hopefully overcome nutritional inadequacies and insure optimal performance and training responsiveness.

Intake of a broad range of herbal compounds as supplements for ergogenic purposes has expanded considerably during the last decade. Aside from the lack of documentation concerning the efficacy of these chemicals, many carry the potential for health risk. The prudent coach and exercise specialist should know the common herbs used by athletes and their purported effects, contraindications, and possible adverse side effects. The table lists the more popular herbs with uses, active ingredients, common dosage, and precautionary information.

Herbs Frequently Used to Improve Health, Reduces Stress, Elevate Emotional and Cognitive
Responses, Enhance Muscular Development and Exercise Performance, and Speed Recovery

| Herb | Other Name | Purported Use/Benefit | Active Ingredients | Dosage | Side Effects/ Interactions/ Comments |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Astragulus | Huang qi | Supports immune system; benefits cardiovascular system; increases energy level; promotes tissue repair | Flavonoids, polssaccharides, triterpene glycosides, amino acids, and trace minerals | $915 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ | None |
| Bilberry | Vaccinium myrtillus | Diabetes; macular degeneration; retinopathy | Anthocyanosides (bioflavonoid) | $240600 \mathrm{mg} \cdot \mathrm{d}^{-1}$ as herbal extract or $2060 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ fruit | None |
| Bee pollen | Buckwheat pollen; puhuang | Allergies; asthma; cholesterol and triacylglycerol lowering | Protein, carbohydrates, minerals, and essential fatty acids | $5001000 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Allergic reactions; avoid with hypoglycemic agents |
| Chamomile | Camomile, roman camomile | Stress reduction; supports immune function; assists sleep; promotes tissue repair | $\alpha$-Bisabol; bioflavonoids | Taken as tea 3 to 4 times per day | Avoid if allergic to plants |
| Echinacea | Echinacea purpurea; echinacea angustifolia | Common cold/sore throat; immune function; infection; influenza | Alkylamides, polyacetylenes; increases interferon production | At onset of cold or flu; <br> $34 \mathrm{~mL} \cdot 2 \mathrm{~h}^{-1}$ <br> or 300 mg <br> powder $\cdot \mathrm{d}^{-10}$ | Avoid if allergic to sunflower plant family |
| Ephedra | Ephedra sinica; Ephedra equisetina | Asthma; cough; weight loss; increases energy level | Alkaloids ephedrine and pseudo-ephedrine | $1.56 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ in tea form; 12.5 $25 \mathrm{mg} \cdot 4 \mathrm{~h}^{-1}$ as over-the-counter drug | Banned substance; amphetamine-like side effects; avoid with hypertension or pregnancy |
| Garlic | Allium sativum | High blood pressure; high triacylglycerols; intermittent claudication | Sulfer compound allicin | $600900 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with stomach problems; heartburn, gastritis or ulcers |

## Herbs Frequently Used to Improve Health, Reduces Stress, Elevate Emotional and Cognitive Responses, Enhance Muscular Development and Exercise Performance, and Speed Recovery (continued)

| Herb | Other Name | Purported Use/Benefit | Active Ingredients | Dosage | Side Effects/ Interactions/ Comments |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Ginseng, Asian | Pannax | Mental alertness; memory; physical endurance; type 2 diabetes; hyperlipidemia; congestive heart failure | Eleutherosides | $200600 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with hypertension, heart disease; pregnancy and lactation; nervousness; fever or sleep disorders |
| Ginseng, Siberian | Eleuthero root | Physical endurance; fatigue prevention; immune function; motion sickness | Eleutherosides | $200600 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with hypertension, heart disease; pregnancy; and lactation; nervousness; fever or sleep disorders |
| Ginkgo biloba | $\begin{aligned} & \text { Maidenhair } \\ & \text { tree } \end{aligned}$ | Age-related cognitive decline; Alzheimer s disease; intermittent claudication; depression; atheroscleroisis; impotence (of vascular origin) | Gingko flavone glycosides (bioflavonoid), terpene (lactones) | $120240 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Mild headaches lasting 1 or 2 days; mild upset stomach |
| Guarana | Paullinia cupana | Fatigue prevention; weight loss | Guaranine (identical to caffeine) | $200800 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with pregnancy, glucoma, heart disease, high blood pressure, history of stroke |
| Kava Kava | Piper methysticum | Anxiety; restlessness; stress, muscle relaxing | Kava-lactones | $200250 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with pregnancy or if lactating; can cause drowsiness |
| Milk thistle | Silybum marianum | Alcohol-related liver disease; hepatitis; liver support | Bioflavonoid complexsilymarin | $200400 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | None |
| Glucosamine sulfate ${ }^{a}$ |  | Osteoarthritis; joint inflammation; joint stiffness |  | $1500 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Avoid with diabetes |
| Grape seed extract |  | Circulatory disorders; varicose veins; atherosclerosis |  | $75300 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | None |
| Saw palmetto | Serenoa repens, sabal serrulata | Benign prostatic hyperplasia; urination problems in males | Liposterolic extract of saw palmetto provides fatty acids, sterols, and esters | $200300 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | None |
| St. John s wort | Hypericum perforatum | Depression; anxiety or nervous unrest; mood disturbance of menopause | Hypericin, flavonoids | $900 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Heightens sun sensitivity; interferes with iron absorption |
| Witch hazel | Hamamelis virginiana | Eczema; hemorrhoids; varicose veins | Tannins and volatile oils | As ointment or cream 3 4 times $\cdot \mathrm{d}^{-1}$ | Not for internal use; causes stomach irritation |
| Yohimbe | Pausinystalia ohimbe | Impotence; depression | Yohimbine (alkaloid) | $1530 \mathrm{mg} \cdot \mathrm{d}^{-1}$ | Use only under medical supervision |
| Valerian | Heliotrope; setwall; vandal root | Stress reduction; improves sleep; benefits cardiovascular system | Essential oils | 300500 mg before sleep | None |

[^40]

Figure 23.1 Track and field world records compared with 2004 Athens Olympic performances. Negative values (red) reflect poorer performances in Athens for men (top) and women (bottom). Note the goldcolored area for the events that emphasize muscular strength and power.


## A NEED TO CRITICALLY EVALUATE THE SCIENTIFIC EVIDENCE

Companies expend considerable money and effort to show a beneficial effect of an aid. Often, however, a placebo effect, not the aid, improves performance because of psychological factors-the individual performs at a higher level because of the suggestive power of believing that a substance or procedure should work. Those in the exercise sciences must evaluate the scientific merit of articles and advertisements about products and procedures. To separate marketing hype from scientific fact, we pose five areas for questioning the validity of research claims concerning the efficacy of chemical, pharmacologic, and nutritional ergogenic aids:

## I. Justification

Scientific rationale: Does the study represent a fishing expedition or is there a sound rationale that the specific treatment should produce an effect? For example, a theoretical basis exists to believe that ingesting creatine elevates intramuscular creatine and phosphocreatine to possibly improve shortterm power output capacity. In contrast, no rationale exists to hypothesize that hyperhydration, breathing hyperoxic gas, or ingesting medium-chain triacylglycerols should enhance 100-m dash performance.

## II. Subjects

Animals or humans: Many diverse mammals exhibit similar physiologic and metabolic dynamics, yet significant species differences exist, which often limit generalizations to humans. For example, the models for disease processes, nutrient requirements, hormone dynamics, and growth and development often differ markedly between humans and different animal groups.
Sex: Sex-specific responses to the interactions between exercise, training, and nutrient requirements and supplementation limit generalizability of findings to the sex studied.
Age: Age often interacts to influence the outcome of an experimental treatment. Effective interventions for the elderly may not apply to growing children or young and middle-aged adults.
Training status: Fitness status and training level can influence the effectiveness (or ineffectiveness) of a particular diet or supplement intervention. Treatments that benefit the untrained (e.g., chemicals or procedures that enhance neurologic disinhibition) often have little effect on elite athletes who practice and compete routinely at maximal arousal levels.
Baseline level of nutrition: The research should establish the subjects nutritional status prior to experimental treatment. Clearly, a nutrient supplement administered to a malnourished group typically improves exercise performance and training responsiveness. Such nutritional interventions
fail to demonstrate whether the same effects occur if subjects received the supplement with their baseline nutrient intake at recommended levels. It should occasion little surprise, for example, that supplemental iron enhances aerobic fitness in a group with iron-deficiency anemia. One cannot infer, however, that iron supplements provide such benefits to all individuals.
Health status: Nutritional, hormonal, and pharmacologic interventions profoundly affect the diseased and infirmed yet offer no benefit to those in good health. Research findings from diseased groups should not be generalized to healthy populations.

## III. Research sample, subjects, and design

Random assignment or self-selection: Apply research findings only to groups similar to the sample studied. If subject volunteers self-select into an experimental group, does the experimental treatment produce the results, or did a change occur from the individual s motivation to take part in the study? For example, desire to enter a weight loss study may elicit behaviors that produce weight loss independent of the experimental treatment per se. Great difficulty exists in assigning truly random samples of subjects into an experimental group and a control group. When subjects volunteer to take part in an experiment, they must be randomly assigned to a control or experimental condition, a process termed randomization.
When all subjects receive the experimental supplement and the placebo treatment (see below), supplement administration is counterbalanced, and half the subjects receive the supplement first, while the other half takes the placebo first.
Double-blind, placebo-controlled: The ideal experiment to evaluate performance-enhancing effects of an exogenous supplement requires that experimental and control subjects remain unaware, or blinded to, the substance administered. To achieve this goal, subjects should receive a similar quantity and/or form of the proposed aid. In contrast, control group subjects receive an inert compound or placebo. The placebo treatment evaluates the possibility of subjects performing well or responding better simply because they receive a substance they believe should benefit them (psychological or placebo effect). To further reduce experimental bias from influencing the outcome, those administering the treatment and recording the response must not know which subjects receive the treatment or placebo. In such a double-blinded experiment, both investigator and subjects remain unaware of the treatment condition. Figure 23.2 illustrates the design of a double-blind, placebocontrolled study with an accompanying crossover


Figure 23.2 Example of a randomized, double-blind, placebo-controlled, crossover study. Following appropriate subject selection, participants are pretested and then randomly assigned to either the experimental (treatment) or control (placebo) group. Following treatment a posttest is administered. Participants then cross over into the opposite group for the same time period as in the first condition. A second posttest follows. Comparisons of the posttests determine the extent of a treatment effect.
where treatment and placebo conditions are reversed.
Control of extraneous factors: Under ideal conditions, experiences should be similar for both experimental and control groups, except for the treatment variable. Random assignment of subjects to control or experimental groups goes a long way to equalize control factors that could influence the study s outcome.
Appropriateness of measurements: Reproducible, objective, and valid measurement tools must evaluate research outcomes. For example, a step test to predict aerobic capacity, or infrared interactance to evaluate components of body composition, represents an imprecise tool to answer meaningful questions about the efficacy of a proposed ergogenic aid.

## IV. Conclusions

Findings should dictate conclusions: The conclusions of a research study must logically follow from the research findings. Frequently, investigators who study ergogenic aids extrapolate conclusions beyond the scope of their data. The
implications and generalizations of research findings must remain within the context of the measurements made, the subjects studied, and the magnitude of the response. For example, increases in anabolic hormone levels in response to a dietary supplement reflect just that; they do not necessarily indicate an augmented training responsiveness or an improved level of muscular function. Similarly, improvement in brief anaerobic power output capacity with creatine supplementation does not justify the conclusion that exogenous creatine improves overall physical fitness. Appropriate statistical analysis: Appropriate inferential statistical analysis must be applied to quantify the potential that chance caused the research outcome. Other statistics must objectify averages, variability, and degree of association between variables. Statistical versus practical significance: The finding of statistical significance of a particular experimental treatment only means a high probability exists that the result did not occur by chance. One must also evaluate the magnitude of an effect for
its real impact on physiology and/or performance. A reduced heart rate of 3 beats per minute during submaximal exercise may reach statistical significance, yet have little practical effect on aerobic fitness or cardiovascular function.

## V. Dissemination of findings

Published in peer-reviewed journal: High-quality research withstands the rigors of critical review and evaluation by colleagues with expertise in the specific area of investigation. Peer review provides a measure of quality control over scholarship and interpretation of research findings. Publications in popular magazines or quasi-professional journals do not undergo the same rigor of evaluation as peer review. In fact, self-appointed experts in sports nutrition and physical fitness pay eager publishers for magazine space to promote their particular viewpoint. In some cases, the expert owns the magazine!

## Findings reproduced by other investigators:

 Findings from one study do not necessarily establish scientific fact. Conclusions become stronger and more generalizable when support emerges from the laboratories of other independent investigators. Consensus reduces the influence of chance, flaws in experimental design, and investigator bias.
## Levels of Evidence

The National Heart, Lung and Blood Institute (NHLBI; part of the National Institute of Health [NIH]) issued guidelines to consider when judging the strength of research evidence. The evidence guidelines presented in Table 23.1 indicate that the strongest and most conclusive evidence comes from
randomized, double-blind, placebo-controlled studies published in peer-reviewed journals. But even the results of the best designed research may not be enough. Reproducible results become an important part of the evaluation process such that strongest evidence emerges from the cumulative body of scientific literature and not simply the results of one study. Clearly, it is highly desirable that research evidence be strong before making recommendations about a given ergogenic aid. This, however, is not always possible, and recommendations are made supported only by fair or limited evidence, often anecdotal in nature. We maintain that until strong evidence supports use of a purported ergogenic substance, athletes and those involved in training, coaching, and advising these individuals should understand the relative strength of available research in this area, as presented in Table 23.1.

## ON THE HORIZON

The day may be near when individuals born lacking certain lucky genes that augment growth and development and exercise performance will simply add them, doping undetectably with DNA, not drugs. In these instances, the use of gene doping misappropriates the medical applications of gene therapy that treats atherosclerosis, cystic fibrosis, and other potentially debilitating and deadly diseases. Gene doping offers the promise to increase the size, speed, and strength of healthy humans. Genes that cause muscles to enlarge would be ideal for sprinters, weightlifters, and other power athletes. Endurance athletes would benefit from genes that boost red blood cell production (e.g., gene for erythropoietin) or stimulate blood vessel development (e.g., gene for vascular endothelial growth factor). The world of sports doping has changed dramatically in the past 15 years, and it seems that thrust will continue, but this time the athletes will have access to a new arsenal of magic bullet genetically engineered drugs.

## TABLE 23.1 Levels of Evidence on Which to Judge Research Findings

| Evidence Category | Source of Evidence | Definition and Comment |
| :---: | :---: | :---: |
| I | Randomized controlled trials (RCTs) involving a rich body of data | Evidence derives from endpoints of well-designed RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of data of findings in the population for which the recommendation is made. Requires substantial number of participants. Very high confidence in findings. |
| II | RCTs involving a limited body of data | Evidence from endpoint of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs, or metaanalysis of RCTs. In general, this line of evidence is less convincing than level I because of some inconsistency in the results between studies. |
| III | Nonrandomized trials and observational studies | Evidence derived from outcomes of uncontrolled or nonrandomized trials or from observational studies. |
| IV | Panel consensus judgment | Expert judgment derived from experimental research described in the literature and/or derived from the consensus of panel members, based on clinical experience or knowledge that does not meet the above listed criteria on other levels. This category is used only in cases where the provision of some guidance was deemed valuable, but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (I or III). |

## Mechanism for How Purported Ergogenic Aids Might Work

Act as a central or peripheral nervous system stimulant (e.g., caffeine, choline, amphetamines, alcohol)
Increase storage and/or availability of a limiting substrate (e.g., carbohydrate, creatine, carnitine, chromium)
Act as a supplemental fuel source (e.g., glucose, medium-chain triacylglycerols)
Reduce or neutralize performance-inhibiting metabolic byproducts (e.g., sodium bicarbonate or sodium citrate, pangamic acid, phosphate) Facilitate recovery (e.g., high-glycemic carbohydrates, water)
Enhance resistance-training responsiveness (anabolic steroids, human growth hormone, carbohydrate/protein supplements immediate postexercise)

## PHARMACOLOGIC AGENTS

Athletes go to great lengths to promote all aspects of their health: they train hard; eat well-balanced meals; consume the latest sports drink with megadoses of vitamins, minerals, and amino acids; and seek and receive medical advice for various injuries (no matter how minor). Yet ironically, they will ingest synthetic agents, many of which precipitate adverse effects ranging from nausea, hair loss, itching, and nervous irritability, to severe consequences such as sterility, liver disease, drug addiction, and even death caused by liver and blood cancer.

The World Anti-Doping Agency (WADA; www. wadaama.org/en/prohibitedlist.ch2) currently bans the following nine categories of substances:

1. Anabolic androgenic steroids
2. Hormones and related substances
3. Beta 2 agonists
4. Hormone antagonists and modulators
5. Diuretics and other masking agents
6. Stimulants
7. Narcotics
8. Cannabinoids
9. Glucocorticosteroids

The Prohibited List was first published in 1963 (www. olympic.org/). Since 2004, as mandated by the World AntiDoping Code, WADA prepares and publishes the List. The List and Code represent an International Standard that identifies substances and methods prohibited in competition, out of competition, and in particular sports. WADA is composed of a Foundation Board, an Executive Committee, and several other committees. The 38-member Foundation Board acts as WADA s supreme decision-making body and consists of representatives from the Olympic Movement and various governments.

## Anabolic Steroids

Anabolic steroids gained prominence in the early 1950s for medical purposes, to treat patients deficient in natural androgens or with muscle-wasting diseases. Other legitimate steroid uses include treatment of osteoporosis and severe breast cancer in women, and countering the excessive decline in lean body mass and increase in body fat often observed in elderly men, HIV patients, and individuals who undergo kidney dialysis.

$$
\text { ? } 1 \begin{aligned}
& \text { INTEGRATIVE QUESTION } \\
& \text { A student maintains that a chemical compound } \\
& \text { added to his diet produced profound improve- } \\
& \text { ments in weightlifting performance. Your review } \\
& \text { of the research literature indicates no ergogenic } \\
& \text { benefits for this compound. How would you } \\
& \text { reconcile the discrepancy? }
\end{aligned}
$$

Current estimates suggest that up to 4 million athletes ( $90 \%$ of male and $80 \%$ of female professional bodybuilders) currently use androgens, often combined with stimulants, hormones, and diuretics. Even in the sport of professional baseball, interviews of strength trainers and current players estimate that up to $30 \%$ of the players use anabolic steroids in their quest to enhance hitting and pitching performance.

## Structure and Action

Anabolic steroids function in a manner similar to testosterone, the chief male hormone. By binding with receptor sites on muscle and other tissues, testosterone contributes to male secondary sex characteristics. This includes gender differences in muscle mass and strength that develop at puberty onset. Testosterone production takes place mainly in the testes ( $95 \%$ ), with the adrenal glands producing the remainder. Synthetically manipulating the steroid s chemical structure to increase muscle growth (from anabolic tissue building and nitrogen retention) reduces the hormone s androgenic or masculinizing effects. A masculinizing effect of synthetically derived steroids still exists, particularly for females.

Athletes typically combine multiple steroid preparations in oral and injectable form, a practice called stacking, because they believe that the various androgens differ in physiologic action. They also progressively increase drug dosage-a practice called pyramiding-usually in 6 - to 12 -week cycles. The drug quantity far exceeds the recommended medical dose, often by 40 -fold. The athlete then progressively reduces drug dosage in the months before competition to lower the chance of detection during drug testing. The difference between dosages used in research studies and those used by athletes contributes to the credibility gap between scientific findings (often, little effect of steroids) and what most in the athletic community know to be true through trial-and-error selfexperimentation.

Designer Drug Unmasked. Researchers in the Department of Molecular and Medical Pharmacology at UCLAs Olympic Analytical Laboratory (www.pathnet. medsch.ucla.edu/OlympicLab/index.html) unmasked an illegal designer compound that mimics the chemical structure of the banned steroids gestrinome and trenbolone. Discovery of this new stand-alone steroid chemical entity, not a pro-steroid or precursor steroid like many performance-boosting substances on the market, introduced a drug with no prior record of manufacture or existence. An anonymous tipster provided a syringe sample of the steroid identified as tetrahydrogestrinone, or THG. The researchers developed a new test to detect THG, apparently taken not by injection but in droplets under the tongue. They then reanalyzed 350 urine samples from participants at the U.S. track and field championships in June 2003 and 100 samples from random out-of-competition tests. A remarkably high half-dozen athletes tested positive. On October 17, 2003, the National Football League began testing players for THG to avoid the scandal that has embarrassed track and field.

## A Drug with a Considerable Following

One often pictures steroid abusers as extremely muscular bodybuilders, but abuse also occurs among competitive athletes in road cycling, tennis, track and field, American collegiate and professional football, canoeists, auto racing, swimming, and other highly competitive sport activities. Surveys of United States Powerlifting Team members indicate that up to two-thirds used androgenic anabolic steroids. ${ }^{65}$ Many competitive and recreational athletes obtain steroids on the black market. Thus, misinformed individuals may take massive and prolonged dosages without medical monitoring and suffer harmful alterations in physiologic function.

Steroid abuse among adolescents and its accompanying risks, including extreme virilization and premature cessation of bone growth, remains particularly worrisome. Boys and girls as young as 11 years of age use anabolic-androgenic steroids. ${ }^{87}$ Teenagers cite improved athletic performance as the most common reason for taking steroids, although $25 \%$ acknowledge enhanced appearance as a main reason. In this regard, a body image disturbance may contribute to anabolic steroid abuse among teenagers and adults. ${ }^{192,292}$ The National Institutes of Drug Abuse, an arm of the National Institutes of Health, claims that steroid use among high school sophomores more than doubled nationwide between 1992 and 2000. A Blue Cross/Blue Shield national survey noted a $25 \%$ increase in steroid and similar drug use from 1999 to 2000 among boys ages 12 to 17 .

## Effectiveness Questioned

For five decades, researchers and athletes have debated the true effect of anabolic steroids on human body composition and exercise performance. Much of the confusion about the ergogenic effectiveness of anabolic steroids stems from variations in experimental design, lack of control groups,
specific drugs and dosages, treatment duration, accompanying nutritional supplementation, training intensity, evaluation techniques, previous experience of subjects, and individual differences in responsiveness to a drug s effectiveness. The relatively small residual androgenic effect of the steroid facilitates central nervous system activation to make the athlete more aggressive (so-called roid rage), competitive, and fatigue resistant. Such facilitatory effects allow the person to train harder for a longer time or to believe that augmented training effects have actually occurred. Abnormal mood alterations and psychiatric dysfunction sometimes accompany androgen use. ${ }^{53,96}$

Research with animals suggests that anabolic steroid treatment combined with exercise and adequate protein intake stimulates protein synthesis and increases muscle protein content (myosin, myofibrillar, sarcoplasmic factors). ${ }^{222}$ In contrast, other research revealed that steroid treatment did not benefit leg muscle weight of rats subjected to functional overload by surgical removal of the synergistic muscle. ${ }^{170}$ Treatment with anabolic steroids did not complement functional overload to stimulate additional muscular development.

The situation with humans is difficult to interpret. Some studies show that steroid use by men who train augments body mass gains and reduces body fat, while other studies show no effect on strength and power or body composition, even with sufficient energy and protein intake to support an anabolic effect. ${ }^{91}$ When steroid use produces body weight gains, the compositional nature of the gains (water, muscle, fat) remains unclear. Patients receiving dialysis and those infected with the HIV virus commonly experience malnutrition, a decrease in muscle mass, and chronic fatigue. Dialysis patients given 6 months of supplementation with the anabolic steroid nandrolone decanoate increased lean body mass and level of daily function. ${ }^{138}$ Similarly, in men with HIV, a moderately supraphysiologic androgen regimen that included the anabolic steroid oxandrolone increased lean tissue accrual and strength gains from resistance training substantially more than physiologic testosterone replacement alone. ${ }^{251}$

## Dosage Is an Important Factor

In many instances, dosage variations contribute to confusion and create a credibility gap between scientist and steroid user regarding effectiveness. One study focused on 43 healthy men with some resistance-training experience. Experimental controls accounted for diet (energy and protein intake) and exercise (standard weightlifting, 3 times weekly) with steroid dosage ( 600 mg of testosterone enanthate injected weekly or placebo) exceeding values in previous studies with humans. Figure 23.3 illustrates changes from baseline values for fat-free body mass (FFM; hydrostatic weighing), triceps and quadriceps cross-sectional muscle areas (magnetic resonance imaging), and muscle strength (1-RM) after 10 weeks of treatment. The men who received the hormone while continuing to train gained about 0.5 kg of lean tissue weekly with no increase in body fat. Even the group receiving the drug without training


## $\square$ Placebo Testosterone

Figure 23.3 Changes from baseline in average fat-free body mass, triceps and quadriceps cross-sectional areas, and muscle strength in bench press and squatting exercises over 10 weeks of testosterone treatment. (From Bhasin S, et al. The effects of supraphysiological doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335:1.)
increased muscle mass and strength compared with men receiving the placebo. Notably, their increases averaged less than men who trained while taking testosterone. The researchers emphasized that that they did not design the study to justify or endorse steroid use for athletic purposes because of the health risks (see next section). These data did, however, indicate a potential for medically supervised anabolic steroid treatment to restore and enhance muscle mass in individuals suffering from tissuewasting diseases.

## Risks Do Exist

Whether anabolic steroid use by athletes carries health risks remains controversial because research on risk generally has involved medical observations of hospitalized patients treated
for anemia, renal insufficiency, impotence, or pituitary gland dysfunction. Prolonged high dosages of steroids (often at levels 10 to 200 times therapeutic recommendations) can lead to long-lasting impairment of normal testosterone endocrine function. In male power athletes, for example, 26 weeks of steroid administration reduced serum testosterone to less than one-half the level when the study began, with the effect lasting throughout a 12 - to 16 -week follow-up. ${ }^{91}$ Infertility, reduced sperm concentrations (azoospermia), and decreased testicular volume pose additional problems for the steroid user. ${ }^{99}$ Gonadal function usually returns to normal within several months after cessation of steroid use. Other hormonal alterations during steroid use by males include a sevenfold increase in estradiol concentration, the major female hormone. The higher estradiol level represented the average value for normal females; this possibly explains the gynecomastia (usually irreversible, excessive development of the male mammary glands, sometimes secreting milk) often reported when taking anabolic steroids.

Steroid use with exercise training may damage connective tissue to decrease tendon tensile strength and elastic compliance. ${ }^{162}$ Steroids also cause the following. ${ }^{3,72,92,105,118,142,254}$

1. Chronic stimulation of the prostate gland (with possible size increase)
2. Injury and functional alterations in cardiovascular function and myocardial cell cultures
3. Decreased diastolic relaxation and exacerbation of normal cardiac hypertrophy with resistance training; potential negative effects on thyroid gland function and hormone action
4. Increased blood platelet aggregation, which could compromise cardiovascular system health and function and possibly increase risk of stroke and myocardial infarction

Dramatic life shortening resulted for adult mice exposed for 6 months to the type and relative levels of steroids used by athletes. One year after termination of steroid exposure, $52 \%$ of mice given a high steroid dose died compared with $35 \%$ given a low steroid dosage and only $12 \%$ of the control animals given no exogenous hormones (Fig. 23.4). Autopsy of steroid-treated mice revealed a broad array of pathologic effects that did not appear until long after steroid use ceased-liver and kidney tumors, lymphosarcomas, and heart damage, frequently in combination. A 6-month exposure represents about one-fifth of a male mouse s life expectancy, a relative duration considerably longer than exposure of most humans to steroid use. Liver damage represents a typical effect in athletes who take steroids. If such findings prove applicable to humans, several decades may elapse before the true negative effects of anabolic steroid use emerge.

Steroid Use and Life-Threatening Disease. Table 23.2 lists adverse effects and medical risks of anabolic steroid use.


## Control $\square$ Low dose $\square$ High dose

Figure 23.4 Life-shortening effects of exogenous anabolic steroid use in mice. (Modified from Bronson FH, Matherne CM. Exposure to anabolic androgenic steroids shortens life span of male mice. Med Sci Sports Exerc 1997;29:615.)

Concern centers on possible links between androgen abuse and abnormal liver function. Because the liver almost exclusively metabolizes androgens, it becomes susceptible to damage from long-term steroid use and toxic excess. The development of localized blood-filled lesions, a condition
called peliosis hepatitis, is one of the serious effects of androgens on the liver. In the extreme case, the liver eventually fails and the patient dies. We present these data not as a scare tactic but to emphasize the potentially serious adverse effects, even when a physician prescribes the drug in the recommended dosage. Patients often take steroids for a longer duration than do athletes, yet some athletes take steroids on and off for years at dosages exceeding typical therapeutic levels of $50200 \mathrm{mg} \cdot \mathrm{d}^{-1}$ versus the usual therapeutic dosage of $520 \mathrm{mg} \cdot \mathrm{d}^{-1}$.

Steroid and Plasma Lipoproteins. Anabolic steroid use (particularly the orally active 17-alkylated androgens) by healthy men and women reduces high-density lipoprotein cholesterol (HDL-C) levels, elevates both low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels, and reduces the HDL-C:LDL-C ratio. ${ }^{56}$ Weightlifters who take anabolic steroids averaged an HDL-C level of 26 mg -$\mathrm{dL}^{-1}$ compared with $50 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ for weightlifters not taking this drug! ${ }^{141}$ Reducing HDL-C to this level increases a steroid user s risk of coronary artery disease. The dramatically low HDL-C levels among weightlifters remain low, even after they abstain for at least 8 weeks between consecutive steroid cycles. ${ }^{228}$ The long-term effects of steroid use on cardiovascular morbidity and mortality remain unknown.

American College of Sports Medicine Position Statement on Anabolic Steroids. As part of their long-range educational program, the American College of Sports Medicine (ACSM; www.acsm.org/) has taken a stand on the use of anabolic-androgenic steroids, which appears in the following FYI ${ }^{6}$ :

TABLE 23.2 Side Effects and Medical Risks of Anabolic Steroid Use

| Males |  |  | Females |  |
| :---: | :---: | :---: | :---: | :---: |
| Increase | Decrease |  | Increase | Decrease |
| Testicular atrophy Gynecomastia | Sperm count <br> Testosterone levels |  | Voice change (deepening) <br> Facial hair <br> Menstrual irregularities <br> Clitoral enlargement | ) Breast tissue |
| Males and Females |  |  |  |  |
| Increase |  | Decrease | Possible |  |
| LDL-C <br> LDL-C/HDL-C <br> Potential for neopl <br> Aggressiveness, Withdrawal and de <br> Acne <br> Peliosis hepatitis | ity id use stops | HDL-C |  | Hypertension <br> Connective tissue damage <br> Myocardial damage <br> Myocardial infarction <br> Impaired thyroid function <br> Altered myocardial structure |

American College of Sports Medicine: Position Stand on Use of Anabolic Steroids

Based on a comprehensive survey of the world literature and a careful analysis of the claims made for and against the efficacy of anabolic androgenic steroids in improving human physical performance, it is the position of the American College of Sports Medicine that:

Anabolic androgenic steroids in the presence of an adequate diet and training can contribute to increases in body weight, often in the lean muscle mass compartment.
The gains in muscular strength achieved through high-intensity exercise and proper diet can occur by the increased use of anabolic androgenic steroids in some individuals.
Anabolic androgenic steroids do not increase aerobic power or capacity for muscular exercise. Anabolic androgenic steroids have been associated with adverse effects on the liver, cardiovascular system, reproductive system, and psychologic status in therapeutic trials and in limited research on athletes. Until further research is completed, the potential hazards of the use of the anabolic androgenic steroids in athletes must include those found in therapeutic trials. The use of anabolic androgenic steroids by athletes is contrary to the rules and ethical principles of athletic competition as set forth by many of the sports governing bodies. The American College of Sports Medicine supports these ethical principles and deplores the use of anabolicandrogenic steroids by athletes.

Specific Risks for Females. Females have additional concerns about dangers from anabolic steroids. These include virilization (more apparent than in men), disruption of normal growth pattern by premature closure of the plates for bone growth (also for boys), altered menstrual function, dramatic increase in sebaceous gland size, acne, hirsutism (excessive body and facial hair), and generally irreversible deepening of the voice, decreased breast size, enlarged clitoris, and hair loss. Serum levels of LH, FSH, progesterone, and estrogens also decline. These may negatively affect follicle formation, ovulation, and menstrual function. The long-term effects on reproductive function, including possible sterility, require further clarification.

## Clenbuterol and Other $\boldsymbol{\beta}_{2}$-Adrenergic Agonists

Extensive, random testing of competitive athletes for steroid use has ushered in a number of steroid substitutes. These have appeared on the health food, mail order, and black market
drug network as competitors try to circumvent detection. One such drug, the sympathomimetic amine clenbuterol (brand names Clenasma, Monores, Novegan, Prontovent, and Spiropent) has become popular among athletes because of its purported tissue-building, fat-reducing benefits. When a bodybuilder discontinues steroid use before competition to avoid detection and possible disqualification, the athlete substitutes clenbuterol to retard loss of muscle mass and facilitate fat burning to achieve the desirable cut look. Clenbuterol has particular appeal to female athletes because it does not produce the androgenic side effects of anabolic steroids.

Clenbuterol, one of a group of chemical compounds (albuterol, clenbuterol, salbutamol, salmeterol, terbutaline, formoterol) classified as $\beta_{2}$-adrenergic agonists, facilitates responsiveness of adrenergic receptors to circulating epinephrine, norepinephrine, and other adrenergic amines. A review of the available studies of animals (to our knowledge, no human exercise studies have been conducted) indicates that when fed to sedentary, growing livestock in dosages in excess of those prescribed in Europe for human use for bronchial asthma, clenbuterol increases skeletal and cardiac muscle protein deposition and slows fat gain (enhanced lipolysis). It also increases FFM and decreases fat mass when administered long term at therapeutic levels to thoroughbred racehorses. ${ }^{144}$ Clenbuterol has been used experimentally in animals to counter the effects on muscle of aging, immobilization, malnutrition, and pathologic tissue-wasting conditions. Under these conditions, $\beta_{2}$-agonists show specific growth-promoting actions on skeletal muscle. ${ }^{76,294}$ For rats, clenbuterol altered muscle fiber type distribution, inducing enlargement and increased proportion of type II muscle fibers. ${ }^{64}$ A decrease in protein breakdown and increase in protein synthesis accounted for the animals increased muscle size. ${ }^{2,22}$

## Potential Negative Effects on Muscle, Bone, and Cardiovascular Function (Animal Studies)

Female rats treated with clenbuterol $\left(2 \mathrm{mg} \cdot \mathrm{kg}^{-1}\right)$ injected subcutaneously versus controls sham-injected with the same volume of fluid carrier each day for 14 days increased muscle mass, absolute maximal force-generating capacity, and hypertrophy of fast- and slow-twitch muscle fibers. ${ }^{73}$ A negative finding was hastened fatigue during short-term, intense muscle actions. In contrast, regular exercise combined with clenbuterol decreased muscular dystrophy progression in mice, reflected by increased muscle force-generating capacity. ${ }^{294}$ However, the group receiving clenbuterol experienced increased muscle fatigability and cellular deformities not noted in the exerciseonly group. This negative effect on muscle structure and function may explain findings that clenbuterol treatment negated the beneficial effects of exercise training on endurance performance, despite increased muscle protein content. ${ }^{127}$ Clenbuterol treatment induced muscular hypertrophy in young male rats but also inhibited longitudinal bone growth. ${ }^{149}$ Negative effects of clenbuterol and salbutamol affected mechanical properties and microarchitecture of trabecular bone of animals. An increase of muscle mass with enhanced bone fragility increases fracture risk
when treated with $\beta_{2}$-agonists as part of a doping regimen. ${ }^{29,30}$ The negative effect on bone contraindicates its use for prepubescent and adolescent humans.

Echocardiographic evaluations of Standard bred mares showed that chronic clenbuterol administration even at low therapeutic levels alters the heart s structural dimensions, which negatively affects cardiac function. ${ }^{240}$ Effects occurred whether the animals exercised or remained inactive. Clenbuterol also caused aortic enlargement after exercise to a degree that indicated increased risk of aortic rupture and sudden death. Clenbuterol treatment when combined with aerobic training blunts the normal training-induced increase in plasma volume in Standard bred mares; this effect accompanied decreased aerobic exercise performance and ability to recover. ${ }^{143}$

## Clenbuterol: Not Approved for Human Use in the United States

Clenbuterol is commonly prescribed abroad as an inhaled bronchodilator to treat obstructive pulmonary disorders. Reported short-term side effects in humans who accidentally overdosed from eating clenbuterol-tainted meat include: skeletal muscle tremor, agitation, palpitations, dizziness, nausea, muscle cramps, rapid heart rate, and headache. Despite these negative side effects, clenbuterol may benefit humans when used to treat muscle wasting (in disease), forced immobilization, and aging. Unfortunately, no data exist for potential toxicity level or its efficacy and long-term safety. Clearly, clenbuterol use cannot be justified or recommended as an ergogenic aid.

## Other Adrenergic Agonists

Research has focused on possible strength-enhancing effects of sympathomimetic $\beta_{2}$-adrenergic agonists other than clenbuterol. Men with cervical spinal-cord injuries took 80 mg of metaproterenol daily for 4 weeks in conjunction with physical therapy. Increases occurred in estimated muscle crosssectional area and elbow flexor and wrist extensor strength compared with a placebo condition. ${ }^{239}$ Albuterol administration ( $16 \mathrm{mg} \cdot \mathrm{d}^{-1}$ for 3 wk ) without exercise training improved muscular strength 10 to $15 \%$. ${ }^{167}$ Therapeutic doses of albuterol also facilitated isokinetic strength gains from slowspeed concentric/eccentric isokinetic training. ${ }^{44}$

## Training State Makes a Difference

Animals. Untrained skeletal muscle of animals responds to the effects of $\beta_{2}$-adrenergic agonists. The increase in muscle mass with clenbuterol treatment plus exercise training is more pronounced in animals without prior training experience than in trained animals that continue training and then receive this drug. ${ }^{184}$

Humans. Some research with humans shows improved muscle power output with albuterol administration. ${ }^{238}$ However, no ergogenic effect occurred from salbutamol on short-term
performance in two 10 -minute cycling trials. ${ }^{58}$ Similarly, no effect occurred in power output during a 30 -second Wingate test in nonasthmatic trained cyclists who received $360 \mu \mathrm{~g}$ (twice the normal dose administered by inhaler in 4 measured doses of $90 \mu \mathrm{~g}$ each) 20 minutes before testing. ${ }^{156}$ For men without asthma, acute therapeutic ( $200 \mu \mathrm{~g}$ ) or supratherapeutic ( $800 \mu \mathrm{~g}$ ) doses of inhaled salbutamol had no effect on quadriceps strength, fatigue, and recovery. ${ }^{67}$ In other research, twice the recommended dose of salbutamol (albuterol: 400 mg administered in four inhalations 20 minutes before exercising) did not enhance anaerobic power output, endurance performance, ventilatory threshold, or dynamic lung function of trained endurance cyclists. ${ }^{186}$ The researchers maintained that competitive athletes should not be prohibited from these compounds because they provide no ergogenic benefit, yet normalize individuals with obstructive pulmonary disorders. Differences in training status may explain discrepancies among studies concerning albuterol s effect on short-term power output.

Albuterol s ergogenic benefit supposedly comes from its stimulating effects on skeletal muscle $\beta_{2}$-receptors to increase muscle force and power. With exercise training, the muscle $\beta_{2-}$ receptors undergo downregulation (become less sensitive to a given stimulus) from chronic exposure to training-induced elevations in blood catecholamine levels. This makes the trained athlete less responsive to a sympathomimetic drug than an untrained counterpart.

## Growth Hormone: Genetic Engineering Comes to Sports

Human growth hormone ( $\mathbf{G H}$ or $\mathbf{h G H}$ ), also known as somatotropin, currently competes with anabolic steroids in the illicit market of alleged tissue-building, performanceenhancing drugs. The adenohypophysis of the pituitary gland produces GH , a potent anabolic and lipolytic agent in tissuebuilding processes and growth. Specifically, GH stimulates bone and cartilage growth, enhances fatty acid oxidation, and reduces glucose and amino acid breakdown. Reduced GH secretion accounts for some of the decrease in FFM and increase in fat mass that accompanies aging. This condition reverses somewhat with exogenous recombinant GH supplements produced by genetically engineered bacteria. Healthy elderly men who received GH supplements increased FFM $(4.3 \%)$ and decreased fat mass $(13.1 \%) .{ }^{190}$ Supplementation did not reverse the negative effects of aging on functional measures of muscular strength and aerobic capacity. Men receiving the supplement also experienced hand stiffness, malaise, arthralgias, and lower-extremity edema. One of the largest studies to date determined the effects of exogenous GH over a 6-month period on changes in body composition and functional capacity of healthy men and women aged mid-60s to late 80 s. ${ }^{27}$ Men who took GH gained 7 pounds of lean body mass and reduced a similar amount of fat mass. Women gained about 3 pounds of lean body mass and lost 5 pounds of body fat compared with counterparts receiving a placebo. Unfortunately, serious side effects afflicted between 24 and $46 \%$ of the subjects. These included swollen feet and
ankles, joint pain, carpal tunnel syndrome (swelling of tendon sheath over a nerve in the wrist), and development of a diabetic or prediabetic condition. As in prior research, no effects occurred for GH treatment on measures of muscular strength or endurance capacity despite increases in lean body mass.

Excessive GH production during skeletal growth produces gigantism, an endocrine and metabolic disorder characterized by abnormal size or overgrowth of the entire body or any of its parts. Excessive hormone production following growth cessation produces the irreversible disorder acromegaly that presents as enlarged hands, feet, and facial features. Medically, children who suffer from kidney failure or who produce insufficient GH receive thrice-weekly biosynthetic GH injections until adolescence to help them achieve nearnormal size. In young adults with hypopituitarism, GH replacement therapy improves muscle volume, isometric strength, and exercise capacity.

## No Unanimity Among Researchers

At first glance, GH use seems appealing to strength and power athletes because at physiologic levels, this hormone stimulates amino acid uptake and muscle protein synthesis while enhancing fat breakdown and conserving glycogen reserves. Unfortunately, few well-controlled studies have examined how GH supplements affect healthy subjects who undertake exercise training. In one study, six well-trained men maintained a highprotein diet while taking either biosynthetic GH or a placebo. ${ }^{63}$ During 6 weeks of standard resistance training with GH, percentage body fat decreased and FFM increased. No changes in body composition occurred for the group training with the placebo. Subsequent investigations failed to replicate these findings. For example, 16 previously sedentary young men who participated in a 12 -week resistance training program received recombinant human GH supplements ( $40 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~d}^{-1}$ ) or a placebo. ${ }^{293}$ FFM, total body water, and whole-body protein synthesis increased more in the GH recipients. No significant differences emerged between groups in fractional rate of protein
synthesis in skeletal muscle, torso and limb circumferences, or muscle function in dynamic and static strength measures (Table 23.3). The authors attributed the greater increase in whole-body protein synthesis in the GH group to a possible increase in nitrogen retention in lean tissue other than skeletal muscle-for example, connective tissue, fluid, and noncontractile protein.

GH occurs naturally in the body, making ready detection as an ergogenic substance difficult. Blood markers are currently available for screening. Nonprescription GH can only be obtained on the black market and often in an adulterated form. Human cadaver-derived GH (used until May 1985 by U.S. physicians to treat children of short stature) greatly increases risk for contracting Creutzfeldt-Jakob disease, an infectious, incurable, and fatal brain-deteriorating disorder. A synthetic form of GH (Protoropin and Humantrope), produced by genetic engineering, currently treats GH-deficient children. Undoubtedly, child athletes who receive GH believing they gain a competitive edge will suffer increased incidence of gigantism, while adults will develop acromegalic syndrome. Additional, less obvious side effects include insulin resistance that leads to type 2 diabetes, water retention, and carpal tunnel compression syndrome. Any potential benefits of GH must be weighed against potential adverse effects. ${ }^{100}$ Claims that growth hormone enhances physical performance are not supported by the scientific literature. Although the limited available evidence suggests that growth hormone increases lean body mass, it may not improve strength; in addition, it may worsen exercise capacity and increase adverse events. More research is needed to conclusively determine the effects of growth hormone on athletic performance. ${ }^{163}$

## DHEA

Dehydroepiandrosterone (DHEA and its sulfated ester, DHEA sulfate, or DHEAS, the most common hormone in the body) is a weak steroid hormone synthesized primarily from cholesterol by the adrenal cortex of primates. The body

TABLE 23.3 Maximal Force Production of Knee Extensor and Flexor Muscle Groups Before and After Training With or Without Growth Hormone Supplements

|  | Exercise plus Placebo |  |  | Exercise plus GH |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Initial | Final | \% Change | Initial | Final | \% Change |
| Concentric |  |  |  |  |  |  |
| Knee extensors | $212 \pm 13^{a}$ | $248 \pm 10$ | 17 | $191 \pm 11$ | $214 \pm 9$ | 12 |
| Knee flexors | $137 \pm 11^{a}$ | $158 \pm 7$ | 15 | $122 \pm 12$ | $143 \pm 6$ | 17 |
| Isometric |  |  |  |  |  |  |
| Knee extensors | $220 \pm 13^{a}$ | $252 \pm 13$ | 14 | $198 \pm 15$ | $207 \pm 7$ | 5 |
| Knee flexors | $131 \pm 8^{a}$ | $158 \pm 8$ | 20 | $127 \pm 13$ | $140 \pm 16$ | 10 |

From Yarasheski KF, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol 1992;262:E261.
${ }^{a}$ Values are mean $\pm$ SE. Maximum force $(\mathrm{N} \cdot \mathrm{m})$ determined using a Cybex dynamometer. Concentric force measured at $60 \cdot \mathrm{~s}^{-1}$ angular velocity. Isometric force measured at 135 of knee extension. The maximum concentric force production of knee flexor and extensor muscles increased significantly in both groups ( $\mathrm{P}<.05$ ), but these increments and the increments in maximum isometric force production were not greater in the exercise plus GH group.


Figure 23.5 Outline of metabolic pathways for dehydroepiandrosterone (DHEA), androstenedione, and related compounds. Directional arrows signify one-way and two-way conversions. Compounds in bold print are DHEA-precursor products currently available on the market.
produces more DHEA than all other known steroids. This mother hormone has a chemical structure that closely resembles testosterone and estrogen; a small amount of DHEA and related prohormone compounds are naturally derived precursors to testosterone or other anabolic steroids. Figure 23.5 outlines the major pathways for synthesizing DHEA, androstenedione, and related compounds.

Because DHEA occurs naturally, the FDA exerts no control over its distribution or claims for its action and effectiveness. The Drug Enforcement Administration (www.usdoj.gov/dea/) does not consider DHEA to be an anabolic steroid as defined in section 102(6) of the Controlled Substances Act (www.usdoj.gov/dea/pubs/csa.html). Instead, DHEA fits the definition of a dietary supplement.

The lay press, mail order, Internet, and health food industry and advertisements tout DHEA as a superhormone a Holy Grail that increases testosterone production; protects against cancer, heart disease, diabetes, and osteoporosis; bolsters the immune system; preserves youth; invigorates sex life; decreases joint pain and fatigue; facilitates lean tissue gain and body fat loss; enhances mood and memory and generally counters the debilitating effects of aging; and extends life. The hormone s detractors consider it the snake oil of the twenty-first century, and WADA has banned DHEA at zero-tolerance levels.

Figure 23.6 illustrates the generalized trend for plasma DHEA levels during a lifetime, with six common claims by manufacturers of supplements. Boys and girls have substantial
levels of DHEA at birth, which then decline sharply (not shown). DHEA production increases steadily from age 6 to 10 years (may contribute to the beginning of puberty and sexuality), and then rises sharply with peak production (higher in males than females) between ages 20 and 25 years. In contrast to the glucocorticoid and mineralocorticoid adrenal steroids, whose plasma levels remain relatively high with aging, DHEA levels undergo a steady decline after age 30 . By age 75, the plasma level averages only about $20 \%$ of that in young adults. This low level means that plasma DHEA levels might serve as a biochemical marker of biologic aging and disease susceptibility.

Popular reasoning concludes that supplementing with DHEA blunts the negative effects of aging by raising plasma levels to more youthful concentrations. Many persons supplement with this natural hormone just in case it proves beneficial-typically without considering the potential for biologic harm.

## An Unregulated Compound with Uncertain Safety

Appropriate DHEA dosage for humans remains uncertain. Concern exists about possible harmful effects on blood lipids, glucose tolerance, and prostate gland health, particularly because medical problems associated with hormone supplementation often do not appear until years after initiation of drug use.


Figure 23.6 Generalized trend for plasma levels of DHEA for men and women over a lifetime.

With humans, cross-sectional observations relating DHEA levels to risk of death from heart disease provided early indirect evidence for a beneficial effect. A high DHEA level conferred protection in men; for women, however, elevated DHEA increased heart disease risk. Subsequent research showed only a moderate protective association for men and no association for women. Studies suggest that DHEA supplements may provide cardioprotection during aging (more beneficial in men than in women), ${ }^{133}$ decrease abdominal fat and improve insulin sensitivity among the elderly, which could play a role in the prevention and treatment of the metabolic syndrome, ${ }^{274}$ boost immune function in disease, ${ }^{270}$ and provide antioxidant protection. ${ }^{7}$

In additional research on humans, eight men and eight women (ages 50 to 65 y ) received either 100 mg of DHEA or a placebo daily for 3 months and the other treatment for the next 3 months. ${ }^{182}$ All subjects showed a $1.2 \%$ increase in lean body mass during DHEA supplementation. Fat mass decreased in men but increased slightly in women. Chemical markers indicated improved immune function. These findings suggest some positive effects of exogenous DHEA on muscle mass and
immune function in middle-aged men and women. Subsequent research evaluated short-term ingestion of 50 mg of DHEA daily on serum steroid hormones and 8 weeks supplementation ( 150 mg daily) on resistance-training adaptations in young men. ${ }^{32}$ Short-term supplementation rapidly increased serum androstenedione (see next section) concentrations but exerted no effect on serum testosterone and estrogen concentrations. Furthermore, long-term DHEA supplementation elevated serum androstenedione levels but did not affect anabolic hormones, serum lipids, liver enzymes, muscular strength, and lean body mass, compared with a placebo for men undergoing similar training. These and similar results verify that relatively low dosages of DHEA do not increase serum testosterone levels, enhance muscular strength, change muscle and fat cross-sectional areas, or facilitate adaptations to resistance training. ${ }^{196,283}$

Concern exists about the effect of unregulated long-term DHEA supplementation (particularly at or above $50-\mathrm{mg}$ daily) on bodily function and overall health. Converting DHEA into potent androgens such as testosterone promotes facial hair growth in females and alters normal menstrual function. Like exogenous anabolic steroids, DHEA lowers HDL-C levels to increase heart disease risk. Conflicting data concern its effects on breast cancer risk. Clinicians have expressed fear that elevating plasma DHEA by supplementation might stimulate the growth of otherwise dormant prostate gland tumors or cause benign hypertrophy of the prostate gland. If cancer exists, DHEA may accelerate its growth. Despite its popularity among exercise enthusiasts, no data support an ergogenic effect of exogenous DHEA on young adult men and women.

## Androstenedione: Benign Prohormone Nutritional Supplement or Potentially Harmful Drug?

The over-the-counter supplement androstenedione (in addition to norandrostenediol and norandrostenedione, which convert to the steroid nandrolone) supposedly does the following:

1. Stimulates production of endogenous testosterone or forms androgen-like derivatives (as shown in Fig. 23.5)
2. Enables more intense training
3. Builds muscle mass
4. Rapidly repairs tissue injury

Found naturally in meat and some plant extracts, androstenedione is often touted as a prohormone, a metabolite only one step away from the biosynthesis of testosterone. The National Football League, NCAA, Men s Tennis Association, and WADA ban its use because they believe it provides unfair competitive advantage and may endanger health.

## INTEGRATIVE QUESTION

Respond to the question: If testosterone, growth hormone, and DHEA occur naturally in the body, what harm could exist in supplementing with these natural compounds?

In the United States in 1994, the FDA developed rules for marketing androstenedione as a food, not as a drug. By calling the substance a supplement and avoiding any claims of medical benefit, savvy marketers and distributors created a lucrative business for androstenedione, mostly via Internet sales and over-the-counter at health food stores. An androstenedione-containing chewing gum and steroid lozenge that dissolves under the tongue are currently available.

Androstenedione, an intermediate (precursor) hormone between DHEA and testosterone, aids the liver in synthesizing other biologically active steroid hormones. Androstenedione is normally produced by the adrenal glands and gonads and converted to testosterone enzymatically by $17 \beta$-hydroxysteroid dehydrogenase found in the body s diverse tissues. It also serves as an estrogen precursor.

Research has demonstrated the effectiveness of exogenous androstenedione for raising testosterone levels. Daily oral treatment with 200 mg of 4 -androstene-3,17-dione or 200 mg of 4 -androstene- $3 \beta, 17 \beta$-diol increased peripheral
plasma total and free testosterone concentrations compared with a placebo. ${ }^{78}$ Androstenedione dosages as high as 300 mg per day have elevated testosterone levels by $34 \%$. ${ }^{155}$ Chronic androstenedione administration also elevates serum estradiol and estrone in men and women, perhaps offsetting any potential anabolic effect.

Little scientific evidence supports claims of androstenedione s ergogenic effectiveness or anabolic qualities. One study systematically evaluated whether short- and long-term androstenedione supplementation elevates blood testosterone concentrations or enhances muscle size and strength gains during resistance training. In one phase of the investigation, young adult men received either a single $100-\mathrm{mg}$ dose of androstenedione or a placebo containing 250 mg of rice flour. Figure 23.7A shows that serum androstenedione rose $175 \%$ during the first 60 minutes following ingestion and then increased further to about $350 \%$ above baseline values between minutes 90 and 270. However, short-term supplementation did not affect serum concentrations of either free or total testosterone.


Figure 23.7 A. Effect of short-term (single-dose) exogenous supplementation with 100 mg of androstenedione or placebo on serum concentrations of androstenedione and free and total testosterone. B. Serum free and total testosterone, and C. serum estradiol and estrone with $300-\mathrm{mg}$ daily supplementation of androstenedione $(N=9)$ and placebo $(N=10)$ during 8 weeks of resistance training. (From King DS, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. JAMA 1999;281:2020.)

In the experiment s second phase, 20 young, untrained men received 300 mg of androstenedione daily $(N=10)$ or 250 mg of a rice flour placebo during weeks $1,2,4,5,7$, and 8 of an 8 -week total-body resistance-training program. Serum androstenedione levels increased $100 \%$ in the androstenedionesupplemented group and remained elevated throughout training. Serum testosterone levels (Fig. 23.7B) remained higher in the androstenedione-supplemented group than the placebo group before and following supplementation. Free and total testosterone levels remained unaltered for both groups. Serum estradiol and estrone concentrations only increased during training for the supplemented group, suggesting increased aromatization of the ingested androstenedione to estrogens (Fig. 23.7C). Resistance training increased muscle strength and lean body mass and reduced body fat for both groups, but no synergistic effect emerged for the group supplemented with androstenedione. The supplement produced a $12 \%$ HDLC reduction after only 2 weeks, which remained lower for the 8 weeks of training and supplementation. Serum liver enzyme concentrations stayed within normal limits for both groups throughout the experiment.

Contrary to marketing and advertising claims, research to date indicates that prohormone nutritional supplements (DHEA, androstenedione, androstenediol, and other prohormone compounds) do not produce anabolic or ergogenic effects in men. ${ }^{225}$ Research findings also indicate no effect of androstenedione supplementation on basal serum concentrations of testosterone or training response for muscle size and strength and body composition. The potential negative effects of the HDL-C reduction on overall heart disease risk and the elevated serum estrogen levels on risk of gynecomastia and possibly pancreatic and other cancers cause concern. Findings must be viewed within the context of this specific study, because subjects took smaller amounts of androstenedione than routinely consumed for ergogenic purposes ( 500 to 1200 mg per day).

## fyi <br> Summary of Research Findings Concerning Androstenedione

Conflicting findings concerning elevation of plasma testosterone concentrations No favorable effect on muscle mass No favorable effect on muscular performance No favorable alterations in body composition Elevates a variety of estrogen subfractions No favorable effect on muscle protein synthesis or tissue anabolism
Impairs blood lipid profile in healthy men
Increases likelihood of a positive steroid test result

## A Modified Version

Norandrostenedione and norandrostenediol are norsteroid compounds available over the counter in the United States. They are chemically similar to androstenedione and
androstenediol, respectively, except with slight chemical modification that supposedly enhances anabolic properties without converting to testosterone but to the steroid nandrolone. These modifications should theoretically confer anabolic effects via the compounds direct activation of the androgen receptors in skeletal muscle. To test this hypothesis, research evaluated 8 weeks of low-dose norsteroid supplementation on body composition, girth measures, muscular strength, and mood states of young adult, resistance-trained men. ${ }^{266}$ The men received 100 mg of 19 -nor-4-androstene-3,17-dione plus 56 mg of 19-nor-4-androstene-3,17-diol ( 156 mg total norsteroid per day) or a multivitamin placebo. Each subject did resistance training 4 days weekly for the duration of the study. Norsteroid supplementation provided no additional effect on any of the body composition or exercise performance variables.

## Competitive Athletes Beware

Elite athletes who take androstenedione can fail a urine test for the banned anabolic steroid nandrolone. This occurs because the supplement often contains contaminates with trace amounts (as low as $10 \mu \mathrm{~g}$ ) of 19-norandrosterone, the standard marker for nandrolone use. Many androstenedione preparations are grossly mislabeled. Analysis of nine different brands of $100-\mathrm{mg}$ doses indicate wide fluctuations in overall content ranging from zero to 103 mg of androstenedione, with one brand contaminated with testosterone. ${ }^{47}$

## INTEGRATIVE QUESTION

Outline the points you would make in a talk to a high school football team concerning whether they should consider using performanceenhancing chemicals and hormones.

## Amino Acid Supplementation

An emerging trend involves using nutrition as a legal alternative to activate the body s normal anabolic mechanisms. Highly specific dietary changes supposedly create a hormonal milieu that facilitates protein synthesis in skeletal muscle. More than 100 companies in the United States promote such alleged ergogenic stimulants. Weightlifters, bodybuilders, and fitness enthusiasts regularly use amino acid supplements, believing they boost the body s natural production of testosterone, GH, insulin, or insulin-like growth factor I (IGF-I) and so improve muscle size and strength and decrease body fat. The rationale for nutritional ergogenic stimulants comes from the clinical use of amino acid infusion or ingestion to regulate anabolic hormones in deficient patients.

Research on healthy subjects does not provide convincing evidence for an ergogenic effect of a generalized regular intake of amino acid supplements above the recommended protein intake on hormone secretion, training responsiveness,
or exercise performance. In studies with appropriate design and statistical analysis, oral supplements of arginine, lysine, ornithine, tyrosine, and other amino acids, either singly or in combination, produced no positive effect on GH levels, ${ }^{57,154}$ insulin secretion, ${ }^{34,90}$ diverse measures of anaerobic power, ${ }^{89}$ or all-out running performance at $\mathrm{VO}_{2 \max } \cdot{ }^{248}$ Elite junior weightlifters who regularly supplemented with all 20 amino acids did not improve physical performance or change resting or exercise levels of testosterone, cortisol, or GH. ${ }^{95}$ Thus, regular intake of amino acids in the quantities recommended in commercial supplements does not benefit the hormonal profile, body composition and muscle size, or exercise performance. Additionally, indiscriminate consumption of amino acid supplements at dosages considered pharmacologic rather than nutritional raises the possibility of direct toxic effects or the creation of an amino acid imbalance.

## Specific Timing of Intake May Stimulate an Anabolic Effect

Manipulation and timing of intake of nutritional variables in the immediate pre- and postexercise periods can affect the responsiveness to resistance training via mechanisms that alter nutrient availability, enzyme activity, circulating metabolites and hormonal secretions, interactions with receptors on target tissues, and gene translation and transcription. ${ }^{82,147,260,277}$ Resistance training stimulates protein synthesis and protein degradation in exercised muscle fibers. Muscle hypertrophy occurs when a net increase in protein synthesis results from a shift in the body s normal dynamic state of synthesis and degradation. The normal hormonal milieu (e.g., insulin and GH levels) in the period following resistance exercise stimulates the muscle fiber s anabolic processes while inhibiting muscle protein degradation. Dietary modifications that increase amino acid transport into muscles, raise energy availability, or increase anabolic hormones, particularly insulin, should theoretically increase the rate of anabolism and/or depress catabolism. Either effect would create a positive body protein balance to improve muscle growth and strength.

Carbohydrate Protein-Creatine Supplementation in Recovery Augments Hormonal Response to Resistance Exercise. Studies of hormonal dynamics and protein anabolism indicate a transient but potential ergogenic effect (up to 4 -fold increase in protein synthesis) ${ }^{208}$ of carbohydrate and/or protein supplements consumed prior to ${ }^{259,291}$ or immediately following a resistance exercise workout. ${ }^{25,129,176}$ Supplementation in the immediate postexercise period may also enhance repair and synthesis of muscle proteins following aerobic exercise. ${ }^{157,158}$

Drug-free male weightlifters with at least 2 years of training experience consumed carbohydrate and protein supplements immediately after a standard workout. ${ }^{48}$ Treatment included either (1) placebo of pure water or a supplement of (2) carbohydrate ( 1.5 g per kg body mass), (3) protein (1.38 g per kg body mass), or (4) carbohydrate protein ( 1.06 g carbohydrate plus 0.41 g protein per kg body mass) consumed
immediately following and then 2 hours following the training session. Each nutritive supplement produced a hormonal environment (elevated plasma insulin and GH concentrations) during recovery more conducive to protein synthesis and muscle tissue growth than the placebo condition. Subsequent research showed that protein carbohydrate supplementation before and immediately following resistance training altered the metabolic and hormonal responses to 3 consecutive days of heavy resistance training. ${ }^{151}$ Changes in the immediate recovery period included increased concentrations of glucose, insulin, GH, and IGF-I and decreased blood lactate concentration. Such data provide indirect evidence for a possible training benefit (e.g., enhanced glycogen and protein synthesis in recovery) from increasing carbohydrate and/or protein intake immediately after a workout.

A recent study compared the effects of supplement timing (i.e., the strategic consumption of protein and carbohydrate before and/or after each workout) compared with supplementation in the hours not close to the workout on muscle fiber hypertrophy, muscular strength, and body composition. Resistance-trained men matched for strength were placed in one of two groups; one group consumed a supplement (1g per kg body weight) containing protein creatine glucose immediately before and after resistance training, while the other group received the same supplement dose in the morning and late evening of the workout day. Measurements of body composition by dual energy X-ray absorptiometry (DXA; see Chapter 28), strength (1-RM), and muscle fiber type, crosssectional area, contractile protein, creatine, and glycogen content from vastus lateralis muscle biopsies took place the week prior to and immediately after a 10 -week training program. Supplementation in the immediate pre post exercise period produced a greater increase in lean body mass and 1-RM strength in two of three measures (Fig. 23.8). Body composition changes were supported by greater increases in muscle cross-sectional area of the type II muscle fibers and contractile protein content. These findings indicate that supplement timing provides a simple but effective strategy to enhance the desired adaptations from resistance training.

Postexercise Glucose Augments Protein Balance After Resistance-Training Workouts. Research with postexercise glucose ingestion complements the previously described studies of carbohydrate protein supplementation following resistance training. Healthy men familiar with resistance training performed 8 sets of 10 repetitions of unilateral knee extensor exercise at $85 \%$ of maximum strength in a placebo-controlled, randomized, double-blind trial. Immediately after the exercise session and 1 hour later, subjects received either a glucose supplement ( 1.0 g per kg body mass) or a placebo of Nutrasweet. Measurements consisted of (1) urinary 3-methylhistidine excretion (3-MH) as a marker of muscle protein degradation, (2) vastus lateralis muscle incorporation rate for the amino acid leucine ( $\mathrm{L}-\left[1-{ }^{13} \mathrm{C}\right]$ leucine) to indicate protein synthesis, and (3) urinary nitrogen excretion to reflect protein breakdown. Figure 23.9A and B shows that glucose supplementation reduced myofibrillar

$\square$ Pre/Post Mor/Eve * Statistically significant greater
Figure 23.8 Effects of receiving a supplement ( 1 g per kg of body weight) or protein, creatine, and glucose immediately before and after resistance (Pre/Post) exercise training or in the early morning (Mor) or late evening (Eve) of the training day on changes in (A) body composition (B) 1-RM strength and (C) muscle cross-sectional area (From Cribb PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exerc 2006;38:1918.)
protein breakdown as reflected by decreased excretion of 3-MH and urinary nitrogen. Although not statistically significant, glucose supplementation also increased the rate of leucine incorporation into the vastus lateralis over the 10 -hour postexercise period (Fig. 23.8C). These alterations indicated that the supplemented condition produced a more positive body protein balance after exercise. The beneficial effect of a postexercise high-glycemic glucose supplementation most likely occurred from increased insulin release with glucose intake, which should enhance muscle protein balance in recovery.

One should view the effects of immediate postexercise carbohydrate and/or protein supplementation in perspective. The question awaiting answer concerns the degree that any transient (albeit positive) change in hormonal milieu favoring anabolism and net protein synthesis caused by postexercise dietary maneuvers contributes to long-term muscle growth and strength enhancement. In this regard, no effect occurred from immediate postexercise ingestion of an amino acid carbohydrate mixture on muscular strength or size gains of older men who did 12 -weeks of knee extensor resistance training. ${ }^{102}$ Differences in study population, criterion variables, specific amino acid mixtures, overall diet composition, and subjects age may account for future discrepancies in research findings.

Dietary Lipid May Affect Hormonal Milieu. The diet s lipid content can modulate resting neuroendocrine homeostasis to modify tissue synthesis and training responsiveness. Research evaluated the effects of an intense re-sistance-exercise bout on postexercise plasma testosterone. In agreement with prior research, testosterone levels increased 5 minutes postexercise. A more impressive finding was a close association between the macronutrient composition of the individual $s$ regular diet and resting testosterone levels. Table 23.4 shows that the quantity and percentage of dietary macronutrients correlated with preexercise testosterone concentrations. Dietary lipid and saturated and monounsaturated fatty acid levels best predicted testosterone concentrations at rest-lower levels of each of these dietary components accompanied lower resting levels of testosterone. These findings support prior studies that showed that a low-fat diet ( $\sim 20 \%$ fat) produced lower testosterone levels than a diet with higher lipid content ( $\sim 40 \%$ fat). ${ }^{206,258}$ The diet s protein percentage correlated inversely with resting testosterone levels-higher dietary protein related to lower testosterone levels (see Table 23.4). Many resistance-trained athletes consume considerable dietary protein, so the implications of this association for the training response remain unresolved. If a low dietary lipid intake decreases resting testosterone levels, then individuals who typically consume low-fat diets (e.g., vegetarians, dancers, gymnasts, wrestlers) may experience a diminished training response. Furthermore, athletes who show low plasma testosterone levels from overtraining may benefit from changing their diet s macronutrient composition to lower protein and higher fat.


TABLE 23.4 Relationships Between Preexercise Testosterone Concentration and Selected Nutritional Variables

| Nutrient | Correlation with <br> Testosterone ${ }^{\boldsymbol{a}}$ |
| :--- | :---: |
| Energy, kJ | -0.18 |
| Protein, $\%^{b}$ | $-0.71^{*}$ |
| $\mathrm{CHO}, \%^{b}$ | -0.30 |
| Lipid, $\%^{b}$ | $0.72^{*}$ |
| SFA, g $1000 \mathrm{kCal}^{-1} \cdot \mathrm{~d}^{-1}$ | 0.77 |
| MUFA, g $1000 \mathrm{kCal}^{-1} \cdot \mathrm{~d}^{-1}$ | 0.79 |
| PUFA, g $1000 \mathrm{kCal}^{-1} \cdot \mathrm{~d}^{-1}$ | 0.25 |
| Cholesterol, g $1000 \mathrm{kCal}^{-1} \cdot \mathrm{~d}^{-1}$ | 0.53 |
| PUFA/SFA | -0.63 |
| Dietary fiber, g $1000 \mathrm{kCal}^{-1} \cdot \mathrm{~d}^{-1}$ | -0.19 |
| Protein/CHO | -0.59 |
| Protein/lipid | 0.16 |
| CHO/lipid | 0.16 |

${ }^{a}$ Pearson product-moment correlations
${ }^{b}$ Nutrient percentage values expressed as percentage of total energy per day.

* $\mathrm{P} \leq .01 ; ~ \mathrm{P} \leq .005 ; ~ \mathrm{P} \leq .05$.

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; CHO , carbohydrate.
From Volek JS, et al. Testosterone and cortisol in relationship to dietary nutrients and resistance exercise. J Appl Physiol 1997;82:49.

## Amphetamines

Amphetamines, or pep pills, comprise a group of pharmacologic compounds that exert powerful stimulating effects on central nervous system function. Amphetamine (Benzedrine) and dextroamphetamine sulfate (Dexedrine) have frequently been used by athletes. Amphetamines exert sympathomimetic effects-their action mimics epinephrine and norepinephrine (sympathomimetic)—to increase blood pressure, heart rate, cardiac output, breathing rate, metabolism, and blood glucose. Five to 20 mg of amphetamine usually exerts its effect for 30 to 90 minutes after ingestion, although its influence often persists for longer. Amphetamines increase alertness,

Figure 23.9 Effects of glucose ( 1.0 g per kg body mass) versus Nutrasweet placebo, ingested immediately after exercise and 1 hour later, on protein degradation reflected by 24-hour urinary output of (A) 3-methylhistidine, (B) urinary urea nitrogen, and (C) rate of muscle protein synthesis (MPS) measured by vastus lateralis muscle incorporation of leucine ( $\mathrm{L}-\left[1-{ }^{13} \mathrm{C}\right]$ ). Bars for MPS indicate difference between exercise and control leg for glucose and placebo conditions. (From Roy BD, et al. Effect of glucose supplement timing on protein metabolism after resistance training. J Appl Physiol
1997;82:1882.)

## IN A PRACTICAL SENSE

## Nutrient Timing to Optimize Muscle Response to Resistance Training

An evidence-based nutritional approach may enhance the quality of resistance training and facilitate muscle growth and strength development. This easy-to-follow new dimension to sports nutrition emphasizes not only the specific type and mixture of nutrients but also the timing of nutrient intake. Its goal is to blunt the catabolic state (release of hormones glucagon, epinephrine, norepinephrine, cortisol) and activate the natural muscle-building hormones (testosterone, growth hormone, IGF-1, insulin) to facilitate recovery from exercise and maximize muscle growth. Three phases for optimizing specific nutrient intake are outlined:

1. The energy phase enhances nutrient intake to spare muscle glycogen and protein, enhance muscular endurance, limit immune system suppression, reduce muscle damage, and facilitate recovery in the postexercise period. Consuming a carbohydrate protein supplement in the immediate preexercise period and during exercise extends muscular endurance; the ingested protein promotes protein metabolism, thus reducing demand for amino acid release from muscle. The carbohydrates consumed during exercise suppress release of cortisol. This blunts the suppressive effects of exercise on immune system function and lessens the use of branched-chain amino acids generated by protein breakdown for energy.
The recommended energy phase supplement contains the following nutrients: 20 to 26 g of high-glycemic carbohydrates (glucose, sucrose, maltodextrin), 5 to 6 g of whey protein (rapidly digested, high-quality protein separated from milk in the cheese-making process), 1 g of leucine; 30 to 120 mg of vita$\min \mathrm{C}, 20$ to 60 IU of vitamin E, 100 to 250 mg of sodium, 60 to 100 mg of potassium, and 60 to 220 mg magnesium. Ingestion of the more slowly digested whole protein casein after exercise produces similar increases in muscle protein net balance and a short-term net muscle protein synthesis compared with whey protein.
2. The anabolic phase consists of the 45-minute postexercise metabolic window-a period of enhanced insulin sensitivity for muscle glycogen replenishment and repair and synthesis of muscle tissue. This shift from catabolic to anabolic state occurs largely by blunting the action of the catabolic hormone cortisol and increasing the anabolic, muscle-building effects of the hormone insulin by consuming a standard high-glycemic carbohydrate protein supplement in liquid form (e.g., whey protein and high-glycemic carbohydrates). In essence, the high-glycemic carbohydrate consumed postexercise serves as a nutrient activator to stimulate insulin release, which, in the presence of amino acids, increases muscle tissue synthesis and decreases protein degradation.
The recommended anabolic phase supplement profile contains the following nutrients: 40 to 50 g of high-glycemic carbohydrates (glucose, sucrose, maltodextrin), 13 to 15 g of whey protein, 1 to 2 g of leucine; 1 to 2 g of glutamine, 60 to 120 mg of vitamin C, and 80 to 400 IU of vitamin E.
3. The growth phase extends from the end of the anabolic phase to the beginning of the next workout. It represents the time period to maximize insulin sensitivity and maintain an anabolic
state to accentuate gains in muscle mass and muscle strength. The first several hours (rapid segment) of this phase is geared to maintaining increased insulin sensitivity and glucose uptake to maximize glycogen replenishment. It also speeds elimination of metabolic wastes via increased blood flow and stimulates tissue repair and muscle growth. The next 16 to 18 hours (sustained segment) maintains a positive nitrogen balance. This occurs with a relatively high daily protein intake (between 0.91 and 1.2 g of protein per pound of body weight) that fosters sustained but slower muscle tissue synthesis. An adequate carbohydrate intake emphasizes glycogen replenishment.

The recommended growth phase supplement contains the following nutrients: 14 g of whey protein, 2 g of casein, 3 g of leucine, 1 g of glutamine, and 2 to 4 g of high-glycemic carbohydrates.

[^41] 2006;38:1918.


## TABLE 23.5 Effects of Amphetamines on Athletic Performance

Study Dose (mg) Experiment Effect of Amphetamines

| (1) | 1020 | Two all-out treadmill runs with $10-\mathrm{min}$ rest between runs | None |
| :---: | :---: | :---: | :---: |
|  |  | Consecutive $100-\mathrm{yd}$ swims with $10-\mathrm{min}$ rest intervals | None |
|  |  | 220 440-yd swims for time | None |
|  |  | $220-y d$ track runs for time | None |
|  |  | 100 -yd to 2-mile track runs for time | None |
| (2) | 10 | Bench stepping to fatigue carrying weights equal to one-third body mass, 3 times with 3-min rest intervals | None |
| (3) | 5 | $100-\mathrm{yd}$ swim for speed | None |
| (4) | 15 | All-out treadmill runs | None |
| (5) | 10 | Stationary cycling at work rates of 2752215 $\mathrm{kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ for 2535 min followed by a treadmill run to exhaustion | None on submaximal or maximal $\mathrm{VO}_{2}$, heart rate, ventilation volume, or blood lactate; time on the bicycle and treadmill increased significantly |
| (6) | 20 | Reaction and movement time to a visual stimulus | None; subjective feelings of alertness or lethargy unrelated to reaction or movement time |
| (7) | 5 | Psychomotor performance during a simulated airplane flight | Enhanced performance and lessened fatigue; if preceded by secobarbital (barbiturate), performance decreased |
| 1. Karpovich PV. Effect of amphetamine sulfate on athletic performance. JAMA 1959;170:558. |  |  |  |
| 2. Foltz EE, et al. The influence of amphetamine (Benzedrine) sulfate and caffeine on the performance of rapidly exhausting work by untrained subjects. J Lab Clin Med 1943;28:601. |  |  |  |
| 3. Haldi J, Wynn, W. Action of drugs on efficiency of swimmers. Res Q 1959;17:96. |  |  |  |
| 4. Golding LA, Barnard RJ. The effects of d-amphetamine sulfate on physical performance. J Sports Med Phys Fitness 1963;3:221. |  |  |  |
| 5. Wyndham CH, et al. Physiological effects of the amphetamines during exercise. S Afr Med J 1971;45:247. |  |  |  |
| 6. Pierson WR, et al. Some psychological effects of the administration of amphetamine sulfate and meprobamate on speed of movement and reaction time. Med Sci Sports 1961;12:61. |  |  |  |
| 7. McKenzie RE, Elliot LL. Effects of secobarbital and D-amphetamine on performance during a simulated air mission. Aerospace Med 1965;36:774. |  |  |  |

wakefulness, and capacity to perform work by depressing the sensation of muscle fatigue. The deaths of two famed cyclists in the 1960s during competitive road racing were attributed to amphetamine use. In one of these deaths in 1967, British Tour de France rider Tom Simpson overheated and suffered a fatal heart attack during the ascent of Mont Ventoux in Provence.

## Dangers of Amphetamines

Amphetamine use in athletics makes little sense for the following five reasons:

1. Regular use can lead to either physiologic or emotional drug dependency. This causes a cyclical reliance on uppers (amphetamines) or downers (barbiturates)-the barbiturates reduce or tranquilize the hyper state brought on by amphetamines.
2. General side effects include headache, tremulousness, agitation, fever, dizziness, and confusion, all of which negatively affect sports performance that requires rapid reaction and judgment and a high level of steadiness and mental concentration.
3. Larger doses are required to achieve the same effect because drug tolerance increases with prolonged use; this can aggravate and precipitate cardiovascular disorders.
4. Inhibition or suppression of the body s normal mechanisms for perceiving and responding to pain, fatigue, or heat stress jeopardizes health and safety.
5. Effects of prolonged intake of high doses remain unknown.

## Amphetamine Use and Exercise Performance

TABLE 23.5 summarizes the results of seven experiments on amphetamines and physical performance. In general, amphetamines did not affect exercise capacity or performance of simple psychomotor tasks.

Athletes take amphetamines to get up for the event and keep psychologically ready to compete. The day or evening before a contest, competitors often become nervous and irritable and have difficulty relaxing. Under these circumstances, a barbiturate induces sleep. The athlete then regains the hyper condition by popping an upper prior to competition. WADA and international sport-governing groups disqualify athletes for amphetamine use. Ironically, most research indicates that amphetamines do not enhance physical performance. Perhaps their greatest influence lies in the psychologic realm; athletes are easily convinced that any supplement augments performance. A placebo containing an inert substance often produces similar results!

## Caffeine

Caffeine represents a possible exception to the general rule against taking stimulants for ergogenic effects. Caffeine s classification and prior regulatory status depend on its use as either a drug (over-the-counter for migraine headaches), food (in coffee and soft drinks), or dietary supplement (alertness products). The most widely consumed behaviorally active substance in the world, caffeine belongs to a group of lipidsoluble purines (proper chemical name: 1,3,7-trimethylxanthine) found naturally in coffee beans, tea leaves, chocolate, cocoa beans, and cola nuts and often added to carbonated beverages and nonprescription medicines (Table 23.6). For coffee consumption, this translates to a total of over 500 million cups of coffee consumed daily! Sixty-three plant species contain caffeine in their leaves, seeds, or fruits. In the United States, $75 \%$ ( 14 million kg ) of caffeine intake (per capita, $150 \mathrm{mg} \cdot$ $\mathrm{d}^{-1}$ ) comes from coffee ( 3.5 kg per person per year), $15 \%$ from tea, and the remainder from the other items listed in Table 23.6. Depending on preparation, one cup of brewed coffee contains between 60 and 150 mg of caffeine, instant coffee about 100 mg , brewed tea between 20 and 50 mg , and caffeinated soft drinks about 50 mg . For comparison, 2.5 cups of percolated coffee contain 250 to 400 mg , or generally between 3 and 6 mg per kg of body mass.

The intestinal tract absorbs caffeine rapidly; peak plasma concentration is reached within 1 hour. It also clears from the body relatively quickly, taking about 3 to 6 hours for blood caffeine concentrations to decrease by one-half, compared with about 10 hours for the stimulant methamphetamine.

## Ergogenic Effects

Drinking 2.5 cups of regularly percolated coffee up to 1 hour before exercising often extends endurance in strenuous aerobic exercise under laboratory conditions; it also improves higher intensity, shorter duration exercise, muscular strength and power in prolonged exercise, cognitive performance and complex cognitive ability, and team sport performance. ${ }^{68,74,124,233,252}$ Elite distance runners who consumed 10 mg of caffeine per kg of body mass immediately before a treadmill run to exhaustion improved performance time compared with placebo or control conditions. ${ }^{93}$ Ergogenic effects during exhaustive exercise at $80 \% \mathrm{VO}_{2 \max }$ that follows a $5-\mathrm{mg} \cdot \mathrm{kg}^{-1}$ caffeine dose are maintained 5 hours later in a subsequent exercise challenge. ${ }^{17}$ Thus, no need exists to ingest an additional dose to maintain high blood caffeine levels and ergogenic effects during subsequent exercise within 5 hours. Furthermore, caffeine ingestion does not impede glycogen resynthesis with carbohydrate supplementation after extreme depletion of muscle glycogen. ${ }^{15}$

Data presented in Focus on Research, page 560, show that subjects performed on average 90.2 minutes of exercise with caffeine and 75.5 minutes without it. Consuming caffeine before exercise increased fat catabolism and reduced carbohydrate oxidation during exercise. The ergogenic effect of caffeine also applies to exercise performed at high ambient temperatures. ${ }^{55}$

Caffeine benefits maximal swimming performance. In a double-blind, cross-over research design, seven male and four female competent distance swimmers ( $<25 \mathrm{~min}$ for 1500 m ) consumed caffeine ( $6 \mathrm{mg} \cdot \mathrm{kg}$ body mass ${ }^{-1}$ ) 2.5 hours before swimming 1500 m . Figure 23.10 shows that split times improved with caffeine for each $500-\mathrm{m}$ of the swim. Swim time averaged $1.9 \%$ faster with caffeine than without it (20:58.6 vs. 21:21.8). Enhanced performance with caffeine associated with a lower plasma potassium concentration before exercise and higher blood glucose levels at the end of the trial. These responses suggest a possible caffeine effect on electrolyte balance and glucose availability.

No Dose Response Relationship. Figure 23.11 illustrates the effects of preexercise caffeine intake on endurance time of nine trained male cyclists. Subjects received a placebo or a capsule containing 5,9 , or 13 mg of caffeine per kg of body mass 1 hour before cycling at $80 \%$ of maximal power output on a $\mathrm{VO}_{2 \max }$ test. All caffeine trials showed a $24 \%$ improvement in performance with no additional benefit from caffeine quantities above $5 \mathrm{mg} \cdot \mathrm{kg}$ body mass ${ }^{-1}$.

## Proposed Mechanism for Ergogenic Effect

A precise explanation for the ergogenic boost from caffeine remains elusive. The ergogenic effect of caffeine (or related methylxanthine compounds) in intense endurance exercise has generally been attributed to facilitated fat use as an exercise fuel, thus sparing carbohydrate reserves. In the quantities usually administered to humans, caffeine probably affects metabolism in either of two ways: (1) directly on adipose and peripheral vascular tissues or (2) indirectly by stimulating epinephrine release from the adrenal medulla. Epinephrine then acts as an antagonist of the adenosine receptors on adipocyte cells, which normally repress lipolysis. Caffeine s inhibition of adenosine receptors increases cellular levels of the second messenger cyclic $3^{\prime}, 5^{\prime}$-adenosine monophosphate or cyclic AMP. Cyclic AMP then activates hormone-sensitive lipases to promote lipolysis; this effect causes the release of free fatty acids (FFAs) into the plasma. Elevated FFA levels increase fat oxidation, thus conserving liver and muscle glycogen to benefit intense endurance exercise.

Caffeine s ergogenic effects also appear unrelated to hormonal or metabolic changes. This suggests a possible direct action of caffeine on specific tissues, including the nervous system. Caffeine and its metabolites readily cross the blood brain barrier to produce analgesic effects on the central nervous system, potentially reducing the perception of effort during exercise. Caffeine enhances motoneuronal excitability to facilitate motor unit recruitment. The stimulating effects of caffeine do not occur from its direct action on the central nervous system. Instead, caffeine acts indirectly by blocking the receptors for adenosine (discussed earlier) that also serve a neuromodulator function to calm brain and spinal cord neurons. The following four factors

## TABLE 23.6 Caffeine Content of Common Foods, Beverages, and Over-the-Counter Medications

| Beverages and Food |  | Over-the-Counter Products |  |
| :---: | :---: | :---: | :---: |
| Substance | Caffeine Content (mg) | Substance Co | eine <br> (mg) |
| Coffee |  | Cold Remedies |  |
| Coffee, Starbucks, grande, 160 z | 550 | Dristan Coryban-D, Triaminicin, Sinarest | 3031 |
| Coffee, Starbucks, tall, 12 oz | 375 | Excedrin | 65 |
| Coffee, Starbucks, short, 8 oz | 250 | Actifed, Contac, Comtrex, Sudafed | 0 |
| Coffee, Starbucks, Americano, tall, 12 oz | 70 | Diuretics |  |
| Coffee, Starbucks, latte or cappuccino, grande, 16 oz | 70 | Aqua-ban Pre-Mens Forte | $\begin{aligned} & 200 \\ & 100 \end{aligned}$ |
| Brewed, drip method | 110150 | Pain Remedies |  |
| Brewed, percolator | 64124 | Vanquish | 33 |
| Instant | 40108 | Anacin; Midol | 32 |
| Expresso | 100 | Aspirin, any brand; Bufferin, Tylenol, Excedrin PM | 0 |
| Decaffeinated, brewed or instant; Sanka | 25 | Stimulants |  |
| Tea, 5-oz cup ${ }^{a}$ |  |  |  |
| Brewed, 1 min | 933 | caplet, Caffedrine | 200 |
| Brewed, 3 min | 2046 | NoDoz tablet | 100 |
| Brewed, 5 min | 2050 | Energets lozenges | 75 |
| Iced tea, 12 oz ; instant tea | 1236 | Weight control aids |  |
| Chocolate |  |  |  |
| Baker s semi-sweet, 1 oz; Baker s chocolate chips, ${ }^{1} 4$ cup | 13 | Prolamine | $140$ |
| Cocoa, 5-oz cup, made from mix | 610 | Pain drugs ${ }^{\text {b }}$ |  |
| Milk chocolate candy, 1 oz | 6 | Cafergot | 100 |
| Sweet/dark chocolate, 1 oz | 20 | Migrol | 50 |
| Baking chocolate, 1 oz | 35 | Fiornal | 40 |
| Chocolate bar, 3.5 oz | 1215 | Darvon compound | 32 |
| Jello chocolate fudge mousse | 12 |  |  |
| Ovaltine | 0 |  |  |
| Candy |  |  |  |
| Pit Bull Energy Bar (1 bar 2 oz ) | 165 |  |  |
| Crackheads (1 box 1.3 oz ) | 120 |  |  |
| Blitz energy gum (2 pieces) | 110 |  |  |
| Jolt gum (1 piece) | 60 |  |  |
| Snickers Charged (1 bar 2 oz ) | 60 |  |  |
| Jelly Belly Extreme Sports Beans (14 pieces 1 oz ) | 50 |  |  |
| Warp Energy Mints (10) | 50 |  |  |
| VoJo Extreme Energy Mints (4) | 40 |  |  |
| Headshot Energy (1 bar 1.8 oz ) | 20 |  |  |
| Soft Drinks |  |  |  |
| Sugar-Free Mr. Pibb | 59 |  |  |
| Mellow Yellow, Mountain Dew | 5354 |  |  |
| Tab | 47 |  |  |
| Coca Cola, Diet Coke, 7-Up Gold | 46 |  |  |
| Shasta-Cola, Cherry Cola, Diet Cola | 44 |  |  |
| Dr. Pepper, Mr. Pibb | 4041 |  |  |
| Dr. Pepper, sugar free | 40 |  |  |
| Pepsi Cola | 38 |  |  |
| Diet Pepsi, Pepsi Light, Diet RC, RC Cola, Diet Rite | ite 36 |  |  |
| Energy drinks |  |  |  |
| Jolt ( 23.5 oz ) | 280 |  |  |
| Rockstar-Punched, Roasted, or Zero Carb | 240 |  |  |
| Arizona Green Tea Energy or SoBe No Fear ${ }^{1}$ | 170 |  |  |
| Rockstar-Juiced, Original, or Sugar Free | 160 |  |  |
| Energy, or Monster ${ }^{1}$ |  |  |  |
| SoBe Adrenaline Rush-Sugar Free or regular | 150 |  |  |
| Nestea Enviga (12 oz) or BAWLS | 100 |  |  |
| TAB (10.5 oz) or SoBe Essential | 95 |  |  |
| Red Bull—regular or Sugar Free (8.3 oz) | 80 |  |  |
| Glac au Vitamin Water, Energy (20 oz) | 50 |  |  |
| Propel Invigorating Waters (20 oz) | 50 |  |  |

[^42]

## $\square$ Placebo $\square$ Caffeine

Figure 23.10 Split times for each 500 m of a 1500-m time trial with caffeine and placebo. Caffeine produced significantly faster split times. (From MacIntosh BR, Wright BM. Caffeine ingestion and performance of a 1500-metre swim. Can J Appl Physiol 1995;20:168.)


## $\square$ Caffeine $\square$ Placebo

Figure 23.11 Endurance performance (time to fatigue) following preexercise doses of caffeine in different concentrations. Cycling time (min) represents the average for nine male cyclists. All caffeine trials produced significantly better performance than the placebo condition. No dose response relationship emerged between caffeine concentration and endurance performance. (From Pasman WJ, et al. The effect of different dosages of caffeine on endurance performance time. Int J Sports Med 1995;16:225.)
probably interact to produce caffeine $s$ facilitating effect on neuromuscular activity:

1. Lower threshold for motor unit recruitment
2. Alter excitation contraction coupling
3. Facilitate nerve transmission
4. Increase ion transport within the muscle

Inconsistent Effects. Prior nutrition partly accounts for why individual differences exist in exercise response after consuming caffeine. Those who normally consume a highcarbohydrate diet show a depressed effect for caffeine on FFA mobilization. ${ }^{285}$ Individual differences in caffeine sensitivity, tolerance, and hormonal response from short- and long-term patterns of caffeine consumption also affect this drug s ergogenic qualities. Interestingly, the ergogenic effects of caffeine are less for caffeine in coffee than for an equivalent dose in capsule form. ${ }^{106}$ Apparently, components in coffee counteract caffeine s actions. Beneficial effects do not occur consistently in habitual caffeine users. This indicates that an athlete should consider caffeine tolerance rather than assume that caffeine provides a consistent benefit to all people. From a practical standpoint, the athlete should omit caffeine-containing foods and beverages 4 to 6 days before competition to optimize caffeines potential for ergogenic effects. ${ }^{269}$

## Effects on Muscle

Caffeine acts directly on muscle to enhance exercise capacity, particularly repeated submaximum muscle actions. ${ }^{178,226,264}$ A double-blind research design evaluated voluntary and electrically stimulated muscle actions under caffeine-free conditions and following oral administration of 500 mg of caffeine. ${ }^{164}$ Electrically stimulating the motor nerve allowed the researchers to remove central nervous system control and quantify caffeine s direct effects on skeletal muscle. Caffeine produced no effect on maximal muscle force during voluntary or electrically stimulated muscle actions. For submaximal effort, caffeine increased force output for low-frequency electrical stimulation before and after muscle fatigue. Preexercise caffeine administration also increased by $17 \%$ repeated submaximum isometric muscular endurance. ${ }^{198}$ Caffeine exerts no ergogenic effect on anaerobic metabolic capacity (glycolysis) as measured during repeated high-intensity Wingate exercise tests. ${ }^{112}$ Page 582 of this chapter discusses caffeine s lessening effect on the ergogenic benefits of creatine supplementation on short-term muscular power.

## Warning About Caffeine

Individuals who normally avoid caffeine may experience adverse effects when they consume it. Caffeine stimulates the central nervous system and in quantities greater than 1.5 g per day can produce typical symptoms of caffeinism: restlessness, headaches, insomnia, nervous irritability, muscle twitching, tremulousness, psychomotor agitation, and elevated heart rate and blood pressure; and it can trigger premature leftventricular contractions. From the standpoint of temperature regulation, caffeine acts as a diuretic, although with moderate caffeine consumption ( $<456 \mathrm{mg}$ ) it does not produce water electrolyte imbalances or reduced exercise heat tolerance. ${ }^{8}$

## FOCUS ON RESEARCH

## Ergogenic Benefits of Caffeine

Costill DL, et al. Effects of caffeine ingestion on metabolism and exercise performance. Med Sci Sports Exerc 1978;10:155.
> The potential ergogenic benefits of various substances and procedures have always interested sports competitors and exercise physiologists. Costill and colleagues tested the hypothesis that ingesting caffeine stimulated free fatty acid (FFA) mobilization, retarded depletion of muscle glycogen, and consequently enhanced endurance exercise performance. Previous research with animals and humans demonstrated that elevating plasma FFA spared muscle glycogen and extended exercise capacity. Because caffeine mobilizes FFA,

Costill tested its effects on muscle glycogen levels, the metabolic mixture in exercise, and endurance performance in humans.

Two female and seven male competitive cyclists (average $\mathrm{VO}_{2 \text { max }}=60 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}$ ), consuming the same diet, performed a cycle ergometer $\mathrm{VO}_{2 \text { max }}$ test and two additional endurance exercise trials separated by 3 days. In one trial, they consumed 200 mL of hot water containing 5 g of decaffeinated coffee (D) 60 minutes before the exercise trial. The cycling test continued for as long as possible at a work intensity of $80 \% \mathrm{VO}_{2 \text { max }}$. In the second trial, subjects consumed a hot drink containing 5 g of D plus 330 mg of caffeine (C) 60 minutes before the exercise test. Subjects remained unaware of the experiment s purpose, with test order randomized for C and D trials. Blood samples, taken before and during each trial, provided information on plasma lactate, FFA, glycerol, glucose, and triacylglycerols. In addition, respiratory gas exchange throughout exercise allowed computation of RQ and estimation of the nonprotein metabolic mixture.

The accompanying figure shows that total exercise time to exhaustion increased $19.5 \%$ during trial C ( 90.2 min ) compared with trial D (75.5 min). FFAs did not differ significantly between conditions (although consistently higher in C trial), but the caffeinated drink produced significantly higher plasma glycerol levels and significantly lower RQ values. The RQ allowed the researchers to estimate carbohydrate oxidation during exercise (about 240 g in both trials). In contrast, fat oxidation with caffeine ( 118 g ) exceeded oxidation without caffeine ( 57 g ). Subjects also perceived the exercise as easier in the C condition.

This study demonstrated that consuming caffeine before exercise increased the lipolysis rate during sustained exercise. The effect of increased lipolysis could spare liver and muscle glycogen early in exercise for later use. Subsequent research has confirmed caffeine s ergogenic role in endurance exercise performance.

Caffeine s effect on fluid loss lessens when consumed during exercise because (1) catecholamine release in exercise greatly reduces renal blood flow and (2) exercise enhances renal solute reabsorption and consequently water conservation (osmotic effect).

Although the effects of excess caffeine generally pose no health risk, a caffeine overdose can be lethal. The $\mathrm{LD}_{50}$ (lethal oral dose required to kill $50 \%$ of the population) for caffeine is about $10 \mathrm{~g}\left(150 \mathrm{mg} \cdot \mathrm{kg}\right.$ body mass $\left.{ }^{-1}\right)$ for a $70-\mathrm{kg}$ person. A 50-kg woman has an acute health risk with a caffeine intake of 7.5 g . Moderate caffeine toxicity exists for small children who consume 35 mg per kg of body mass. Such observations provide clear indication of the inverted U-shaped relationship between certain exogenous chemicals and health and safety (and probably exercise performance). Ingesting even small quantities of caffeine usually produces desirable effectsconsuming an excess can wreak havoc.

## Ginseng and Ephedrine

The popularity of herbal and botanical remedies to improve health, control body weight, and improve exercise performance has soared. Ginseng and ephedrine have been commonly marketed as nutritional supplements to reduce tension, revitalize, burn calories, and optimize mental and physical performance, particularly during fatigue and stress. Ginseng also plays a role as an alternative therapy to treat diabetes and male impotence and stimulate immune function.

## Ginseng

The ginseng root (Panax ginseng, C. A. Meyer), often sold as Panax or Chinese or Korean ginseng, serves no recognized medical use in the United States except as a soothing agent in skin ointments. Commercial ginseng root preparations generally take the form of powder, liquid, tablets, or capsules; widely marketed foods and beverages also contain various types and amounts of ginsenosides. Dietary supplements need not meet the same quality control for purity and potency as pharmaceuticals. Considerable variation exists in the concentrations of marker compounds for ginseng, including potentially harmful levels of impurities and toxins such as pesticides and heavy metals. ${ }^{116}$

Common claims for ginseng in the Western world are as an energy booster, to diminish the negative effects of overall stress, and to reduce the severity of cold symptoms. Little objective evidence exists to support the effectiveness of ginseng as an ergogenic aid. ${ }^{159,276}$ For example, volunteers consumed either 200 or 400 mg of the standardized ginseng concentrate daily for 8 weeks in a double-blind research protocol. ${ }^{83}$ Neither treatment affected submaximal or maximal exercise performance, ratings of perceived exertion, or physiologic parameters of heart rate, oxygen consumption, or blood lactate concentrations. No ergogenic effects occurred for physiologic and performance variables following a 1 week treatment with a ginseng saponin extract administered in doses of either 8 or 16 mg per kg of body mass. ${ }^{181}$ Similarly, 8 weeks of
ginseng supplementation failed to affect performance or recovery from 30 -second Wingate tests. Supplementation had no effect on mucosal immunity indicated by changes in secretory IgA at rest or following intense exercise. ${ }^{84}$ When effectiveness has been demonstrated, the research failed to use adequate controls, placebos, or double-blind testing protocols.

## Ephedrine

Unlike ginseng, Western medicine recognizes the potent amphetamine-like alkaloid compound ephedrine (with sympathomimetic physiologic effects) present in several species of the plant ephedra (dried plant stem called ma huang [ma wong; Ephedra sinica]). The ephedra plant contains two major active components, first isolated in 1928, ephedrine and pseudoephedrine. The medicinal role includes treatment of asthma, symptoms of the common cold, hypotension, and urinary incontinence, and as a central stimulant to treat depression. Physicians in the United States discontinued ephedrine as a decongestant and asthma treatment in the 1930s in favor of safer medications. The milder pseudoephedrine remains common in nonprescription cold and flu medications and clinically treats mucosal congestion that accompanies hay fever, allergic rhinitis, sinusitis, and other respiratory conditions. This drug has been removed from the banned substance list by the IOC and placed on the monitoring program because of lack of evidence for an ergogenic effect. Labeling that indicates ephedra-containing compounds includes ephedra, ma huang, ephedrine, Ephedra sinica, sida cordifolia, epitonin, pseudoephedrine, and methyl ephedrine.

Ephedrine exerts central and peripheral effects, with the latter reflected in increased heart rate, cardiac output, and blood pressure. Ephedrine produces bronchodilation in the lungs owing to its $\beta$-adrenergic effect. High ephedrine dosages produce hypertension, insomnia, hyperthermia, and cardiac arrhythmias. Other side effects include dizziness, restlessness, anxiety, irritability, personality changes, gastrointestinal symptoms, and difficulty concentrating.

Despite the legal and scientific categorizations of ephedrine as a potent drug, one could legally sell it as a dietary supplement. Its claim for accelerated metabolism and enhanced exercise performance greatly increased ephedrine s popularity as a nutritional supplement. Many commercial weight-loss products have contained high-dosage combinations of ephedrine and caffeine designed to speed up metabolism, yet no credible evidence exists that any initial weight loss lasts beyond 6 months. ${ }^{235}$

The potent physiologic effects of ephedrine have led researchers to investigate its potential as an ergogenic aid. No effect of a $40-\mathrm{mg}$ dose of ephedrine occurred on indirect indicators of exercise performance or ratings of perceived exertion (RPE). ${ }^{70}$ The less concentrated pseudoephedrine also produced no effect on $\mathrm{VO}_{2 \text { max }}$, RPE, aerobic cycling efficiency, ${ }^{122,253}$ anaerobic power output (Wingate test), time to exhaustion on a bicycle and a $40-\mathrm{km}$ cycling trial, ${ }^{101}$ or physiologic and performance measures during 20 minutes of running at $70 \%$ of $\mathrm{VO}_{2 \max }$ followed by a $5000-\mathrm{m}$ time trial. ${ }^{50}$

In contrast, a series of double-blind, placebo-controlled studies by the Canadian Defense and Civil Institute of Environmental Medicine using a preexercise ephedrine dosage ( 0.8 to 1.0 mg per kg body mass), either alone or combined with caffeine, produced small but statistically significant effects on endurance performance ${ }^{16,18,20}$ and anaerobic power output during the early phase of the Wingate test. ${ }^{19}$ Furthermore, an ergogenic effect of a relatively high dosage of pseudoephedrine ( 2.5 mg per kg body mass) was shown to enhance runners times by $2.1 \%$ in a $1500-\mathrm{m}$ time trial. ${ }^{123}$ Ephedrine supplementation also increased muscular endurance during the first set of traditional resistance-training exercise. ${ }^{132}$ Whether central mechanisms that increase arousal and tolerance to discomfort, peripheral mechanisms that influence substrate metabolism and muscle function, or the combined effect of both account for any ergogenic effect remains undetermined.

## Not Without Risk

Products containing ephedra represent less than $1 \%$ of sales of all herbal supplements, yet they account for $64 \%$ of all reported adverse reactions. Consequently, ephedra poses a 200-fold greater risk than all other herbal supplements combined. Nearly 1400 adverse effects from ephedra use have been reported to the FDA (www.fda.gov) from January 1993 to February 2000. Incidents included 81 deaths, 32 heart attacks, 62 cases of cardiac arrhythmia, 91 cases of increased blood pressure, 69 strokes, and 70 seizures. An evaluation of more than 16,000 adverse reactions showed five deaths, five heart attacks, 11 cerebrovascular accidents, four seizures, and eight psychiatric cases as sentinel events associated with prior consumption of ephedra or ephedrine. ${ }^{235}$ In general, the cardiovascular toxic effects of ephedra (increased heart rate and blood vessel constriction) are not limited to massive doses but rather to the amount recommended by the manufacturer. In 2002, an Alabama jury awarded $\$ 4.1$ million to four persons who suffered strokes or heart attacks after taking an ephedra-based appetite suppressant produced by Metabolite International. In baseball spring training of 2003, ephedrine use was implicated in the death from organ failure complications in heat stroke of Baltimore Orioles pitcher Steve Bechler. He allegedly used the ephedrine-containing supplement Xenadrine RFA-1 to facilitate weight loss.

Most sports organizations now ban ephedrine, and the National Football League (NFL) was the first professional sports league to do so. Professional baseball discourages ephedrine use, but it does not ban it. Based on analysis of existing data, the FDA banned ephedra on December 31, 2003, the first time this federal agency banned a dietary supplement. In 2007, a petition for rehearing the ban in front of the tenth circuit of the U.S. Court of Appeals was denied by the U.S. Supreme Court, upholding the FDA ban on sale of ephedra.

## Buffering Solutions

Maximal exercise for 30 to 120 seconds dramatically alters the chemical balance between intra- and extracellular fluids
because the active muscle fibers rely predominantly on anaerobic energy transfer. Lactate accumulates with a concurrent fall in intracellular pH . Increased acidity ultimately inhibits energy transfer and contractile dynamics in the active muscle fibers, and exercise performance deteriorates.

The bicarbonate aspect of the body s buffering system (see Chapter 14) provides a rapid first line of defense against intracellular increases in $\mathrm{H}^{+}$concentration. Maintaining extracellular bicarbonate at a high level facilitates $\mathrm{H}^{+}$efflux from the cell, which reduces intracellular acidosis. Increasing the bicarbonate reserve before short-term anaerobic exercise might enhance performance by delaying the fall in intracellular pH associated with exhaustive effort. Variations in preexercise dosage of sodium bicarbonate and type of exercise to evaluate preexercise alkalosis have produced conflicting results about the ergogenic effectiveness of buffering agents. ${ }^{108,124,231,249,268}$

To improve experimental design, one study investigated the effects of acute metabolic alkalosis on exhaustive exercise that increased anaerobic metabolites. Six trained middledistance runners ran an $880-\mathrm{m}$ race under control conditions and following alkalosis induced by ingesting a sodium bicarbonate solution ( 300 mg per kg body mass) or a calcium carbonate placebo of similar concentration. Table 23.7 shows that the alkaline drink raised pH and standard bicarbonate level before exercise. Subjects ran on average 2.9 seconds faster under alkalosis and exhibited higher postexercise blood lactate, pH , and extracellular $\mathrm{H}^{+}$concentration than in the placebo condition. Augmented anaerobic energy transfer and/or delayed onset of intracellular acidification during intense exercise most likely explains the ergogenic effect of preexercise alkalosis. ${ }^{26,204,211}$ Increased extracellular buffering from preexercise sodium bicarbonate ingestion facilitates $\mathrm{H}^{+}$efflux from active muscle fibers during exercise in a dose dependent manner. ${ }^{75}$ This delays the fall in intracellular pH and its subsequent negative effects on muscle function. An improvement of 2.9 seconds in 800-m race time represents a dramatic performance improvement-a distance of 19 m at race pace brings a last-place finisher to first place in most $800-\mathrm{m}$ races!

The ergogenic effect of preexercise alkalosis (use not banned by WADA) also occurs for women (Fig. 23.12). Physically active women performed one bout of maximal cycle ergometer exercise for 60 seconds on separate days under three conditions in a double-blind research design: (1) control, no treatment; (2) sodium bicarbonate dose of 300 mg - kg body mass ${ }^{-1}$ in 400 mL of low-calorie flavored water 90 minutes before testing; and (3) placebo of equimolar dose of sodium chloride (to maintain intravascular fluid status similar to bicarbonate condition) administered like the bicarbonate treatment. Exercise capacity represented total work accomplished in the 60 -second ride. The figure s inset box shows that total work and peak power output reached higher levels with preexercise bicarbonate treatment than under either control or placebo conditions. The bicarbonate treatment produced a higher blood lactate level in the immediate and 1-minute postexercise period; the effect explains the greater work capacity attained in the short-term, anaerobic exercise

TABLE 23.7 Performance Time and Acid Base Profiles for Subjects Under Control (Placebo) and Induced Preexercise Alkalosis Conditions Before and After an 800-M Race

| Variable | Condition | Pretreatment | Preexercise | Postexercise |
| :--- | :--- | :---: | :---: | :---: |
| pH | Control | 7.40 | 7.39 | 7.07 |
|  | Placebo | 7.39 | 7.40 | 7.09 |
|  | Alkalosis | 7.40 | $7.49^{a}$ | $7.18^{b}$ |
| Lactate | Control | 1.21 | 1.15 | 12.62 |
| $\left(\mathrm{mmol} \cdot \mathrm{L}^{-1}\right)$ | Placebo | 1.38 | 1.23 | 13.62 |
|  | Alkalosis | 1.29 | 1.31 | $14.29^{b}$ |
| Standard $\mathrm{HCO3}^{-1}$ | Control | 25.8 | 24.5 | 9.90 |
| $\left(\mathrm{mEq} \cdot \mathrm{L}^{-1}\right)$ | Placebo | 25.6 | 26.2 | 11.00 |
|  | Alkalosis | 25.2 | $33.5^{a}$ | $14.30^{b}$ |
|  |  | Control | Placebo | Alkalosis |
| Performance time (min:s) |  | $2: 05.8$ | $2: 05.1$ | $2: 02.9^{c}$ |

[^43]

## $\square$ Control $\square$ Placebo $\square$ Bicarbonate

Figure 23.12 Effects of bicarbonate loading on total work, peak power output, and postexercise blood lactate levels in moderately trained women. * Significantly higher than either control or placebo. (From McNaughton LR, et al. Effect of sodium bicarbonate ingestion on high intensity exercise in moderately trained women. J Strength Cond Res 1997;11:98.)
trial. Similar ergogenic benefits occur with exogenous sodium citrate as the preexercise alkalinizing agent. ${ }^{120,171}$

## Effect Related to Dosage and Degree of Anaerobiosis

Bicarbonate dosage and the cumulative anaerobic nature of exercise interact to influence the potential ergogenic effect of preexercise bicarbonate loading. Doses of at least 0.3 g per kg body mass facilitate $\mathrm{H}^{+}$efflux from the cell and enhance a single 1- to 2-minute maximal effort and longer-term arm or leg exercise that exhausts within 6 to 8 minutes. ${ }^{168,174,218}$ No ergogenic effect emerges for performance typical of heavyresistance training, perhaps because of the lower absolute anaerobic metabolic load than in supramaximal whole-body running or cycling. ${ }^{202}$ Bicarbonate loading with all-out effort of less than 1 minute exerts an ergogenic effect with repetitive (intermittent) exercise. ${ }^{61}$

## INTEGRATIVE QUESTION

Advise an Olympic-caliber weightlifter who plans to bicarbonate load because the competitive event requires all-out effort of an anaerobic nature.

## High-Intensity Endurance Performance

Preexercise-induced alkalosis does not benefit lowintensity, aerobic exercise because pH and lactate remain at near-resting levels, but it may enhance aerobic exercise of higher intensity. Intense endurance exercise, while predominantly aerobic, increases blood lactate and decreases pH , which negatively affects performance. Eight trained male cyclists consumed sodium citrate ( 0.5 g per kg body mass) before a $30-\mathrm{km}$ time trial. ${ }^{203}$ Race times were faster and plasma pH and lactate concentrations higher after sodium citrate ingestion than with the placebo. Despite the relatively small anaerobic component in high-intensity aerobic exercise (compared with short-term, maximal exercise), ingesting a buffer before such exercise facilitates lactate and hydrogen ion efflux and improves muscle function. ${ }^{172}$

Individuals who bicarbonate load often experience abdominal cramps and diarrhea about 1 hour after ingestion. This adverse effect would surely minimize any potential ergogenic effect. Substituting sodium citrate ( 0.4 to 0.5 g per kg body mass) for sodium bicarbonate reduces or eliminates adverse gastrointestinal effects while still providing ergogenic benefits. ${ }^{161,171}$

## Anticortisol Compounds: Glutamine and Phosphatidylserine

The hypothalamus normally secretes corticotrophin-releasing factor in response to emotional stress, trauma, infection, surgery, and physical exertion. This releasing factor stimulates
the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which induces the adrenal cortex to discharge the glucocorticoid hormone cortisol (hydrocortisone). Cortisol decreases amino acid transport into the cell; this depresses anabolism and stimulates protein breakdown to its building-block amino acids in all cells except the liver. The circulation delivers these liberated amino acids to the liver for glucose synthesis (gluconeogenesis). Cortisol also serves as an insulin antagonist by inhibiting cellular glucose uptake and oxidation.

A prolonged, elevated serum concentration of cortisolusually from therapeutic exogenous glucocorticoid intake in drug form-leads to excessive protein breakdown, tissue wasting, and negative nitrogen balance. The potential catabolic effect of cortisol has convinced many strength and power athletes to use supplements thought to inhibit normal cortisol release. They believe that depressing cortisol s normal rise following exercise augments muscular development by attenuating catabolism. In this way, muscle tissue synthesis progresses unimpeded in recovery. Glutamine and phosphatidylserine are two supplements used to produce an anticortisol effect.

## Glutamine

Glutamine, a nonessential amino acid, is the most abundant amino acid in plasma and skeletal muscle. It accounts for more than one-half of the muscles free amino acid pool. Glutamine exerts many regulatory functions, one of which provides an anticatabolic effect that augments protein synthesis. From a clinical perspective, glutamine supplementation effectively counteracts the decline in protein synthesis and muscle wasting from repeated glucocorticoid use. ${ }^{121}$ Infusing glutamine following exercise promotes muscle glycogen accumulation, perhaps by serving as a gluconeogenic substrate in the liver. ${ }^{272}$

The potential anticatabolic and glycogen synthesizing effects of exogenous glutamine have promoted speculation that supplementation might benefit resistance training effects. Daily glutamine supplementation ( 0.9 g per kg lean tissue mass) during 6 weeks of resistance training in healthy young adults did not affect muscle performance, body composition, or muscle protein degradation compared with a placebo. ${ }^{42}$

Glutamine and the Immune Response. Glutamine plays an important role in normal immune function. One protective aspect concerns glutamine s use as metabolic fuel by infectionfighting cells, particularly lymphocytes and macrophages. Glutamine plasma concentration decreases following prolonged intense exercise, so glutamine deficiency has been linked to immunosuppression from strenuous exercise (see Chapter 7). ${ }^{28,224}$

Glutamine supplementation might lessen increased susceptibility to upper respiratory tract infection (URTI) following prolonged competition or a bout of strenuous training. Marathoners who consumed a glutamine drink ( 5 g L-glutamine in 330 mL mineral water) at the end of a race and then 2 hours later reported fewer URTI symptoms than unsupplemented athletes. ${ }^{45}$ More
specifically, $65 \%$ more athletes reported no symptoms of infection than did a placebo group. The mechanism for glutamine s effect on postexercise infection risk remains elusive. For example, subsequent studies by the same researchers showed no effect of glutamine supplementation on changes in blood lymphocyte distribution. ${ }^{46}$ Dietary glutamine supplementation did not benefit lymphocyte metabolism or immune function with more moderate exercise training in rats. ${ }^{236}$ Research with humans indicates that preexercise glutamine supplementation does not affect the immune response following repeated bouts of intense exercise. ${ }^{213,284}$ Supplements of nine equal doses of 100 mg of L-glutamine per kg of body mass taken 30 minutes before the end of exercise, at the end of exercise, and 30 -minutes into recovery abolished the postexercise decline in glutamine following a race but did not impact immune function. ${ }^{212}$

## Phosphatidylserine

Phosphatidylserine (PS) is a glycerophospholipid typical of a class of natural lipids that compose the structural components of the internal layer of the plasma membrane that surrounds all cells. Through its potential for modulating functional events in the plasma membrane (e.g., number and affinity of membrane receptor sites), PS might modify the neuroendocrine response to stress. In one study, healthy men consumed 800 mg of PS derived from bovine cerebral cortex daily for 10 days. ${ }^{180}$ Three 6-minute intervals of cycle ergometer exercise of increasing intensity induced physical stress. Compared with the placebo condition, PS treatment diminished ACTH and cortisol release without affecting growth hormone release. These results confirmed that a single intravenous PS injection counteracted hypothalamic-pituitary adrenal axis activation with exercise. ${ }^{179}$ A 750 mg per day supplement of PS for 10 days did not protect against delayed onset muscle soreness or markers of muscle damage, inflammation, and oxidative stress following a bout of prolonged downhill running. ${ }^{148}$ Soybean lecithin provides most PS for supplementation, yet research showing physiologic effects has used bovine-derived PS. Subtle differences in the chemical structure of these two forms of PS may create differences in physiologic action, including the potential for ergogenic effects.

## $\beta$-Hydroxy $\beta$-methylbutyrate

$\boldsymbol{\beta}$-Hydroxy $\boldsymbol{\beta}$-methylbutyrate (HMB), a bioactive metabolite generated in the breakdown of the essential branchedchain amino acid leucine, decreases protein loss during stress by inhibiting protein catabolism. In rats and chicks, less protein breakdown and slight increase in protein synthesis occurred in muscle tissue (in vitro) exposed to HMB. ${ }^{151}$ An HMB-induced increase occurred in fatty acid oxidation in mammalian muscle cells exposed to HMB. ${ }^{49}$ Depending on the quantity of HMB in food (relatively rich sources include catfish, grapefruit, and breast milk), humans synthesize between 0.3 and 1.0 g of HMB daily, with about $5 \%$ from
dietary leucine catabolism. HMB supplements are taken because of their potential nitrogen-retaining effects to prevent or slow muscle damage and inhibit muscle breakdown (proteolysis) with intense physical effort.

Research has studied the effects of exogenous HMB on skeletal muscle s response to resistance training. In part 1 of a 2-part study (Fig. 23.13), young adult men participated in two randomized trials. In the first study, 41 subjects received $0,1.5$, or 3.0 g of HMB daily at two protein levels, either 117 g or 175 g daily, for 3 weeks. The men resistance trained during this time for 1.5 hours, 3 days a week. In the second study, 28 subjects consumed either 0 or 3.0 g of HMB daily and resistance trained for 2 to 3 hours, 6 days a week, for 7 weeks. In the first study, HMB supplementation depressed


Figure 23.13 A. Change in muscle strength (total weight lifted in upper- and lower-body exercises) during study 1 (week 1 to week 3) in subjects who supplemented with HMB. Each group of bars represents one complete set of upper- and lower-body workouts. B. Total body electrical conductivityassessed change in FFM during study 2 for a control group that received a carbohydrate drink (placebo) and a group that received 3 g of Ca-HMB each day mixed in a nutrient powder (HMB + nutrient powder). (From Nissen S, et al. Effect of leucine metabolite $\beta$-hydroxy $\beta$-methylbutyrate on muscle metabolism during resistance-exercise training. J Appl Physiol 1996;81:2095.)
the exercise-induced rise in muscle proteolysis (reflected by urinary 3-methylhistidine and plasma creatine phosphokinase [CPK] levels) during the first 2 weeks of exercise training. These biochemical indices of muscle damage were 20 to $60 \%$ lower in the HMB-supplemented group. In addition, the supplemented group lifted more total weight during each training week (Figure. 23.13A), with the greatest effect in the group receiving the largest HMB supplement. Muscular strength increased $8 \%$ in the unsupplemented group and more in the HMB-supplemented groups ( $13 \%$ for the $1.5-\mathrm{g}$ group and $18.4 \%$ for the $3.0-\mathrm{g}$ group). Added protein (not indicated in graph) did not affect any of the measurements; one should view this lack of effect in proper context-the lower protein quantity ( $115 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ ) equaled twice the RDA.

In the second study, individuals who received HMB supplementation had higher FFM than the unsupplemented group at 2 and 4 to 6 weeks of training (Fig. 23.13B). However, at the last measurement during training, the difference between groups decreased and failed to differ from the difference between pretraining baseline values.

The mechanism for any HMB effect on muscle metabolism, strength improvement, and body composition remains unknown. Perhaps this metabolite inhibits normal proteolytic processes that accompany intense muscular overload. Although the results demonstrate an ergogenic effect for HMB supplementation, it remains unclear just what component of the FFM (protein, bone, water) HMB affects. Furthermore, the data in Figure 23.13B indicate potentially transient body composition benefits of supplementation that tend to revert toward the unsupplemented state as training progresses.

Not all research shows beneficial effects of HMB supplementation with resistance training. ${ }^{207}$ One study evaluated the effects of variations in HMB supplementation (approximately 3 vs. $6 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ ) on muscular strength during 8 weeks of whole-body resistance training in untrained young adult men. ${ }^{97}$ The study s primary finding indicated that HMB supplementation, regardless of dosage, produced no difference in most of the strength data (including 1-RM strength) compared with the placebo group. In contrast to the findings presented in Figure 23.13A, increases in training volume remained similar among groups. In both HMB-supplemented groups, lower CPK levels in recovery indicated some potential effect of HMB to inhibit muscle breakdown. The group that consumed the lower HMB dosage increased more in FFM than the other two groups. Inferences from these findings are limited because skinfolds assessed body composition changes. HMB supplementation with a daily dosage as high as $6 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ during 8 weeks of resistance training does not adversely affect hepatic enzyme function, blood lipid profile, renal function, or immune function. ${ }^{98}$ Additional studies must assess the long-term effects of HMB supplements on body composition, training response, and overall health and safety. Age does not affect responsiveness to HMB supplementation. ${ }^{280}$

## NONPHARMACOLOGIC APPROACHES

Athletes often use physical, mechanical, physiologic, and nutritional means to potentiate ergogenic effects.

## Red Blood Cell ReinfusionBlood Doping

Red blood cell reinfusion, often called induced erythrocythemia, blood boosting, or blood doping, gained public prominence as a possible ergogenic technique during the 1972 Munich Olympics, when a relatively unknown Finnish runner allegedly used this procedure prior to his two gold medal winning 5000- and $10,000-\mathrm{m}$ runs.

## How It Works

Red blood cell reinfusion involves withdrawing 1 to 4 units ( 1 unit $=450 \mathrm{~mL}$ of whole blood) of a person s blood, immediately reinfusing the plasma, and placing the packed red cells in frozen storage for later infusion (autologous transfusion). Homologous transfusion infuses a typematched donor s blood. To prevent dramatic reductions in blood-cell concentration, each unit of blood withdrawal takes place at 3- to 8 -week intervals because it takes this time to reestablish normal red blood cell levels. Stored blood cells are then infused 1 to 7 days before an endurance event; this increases red blood cell count and hemoglobin levels from 8 to $20 \%$.

Hemoconcentration translates to an average hemoglobin increase for men from a normal 15 g per dL of blood to 19 g per dL (hematocrit increases 40 to $60 \%$ ). Hematologic parameters remain elevated for at least 14 days. Theoretically, the added blood volume contributes to a larger maximal cardiac output, while red blood cell packing increases the blood s oxygen-carrying capacity. Enhanced oxygen transport and delivery to active tissues provides meaningful performance benefits to endurance athletes.

An ergogenic effect occurs with infusion of 900 to 1800 mL of freeze-preserved autologous blood. Each $500-\mathrm{mL}$ infusion of whole blood (equivalent to 275 mL of packed red cells) adds about 100 mL of oxygen to the bloods total oxygen-carrying capacity-each 100 mL of whole blood carries about 20 mL of oxygen. An elite endurance athlete s total blood volume circulates 5 to 6 times each minute in intense exercise, so the potential extra oxygen available to the tissues from red cell reinfusion averages 500 mL ( 0.5 L ).

Blood doping might also produce effects opposite to those intended. For example, a large red blood cell infusion (and increase in blood cell concentration) could increase blood viscosity, or thickness, and thus decrease cardiac output, blood flow velocity, and peripheral oxygen supply-effects that reduce aerobic capacity and endurance performance. Any increase in blood viscosity could also compromise blood flow through narrowed, atherosclerotic vessels of individuals with artery disease to increase their risk for heart attack or stroke.

## Does It Work?

A theoretical basis for blood doping exists and experimental evidence justifies its use for physiologic reasons. ${ }^{230}$ Much of the early conflict concerning ergogenic benefits came from poor experimental design, inconsistent criteria for exercise performance, diverse blood storage techniques, and variations in timing and quantity of blood withdrawn and replaced. Early research in this area noted a rapid increase in $\mathrm{VO}_{2 \text { max }}$ following infusion of whole blood. ${ }^{78}$ One study reported a $23 \%$ overnight increase in exercise performance and a $9 \%$ increase in $\mathrm{VO}_{2 \text { max }}$ with blood doping. ${ }^{81}$ Subsequent investigations (including a study by a past critic of the technique) support previous findings and show physiologic and performance improvements with red blood cell reinfusion. ${ }^{217,242}$

Differences in results among various studies of exercise performance following red blood cell reinfusion largely result from variations in blood storage methods. Freezing red blood cells permits storage for more than 6 weeks without significant loss of cells. With storage at 4 C (used in some earlier studies), substantial hemolysis occurs after only 3 weeks. This represents an important difference because it usually takes a person 5 to 6 weeks to reestablish blood cells lost after withdrawal of two units of whole blood (Fig. 23.14).

With appropriate blood storage methods, red blood cell reinfusion elevates hematologic parameters of men and women. This in turn translates to a 5 to $13 \%$ increase in aerobic capacity, decreased heart rate and blood lactate during submaximal exercise, and augmented endurance at sea level and altitude. In addition, thermoregulatory benefits during exercise in the heat (reduced body heat storage and improved sweating response) result from red blood cell reinfusion. Increased oxygen content in arterial blood in the infused state likely frees blood for delivery to the skin for heat dissipation during exercise heat stress while adequately supplying active tissues. TABLE 23.8 illustrates hematologic, physiologic, and performance responses for five adult men during submaximal and maximal exercise before and 24 hours after infusion of 750 mL of packed red blood cells. These response patterns generally represent the current thinking in this area.


Figure 23.14 Time course of hematologic changes after removal and reinfusion of 900 mL of freeze-preserved blood. (From Gledhill N. Blood doping and related issues: a brief review. Med Sci Sports Exerc 1982;14:183.)

## A New Twist: Hormonal Blood Boosting

Endurance athletes now use epoetin, a synthetic form of erythropoietin (EPO), to eliminate the cumbersome and lengthy blood doping process, This hormone, produced by the kidneys, regulates red blood cell production within the marrow of the long bones, but also is essential in the synthesis and proper functioning of several erythrocyte membrane proteins, particularly those facilitating lactate exchange. ${ }^{9,33,59}$ Medically, exogenous recombinant human EPO, commercially available since 1988, has proved useful in combating anemia in patients undergoing chemotherapy or with severe renal disease. Normally, a decrease in red blood cell concentration or decline in the pressure of oxygen in arterial blood-as in severe pulmonary disease or on ascent to high altitude-releases this hormone to stimulate erythrocyte production. The $12 \%$ increase in hemoglobin and hematocrit that typically follows a 6-week EPO treatment greatly improves endurance exercise performance. ${ }^{80,227}$ Unfortunately, self-administration in an unregulated and unmonitored manner-simply injecting the

TABLE 23.8 Physiologic, Performance, and Hematologic Characteristics Before and 24 Hours After Reinfusion of 750 ml of Packed Red Blood Cells

| Variable | Preinfusion | Postinfusion | Difference | Difference, \% |
| :---: | :---: | :---: | :---: | :---: |
| Hemoglobin, g • dL blood ${ }^{-1}$ | 13.8 | 17.6 | $3.8{ }^{\text {b }}$ | $+27.5{ }^{\text {b }}$ |
| Hematocrit ${ }^{\text {a }}$, \% | 43.3 | 54.8 | $11.5^{\text {b }}$ | $+26.5{ }^{\text {b }}$ |
| Submaximal $\mathrm{VO}_{2}, \mathrm{~L} \cdot \mathrm{~min}^{-1}$ | 1.60 | 1.59 | -0.01 | -0.6 |
| Submaximal HR, b $\cdot \mathrm{min}^{-1}$ | $127.4$ | $109.2$ | $18.2^{\text {b }}$ | $-14.3{ }^{\text {b }}$ |
| $\mathrm{VO}_{2 \text { max }}, \mathrm{L} \cdot \min ^{-1}$ | 3.28 | 3.70 | $0.42{ }^{\text {b }}$ | $+12.8{ }^{\text {b }}$ |
| $\mathrm{HR}_{\max }, \mathrm{b} \cdot \min ^{-1}$ | $181.6$ | $180.0$ | $-1.6$ | $-0.9$ |
| Treadmill run time, s | 793 | 918 | $125^{b}$ | $15.8{ }^{\text {b }}$ |

[^44]hormone requires much less sophistication than blood doping procedures-can increase hematocrit more than $60 \%$. This dangerously high hemoconcentration (and corresponding increase in blood viscosity) increases the likelihood for stroke, heart attack, heart failure, and pulmonary edema.

EPO use has become particularly prevalent in cycling competition and allegedly contributed to at least 18 deaths (mainly from heart attack) among competitive cyclists. Because EPO cannot be detected in urine, the blood hematocrit serves as a surrogate marker. The International Cycling Union has set a hematocrit threshold of $50 \%$ for males and $47 \%$ for females; the International Skiing Federation uses a hemoglobin concentration of $18.5 \mathrm{~g} \cdot \mathrm{dL}^{-1}$ as the threshold for disqualification. Hematocrit cutoff values of $52 \%$ for men and $48 \%$ for women (roughly 3 standard deviations above the mean) represent abnormally high or extreme values in triathletes. ${ }^{188}$ Use of hematocrit level cutoff raises the unanswered question of the number of disqualified clean cyclists. Estimates place this number between 3 and $5 \%$ because of factors that affect normal variation in hematocrit such as genetics, posture, altitude training, and hydration level.

Current concern centers on an anomaly in iron metabolism frequently observed among high-level international cyclists. Many of these athletes show serum iron levels above $500 \mathrm{ng} \cdot \mathrm{L}^{-1}$ (normal: $100 \mathrm{ng} \cdot \mathrm{L}^{-1}$ ), with some values as high as $1000 \mathrm{ng} \cdot \mathrm{L}^{-1}$. The elevated iron level results from their regular injections of supplemental iron to support increased synthesis of red blood cells induced by repeated EPO use. Chronic iron overload increases the risk of liver dysfunction among these athletes.

The enhancement of oxygen availability to muscles by EPO analog and mimetics constitutes one of the main challenges to doping control. The concern of sports governing bodies has now shifted from simple red blood cell reinfusion to concern about transfection to an athlete s genes that code for erythropoietin and its subsequent impact on exercise performance. ${ }^{193}$ Sports authorities have incorporated such gene doping among the prohibited practices.

## Other Means to Enhance Oxygen Transport

New classes of substances may emerge to enhance aerobic exercise performance. These doping threats include perfluorocarbon emulsions and solutions formulated from either bovine or human hemoglobin that improve oxygen transport and delivery to muscle. Despite their potential benefits in clinical use, these substances exhibit potentially lethal side effects that include increased systemic and pulmonary blood pressure, renal toxicity, and impaired immune function.

## Warm-Up (Preliminary Exercise)

Coaches, trainers, and athletes at all levels of competition generally recommend engaging in some type of physical activity or warm-up prior to vigorous exercise. Conventional
wisdom maintains that preliminary exercise helps the performer prepare physiologically or psychologically and reduces the likelihood of joint and muscle injury. With animals, injuring a warmed-up muscle requires more force and greater muscle length than injuring a muscle in the cold condition. ${ }^{229}$ The warming-up process stretches the muscletendon unit to allow greater length and less tension on exposure to a given external load.

Warm-up generally fits into one of two categories (although overlap exists):

1. General warm-up uses body movements or loosening-up exercises unrelated to the specific neuromuscular actions of the anticipated performance. Examples include calisthenics and stretching.
2. Specific warm-up applies big-muscle, rhythmic movements that provide skill rehearsal in the activity. Examples include swinging a golf club, throwing a baseball or football, tennis practice, basketball shooting and movements, and preliminary lead-up in the high jump or pole vault.

## Psychologic Considerations

Competitors at all levels generally believe that performing some prior skill-related activity prepares them mentally to focus on the upcoming performance. A specific warm-up related to the intended activity also may improve the necessary skill and coordination requirements. Consequently, sports that require accuracy, timing, and precise movements generally benefit from some type of specific or formal preliminary practice.

The notion also exists that prior exercise before strenuous effort gradually prepares a person to go all out without fear of injury. The ritual warm-up of baseball pitchers exemplifies this belief. Is it conceivable that a pitcher would enter a game, throwing at competitive speeds, without previously warming up? Would any athlete begin competition without first stretching and engaging in a particular form, intensity, or duration of warm-up? Most performers would respond with a definite no, yet objective support for this response remains elusive. One reason is the difficulty designing a well-controlled experiment with topflight athletes to determine the necessity of warming up and whether it improves subsequent performance with reduced injury risk. For preexercise stretching, research with army recruits indicates that a typical muscle-stretching protocol in the preexercise warm-up produces no clinically meaningful reductions in risk of exercise-related injury compared with subsequent exercise without warm-up. ${ }^{201}$ In addition, strength loss, loss of motion, soreness, or markers of muscle damage from eccentric exercise were no different between groups that received preexercise passive warm-up with shortwave diathermy, active warm-up with concentric muscle actions, or no warm-up. ${ }^{86}$

Certain sport-related situations require peak performance with little time for warming up. A reserve player entering the last few minutes of a game has no time for stretching,
vigorous calisthenics, or taking practice shots; the player must go all out and achieve optimal performance without warm-up except that done before the game or at intermission. Do more injuries occur in such cases? Does physical performance (e.g., shooting, rebounding, or basketball defense) deteriorate during the first few minutes of this unwarmed condition from that proceeded by a warm-up? Future research must address such questions.

Psychologic factors, including an athlete s ingrained belief in the importance of warming up, establish a definite bias when comparing maximum performance with and without warm-up. It is difficult if not impossible to obtain a maximum effort without warm-up if a subject believes in the importance of preliminary exercise.

## Physiologic and Performance Effects

One study evaluated the effect of warm-up on 2-minute sprint-cycling performance at $120 \%$ of the power output at $\mathrm{VO}_{2 \text { max }}$. Warm-up produces a higher muscle temperature, increased local muscle oxygen availability and oxygen uptake, lower blood lactate level, and higher oxygen consumption during the early phase of exercise than the no-warm-up condition. ${ }^{69,216}$ Warm-up exercise performed at moderate- and high-intensity improved intense cycling performance by 2 to $3 \% .{ }^{39}$ Also, a pre-exercise warm-up irrespective of intensity enhanced a 3 to 4 minute ( $3-\mathrm{km}$ ) cycling time trial time. This effect likely resulted from an acceleration of oxygen uptake kinetics from augmented blood flow at the onset of exercise. ${ }^{113}$ An active warm-up 5 minutes prior to a 30 -second maximal sprint on a bicycle ergometer produced less blood and muscle lactate than equivalent effort without a physical warm-up. ${ }^{109}$ Differences in muscle temperature with an active warm-up could not account for the ergogenic effect because exercise in the control condition also involved passively heating the muscle to the same temperature. These findings suggest a decreased reliance on anaerobic sources of energy during the exercise period preceded by a physical warm-up.

Five mechanisms explain why warm-up should improve physical performance and exercise capacity because of subsequent increases in blood flow and muscle and core temperature:

1. Faster muscle contraction and relaxation
2. Greater economy of movement from lowered viscous resistance within active muscles
3. Facilitated oxygen delivery and use by muscles because hemoglobin releases oxygen more readily at higher temperatures (Bohr effect)
4. Facilitated nerve transmission and muscle metabolism because increased temperature accelerates bodily processes; a specific warm-up may also facilitate recruitment of required motor units
5. Increased blood flow through active tissues as the local vascular bed dilates from increased metabolism and higher muscle temperature

## Clinical Considerations: Warm-Up Prior to Sudden Strenuous Exercise

Sudden exertion can trigger the onset of myocardial infarction, particularly in sedentary persons and those with latent coronary artery disease. ${ }^{35,177}$ With this in mind, consideration of possible benefits from warming up takes on clinical significance. Several studies have evaluated the effects of preliminary exercise on the cardiovascular response to sudden, strenuous exercise. The findings provide an essentially different physiologic framework to justify warm-up that relates importantly to adult fitness and cardiac rehabilitation programs and occupations and sports that require sudden bursts of physical effort.

In one study, 44 men free of overt symptoms of coronary artery disease ran on a treadmill at high intensity for 10 to 15 seconds without prior warm-up. ${ }^{13}$ Evaluation of postexercise ECGs revealed that $70 \%$ of the subjects displayed abnormal changes attributable to inadequate myocardial oxygen supply unrelated to age or fitness level. To evaluate the effect of a warm-up, 22 of the men with an abnormal ECG from the treadmill run jogged in place at moderate intensity (heart rate, $145 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ ) for 2 minutes before treadmill running. With this warm-up, 10 men now showed normal tracings during sudden exertion, while another 10 men displayed improved ECG responses; only two subjects showed significant abnormalities. In a subsequent study, the exercise blood pressure response also improved with prior warm-up. ${ }^{14}$ For seven men with no warm-up, systolic blood pressure averaged 168 mm Hg immediately after the 15 -second treadmill run. This decreased to 140 mm Hg when the 2-minute jog-in-place warm-up preceded exercise.

Coronary blood flow does not adjust instantaneously to a sudden increase in myocardial work; transient myocardial ischemia (poor oxygen supply) can occur in apparently healthy and fit individuals. Prior warm-up (at least 2 min of easy jogging) benefits the subsequent ECG and blood pressure responses to vigorous exercise to indicate a more favorable relationship between myocardial oxygen supply and demand. Warming up before strenuous exercise is particularly important for individuals with limited myocardial blood flow from coronary artery disease. A brief warm-up provides more optimal blood pressure and hormonal adjustments at the onset of subsequent strenuous exercise. The warm-up serves two beneficial purposes under these conditions:

1. Reduces myocardial workload and thus the myocardial oxygen requirement
2. Augments blood flow through the coronary arteries

## Oxygen Inhalation (Hyperoxia)

Athletes breathe oxygen-enriched or hyperoxic gas mixtures during time-outs, at half-time, or following strenuous exercise. They believe this procedure enhances the blood s oxygen-carrying capacity to facilitate oxygen transport to active or recovering muscles. The fact remains that when healthy persons breathe ambient air at sea level, hemoglobin
in blood leaving the lungs normally remains 95 to $98 \%$ saturated with oxygen (see Chapter 13). In physiologic terms, consider these two factors:

1. Breathing air with a higher than normal oxygen concentration increases oxygen transport by hemoglobin to only a small extent-by about 1 mL of extra oxygen for every deciliter of blood ( $10 \mathrm{~mL} \mathrm{O}_{2}$ per liter).
2. Oxygen that dissolves in plasma when breathing a hyperoxic mixture also increases by about 0.4 mL per deciliter of blood ( $4.0 \mathrm{~mL} \mathrm{O}_{2}$ per liter), or from the normal 0.3 mL per deciliter ( 3.0 mL per liter) to about 0.7 mL per deciliter ( 7.0 mL per liter) of blood.

Based on these two factors, the blood s oxygen-carrying capacity under hyperoxic conditions potentially increases by only about 14 mL of oxygen for every liter of blood- 10 mL extra attached to hemoglobin and 4 mL extra dissolved in plasma.

## Preexercise Oxygen Breathing

Blood volume for a $70-\mathrm{kg}$ person averages about 5000 $\mathrm{mL}(5.0 \mathrm{~L})$. Breathing hyperoxic gas adds about 70 mL of oxygen to the total blood volume ( 5.0 L of blood $\times 14 \mathrm{~mL}$ extra $\mathrm{O}_{2}$ per liter of blood). Despite any potential psychologic benefit for the athlete who believes that preexercise oxygen breathing helps subsequent performance, this procedure confers only a trivial physiologic advantage from any additional oxygen per se. This small benefit emerges only if subsequent exercise takes place without breathing ambient air in the interval between hyperoxic breathing and exercise. This occurs because ambient air s lower oxygen pressure causes any additional oxygen in the blood to exit the body.

The athlete who breathes an oxygen-rich mixture on the sideline before returning to the competition does not gain a competitive edge from physiologic benefits. This is particularly ironic in football, because metabolic reactions that do not require oxygen generate almost all of the energy to power each play.

## Oxygen Breathing During Exercise

Breathing hyperoxic gas during submaximal and maximal aerobic exercise enhances endurance performance. Oxygen breathing during vigorous exercise accelerates oxygen consumption at the onset of exercise (smaller oxygen deficit in repeated bouts of intense effort); reduces blood lactate, heart rate, and pulmonary ventilation in submaximal exercise; and increases $\mathrm{VO}_{2 \max }$ and the exercise training intensity. ${ }^{166,194,214}$ In one study, subjects performed a 6.5-minute endurance ride on a bicycle ergometer at an exercise level equal to $115 \%$ of $\mathrm{VO}_{2 \max }$ while breathing either room air or $100 \%$ oxygen. ${ }^{286}$ Tanks of compressed gas supplied both air and oxygen to mask a subject s knowledge of the breathing mixture. Figure 23.15A shows superior endurance (less drop-off in pedal revolutions) while breathing oxygen during exercise. Figure 23.15B shows that the hyperoxic condition produced higher oxygen consumptions throughout exercise.

Figure 23.16 shows that oxygen consumption of the quadriceps muscle of seven trained subjects during maximum knee-extension exercise varied with the level of inspired oxygen, averaging lower in hypoxia $\left(12 \% \mathrm{O}_{2}\right)$ than in normoxia $\left(21 \% \mathrm{O}_{2}\right)$ and higher in hyperoxia $\left(100 \% \mathrm{O}_{2}\right)$ than normoxia. The figure also includes confirmatory results (dotted yellow line) from a previous study of cycle ergometry under


Figure 23.15 A. Endurance (measured by pedal revolutions each minute) while breathing $100 \%$ oxygen or ambient air. B. Oxygen consumption curves during the endurance rides show enhanced oxygen consumption while breathing oxygen. (Data from Weltman A, et al. Effects of increasing oxygen availability on bicycle ergometer endurance performance. Ergonomics 1978;21:427.)


Пycle exercise $\square$ Knee-extensor exercise
Figure 23.16 Relationship between skeletal muscle $\mathrm{VO}_{2 \text { peak }}$ and oxygen delivery per 100 g of muscle during conventional maximal cycle ergometry exercise (yellow) and kneeextension exercise (purple) under hypoxia, normoxia, and hyperoxia. (From Richardson RS, et al. Evidence of $\mathrm{O}_{2}$ supply dependent $\mathrm{VO}_{2 \text { max }}$ in exercise-trained human quadriceps. J Appl Physiol 1999;86:1048.)
comparable conditions. ${ }^{150}$ Cycle ergometry produced lower muscle-specific $\mathrm{VO}_{2 \text { peak }}$ values than knee-extension exercise. However, the slopes of the lines relating oxygen delivery to peak muscle oxidative metabolism were remarkably similar for both exercise modes. For maximal knee-extension exercise, oxygen content of venous blood leaving the active muscles remained essentially equal among conditions averaging $4 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$. Oxygen delivery in arterial blood increased from 17.3 to 19.5 to $21.8 \mathrm{~mL} \cdot \mathrm{dL}^{-1}$ with increasing levels of oxygen inhalation. Consequently, the hyperoxic condition during maximal exercise produced the largest skeletal muscle $\mathrm{a}-\mathrm{vO}_{2}$ difference and $\mathrm{VO}_{2 \text { peak }}$. Similarly, maximal exercise intensity decreased $25 \%$ when breathing $12 \%$ inspired oxygen and increased $14 \%$ under $100 \%$ inspired oxygen compared with normoxic conditions. Oxygen delivery to active muscles in the circulation, not use via mitochondrial metabolism, limits aerobic exercise.

Breathing hyperoxic gas does not increase maximal cardiac output; thus, an expanded a-vO 2 difference must account for the increased exercise oxygen consumption. The small increases in arterial hemoglobin saturation and dissolved plasma oxygen with hyperoxic breathing increase total oxygen availability as blood volume circulates 4 to 7 times each minute in strenuous exercise. The additional but relatively small 14 mL of oxygen in each 1 L of blood from breathing hyperoxic gas represents considerable extra oxygen when
exercising at a $20-$ to $30-\mathrm{L}$ cardiac output. If the muscles metabolized the added oxygen during exercise, $\mathrm{VO}_{2 \max }$ would increase by 5 to $10 \%$. The increased partial pressure of oxygen in solution from breathing hyperoxic gas also facilitates its diffusion across the tissue capillary membrane into the mitochondria. More rapid oxygen diffusion may account for the higher oxygen consumption early in exercise under hyperoxic conditions. Reduced pulmonary ventilation under hyperoxic conditions lowers the oxygen cost of breathing. Theoretically, this liberates oxygen for use by the active, nonventilatory skeletal muscles. Hyperoxia also increases sustained muscle performance in intense static and dynamic movements not affected by central circulatory factors. The high oxygen pressure in blood and fluids within the active muscle environment may explain this ergogenic effect.

Breathing hyperoxic mixtures offers positive ergogenic benefits during endurance exercise, but offers limited practical sports application. The legality of using an appropriate breathing system during actual competition seems unlikely.

## Oxygen Breathing During Recovery

Breathing hyperoxic mixtures does not facilitate recovery from exercise or improve performance in a subsequent exercise bout. Figure 23.17 illustrates the effects of breathing hyperoxic gas in recovery from strenuous exercise on subsequent exercise performance. Following 1 minute of all-out bicycle ergometer exercise, subjects recovered while breathing either room air or $100 \%$ oxygen for 10 or 20 minutes. They then repeated the all-out bicycle ride. No significant differences emerged in cumulative revolutions (graph A) and 6-second-by-6-second revolutions (graph B) for the 1-minute ride after breathing room air or $100 \%$ oxygen during recovery from previous exercise. Also, breathing either room air or oxygen yielded similar blood lactate levels in the 10 - or 20-minute recovery periods. This indicated that breathing oxygen in recovery did not facilitate lactate removal. Subsequent research supports these findings; breathing oxygen after short intervals of submaximal and maximal exercise did not affect recovery kinetics for minute ventilation, heart rate, or serum lactate or the level of ensuing exercise performance. ${ }^{215,289}$

## Modification of Carbohydrate Intake

Increased carbohydrate intake before and during intense aerobic exercise, including periods of strenuous training, is a sound macronutrient manipulation that benefits exercise performance, lowers ratings of perceived exertion, and improves psychologic state. ${ }^{1,262}$ Vigilance and mood also improve with a carbohydrate beverage administered during a day of sustained aerobic activity interspersed with rest periods. ${ }^{160}$ One of the more popular nutritional exercise modifications used by endurance athletes to augment glycogen reserves involves carbohydrate loading, or glycogen supercompensation. The procedure produces considerably higher packing of muscle glycogen than simply maintaining a high-carbohydrate diet. Normally, each


Figure 23.17 Cumulative (A) and absolute (B) 6 -second pedal revolutions on a bicycle ergometer during 1 minute of maximal exercise after breathing either 100\% oxygen or ambient air during recovery from a previous maximal exercise bout. (From Weltman A, et al. Exercise recovery, lactate removal, and subsequent high-intensity exercise performance. Res Q 1977;48:786.)

100 g of muscle contains about 1.7 g of glycogen; carbohydrate loading packs up to 4 to 5 g of glycogen.

## Nutrient-Related Fatigue in Prolonged Exercise

Glycogen stored in the liver and active muscle supplies most of the energy for intense aerobic exercise. Prolonging such exercise reduces the body s glycogen reserves. This allows fat catabolism-from adipose tissue and liver fatty acid mobilization and intramuscular fat stores-to supply a progressively greater percentage of energy. A substantially lowered muscle glycogen level precipitates fatigue, although active muscle maintains sufficient oxygen with an almost unlimited potential energy from fat. Consuming a glucose and water solution near the point of fatigue allows exercise to continue, but for all practical purposes, the muscles fuel tank reads empty. Reliance on fat catabolism decreases power output from the considerably slower mobilization and breakdown of fat than carbohydrate. Marathon runners use the term hitting the wall (endurance cyclists use bonking) to describe sensations of fatigue and muscle pain associated when exercising with severe glycogen depletion.

In the late 1930s, Nordic scientists reported enhanced endurance performance when athletes consumed carbohydraterich diets. Conversely, switching to high-fat diets drastically reduced endurance capacity. Modifying the diet s macronutrient composition alters carbohydrate stores and profoundly affects subsequent prolonged high-intensity exercise performance. In a classic series of experiments, endurance capacity for subjects
fed a high-carbohydrate diet was triple that when the same subjects consumed a high-fat diet of similar energy content (see Fig. 1.9). ${ }^{23}$ Carbohydrate represents the important energy substrate during 1 to 2 hours of high-intensity exercise, so researchers searched for additional ways to increase preexercise glycogen reserves.

## Classic Loading Procedure

Table 23.9 presents the classic procedure for achieving the supercompensation effect. The first phase involves reducing the muscle s glycogen content with prolonged exercise about 6 days before competition. Glycogen supercompensation occurs only in the specific muscles depleted by exercise, so athletes must engage the muscles activated in their sport. Preparing for marathon running, endurance swimming, or bicycling requires 90 minutes of moderately intense submaximal exercise in the specific activity. The athlete then maintains a low-carbohydrate diet (about 60 to $100 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ ) for several days to further deplete glycogen stores. (Note: Glycogen depletion increases intermediate forms of the glycogen-storing enzyme glycogen synthase within the depleted muscle fibers.) Moderate training continues during this time. Then, 3 days before competing, the athlete switches to a high-carbohydrate diet ( 400 to $700 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ ) and maintains this intake up to the precompetition meal. The supercompensation diet should also contain adequate daily protein, minerals and vitamins, and abundant water. Supercompensated muscle glycogen levels remain stable for at least 3 days during a maintenance phase (in a nonexercising individual) if the diet contains $60 \%$ of calories as carbohydrate. ${ }^{103}$

## TABLE 23.9 Two-Stage Dietary Plan to Increase Muscle Glycogen Storage

## Stage 1Bepletion

Day 1: Exhausting exercise to deplete muscle glycogen in specific muscles
Days $2,3,4$ : Low-carbohydrate intake ( $60100 \mathrm{~g} \cdot \mathrm{~d}^{-1}$; high percentage of protein and lipid in daily diet)
Stage 2Carbohydrate loading
Days 5, 6, 7: High-carbohydrate intake (400 $700 \mathrm{~g} \cdot \mathrm{~d}^{-1}$; normal percentage of protein in daily diet)
Competition day
High-carbohydrate precompetition meal

Athletes should learn all they can about carbohydrate loading before manipulating dietary and exercise habits to achieve a supercompensation effect. If an athlete decides to supercompensate after weighing the pros and cons, the new food regimen should proceed in stages during training, not for the first time before competition. For example, the athlete should start with a long run followed by a high-carbohydrate diet. A detailed $\log$ should record how the dietary manipulation affects performance. A record of subjective feelings should include exercise depletion and replenishment phases. With positive results, the athlete can try the entire seriesdepletion, low-carbohydrate diet, and high-carbohydrate
diet-but maintain the low-carbohydrate diet for only 1 day. With no adverse effects, the low-carbohydrate diet can gradually extend to a maximum of 4 days.

Sample Diets to Achieve the Supercompensation Effect. Table 23.10 provides a sample meal plan for carbohydrate depletion (stage 1) and carbohydrate loading (stage 2) preceding an endurance event.

Limited Applicability. Carbohydrate loadings benefits to exercise performance apply only to intense aerobic activities lasting longer than 60 minutes. Exercise lasting less than 60 minutes requires only normal carbohydrate intake and glycogen reserves. ${ }^{12,115,165,189,197}$ For example, carbohydrate loading did not benefit trained runners in a $20.9-\mathrm{km}$ (13-mile) run compared with a run following a low-carbohydrate diet. Similarly, no ergogenic effect emerged for time trial performance, heart rate, and rating of perceived exertion (RPE) for endurancetrained cyclists in a $100-\mathrm{km}$ trial that simulated continuous changes in exercise intensity typical of competition. ${ }^{38}$

For sports competition and exercise training, a daily diet that contains about 60 to $70 \%$ of calories as carbohydrates provides adequate muscle and liver glycogen reserves. This diet ensures about twice as much muscle glycogen as a typical diet of 45 to $50 \%$ carbohydrate. For well-nourished athletes, the supercompensation effect remains relatively small. During intense training, athletes who do not upgrade daily calorie and carbohydrate intakes to meet energy demands can experience chronic muscle fatigue and staleness. ${ }^{62}$

TABLE 23.10 Sample Meal Plan for Carbohydrate Depletion and Carbohydrate Loading Preceding an Endurance Event

| Meal | Stage 1 <br> Depletion | Stage 2 <br> Carbohydrate Loading |
| :---: | :---: | :---: |
| Breakfast | 0.5 cup fruit juice | 1 cup fruit juice |
|  | 2 eggs | 1 bowl hot or cold cereal |
|  | 1 slice whole-wheat toast | 1 to 2 muffins |
|  | 1 glass whole milk | 1 Tbsp butter |
| Lunch | 6 oz hamburger | 23 oz hamburger with bun |
|  | 2 slices bread | 1 cup juice |
|  | salad (normal size) | 1 orange |
|  | 1 Tbsp mayonnaise and salad dressing | 1 Tbsp mayonnaise pie or cake (one 8 -in slice) |
|  | 1 glass whole milk | 1 cup yogurt, fruit, or cookies |
| Snack | 1 cup yogurt | 11.5 pieces of chicken, baked |
| Dinner | 23 pieces of chicken, fried | 1 cup vegetables |
|  | 1 baked potato with sour cream 0.5 cup vegetables iced tea (no sugar) | 0.5 cup sweetened pineapple iced tea (sugar) |
|  | 2 Tbsp butter | 1 glass chocolate milk with 4 cookies |
| Snack | 1 glass whole milk |  |



Figure 23.18 Muscle glycogen concentrations pre- and post-carbohydrate loading (12 g carbohydrate per kg lean body mass) in exercise-trained men and women. (From James AP, et al. Muscle glycogen supercompensation: absence of a gender-related difference. Eur J Appl Physiol 2001;85:533.)

## Gender Differences in Glycogen Storage and Catabolism in Exercise

Gender-related differences in muscle glycogen supercompensation remain controversial. One study reported a relatively small $13 \%$ increase in the muscle glycogen content of women when they switched from a mixed diet to a high-carbohydrate diet. ${ }^{281}$ Other research indicated that women do not increase glycogen storage when dietary carbohydrate increases from 60 to $75 \%$ of total caloric intake. ${ }^{256}$ Importantly, this increase in carbohydrate intake as a percentage of total calories represents considerably less total carbohydrate intake relative to lean body mass for women than for men. Figure 23.18 illustrates that equalizing daily carbohydrate intake for endurance-trained men and women at 12 g per kg of lean body mass for 3 consecutive days produced no gender differences in glycogen loading. These and other findings show that men and women possess an equal capacity to accumulate muscle glycogen when fed comparable amounts of carbohydrate relative to lean body mass. ${ }^{255,257}$ Women oxidize more lipid and less carbohydrate and protein compared with men during endurance exercise. ${ }^{54,94,125}$ The increase in fat oxidation is associated with higher intramyocellular lipid content and use as well as greater adipocyte lipolysis. The greater fat oxidation for women during submaximal endurance exercise seems to occur partly through a sex hormone mediated enhancement of lipid-oxidation pathways. ${ }^{255}$

## Glycogen Supercompensation Enhanced by Prior Creatine Supplementation

A synergy exists between glycogen storage and creatine supplementation. For example, preceding glycogen loading with a 5 -day creatine loading protocol ( 20 g per day) produced $10 \%$ greater glycogen packing in the vastus lateralis muscle than achieved with only glycogen loading. ${ }^{220}$ More than likely, increases in creatine and cellular volume with creatine supplementation facilitate subsequent storage of muscle glycogen.

## Negative Aspects of Carbohydrate Loading

The addition of 2.7 g of water with each gram of glycogen makes it a heavy fuel compared with equivalent energy stored as fat. Athletes often feel heavy and uncomfortable with this added water weight; any extra load also directly adds to the energy cost of weight-bearing activities. The extra weight may negate any potential benefits from increased glycogen storage. On the positive side, water liberated during glycogen breakdown aids in temperature regulation, which benefits exercise in hot environments.

The classic model for supercompensation may pose potential hazards for individuals with specific health problems. A severe chronic carbohydrate overload, interspersed with periods of high lipid and/or high protein intake, can increase blood cholesterol and urea nitrogen levels. High lipid intake often causes gastrointestinal distress plus poor recovery from the exercise-depletion sequence of the loading procedure. During the low-carbohydrate phase of loading, marked ketosis can occur in individuals who exercise while carbohydrate depleted. Failure to eat a balanced diet also produces mineral and vitamin deficiencies, particularly of the water-soluble vitamins. The glycogen-depleted state reduces the ability to train, possibly leading to a detraining effect during portions of the loading sequence. Dramatically reducing dietary carbohydrate for 3 or 4 days also could set the stage for lean tissue loss because muscle protein serves as gluconeogenic substrate to maintain blood glucose levels in the glycogen-depleted state.

## Modified Loading Procedures

A less stringent modified loading procedure outlined in Figure 23.19 eliminates many potential negative aspects of the classic glycogen-loading sequence. The protocol increases glycogen synthase activity without requiring dramatic glycogen depletion with exercise as with the classic loading procedure; it increases glycogen storage to nearly the same level. The 6-day protocol does not require prior exercise to exhaustion. Rather, the athlete trains at about $75 \%$ of $\mathrm{VO}_{2 \max }$ ( $85 \% \mathrm{HR}_{\max }$ ) for 1.5 hours and then, on successive days, gradually reduces (tapers) exercise duration. During the first 3 days, carbohydrates represent about $50 \%$ of total calories. Three days before competition, the diet s carbohydrate content increases to $70 \%$ of total energy intake.


## Exercise time $\square$ Dietary carbohydrate

Figure 23.19 A modified approach to carbohydrate loading. Recommended combination of diet and exercise for overloading muscle glycogen stores in the week before an endurance contest. Exercise time is gradually reduced during the week, while the diet s carbohydrate content increases for the last 3 days. (From Sherman WM, et al. Effect of exercisediet manipulation on muscle glycogen and its subsequent utilization during performance. Int J Sports Med 1981;2:114.)

## INTEGRATIVE QUESTION

What advice would you give to a sprint athlete who plans to carbohydrate load for competition?

Rapid Loading Procedure: A One-Day Requirement. The 2 to 6 days required to achieve supranormal muscle glycogen levels represents a limitation of typical carbohydrate-loading procedures. The desired loading effect occurs with a shortened duration that combines a brief bout of high-intensity exercise with only 1 day of high-carbohydrate intake. Endurance-trained athletes cycled for 150 seconds at an exercise intensity of $130 \%$ $\mathrm{VO}_{2 \text { max }}$ followed by 30 seconds of all-out cycling. In the recovery period, the men consumed $10.3 \mathrm{~g} \cdot \mathrm{~kg}$ body mass ${ }^{-1}$ of high glycemic carbohydrate foods. Biopsy data presented in Figure 23.20 indicated that glycogen in the vastus lateralis muscle increased from a $109.1 \mathrm{mmol} \cdot \mathrm{kg}^{-1}$ preloading average to $198.3 \mathrm{mmol} \cdot \mathrm{kg}^{-1}$ after only 24 hours. This $82 \%$ increase in glycogen storage equaled or exceeded values reported by others using a 2 - to 6 -day regimen. The short-duration loading procedure benefits individuals who do not wish to disrupt normal training with the time required and potential negative aspects of longer loading protocols. ${ }^{234}$

## Chromium

The trace mineral chromium serves as a cofactor (as trivalent chromium) for a low molecular-weight protein that potentiates


Figure 23.20 Muscle glycogen concentration of the vastus lateralis before (preloading) and after 180 seconds of nearmaximal intensity cycling exercise followed by 1 day of highcarbohydrate intake (postloading). (From Fairchild TJ, et al. Rapid carbohydrate loading after short bout of near maximalintensity exercise. Med Sci Sports Exerc 2002;34:980.)
insulin function, yet its precise mechanism of action remains unclear. Insulin promotes carbohydrate transport into cells, augments fatty acid catabolism, and triggers cellular enzyme activity that facilitates muscle protein synthesis. Chronic chromium deficiency can increase blood cholesterol and decrease the body s sensitivity to insulin, thus raising the risk for type 2 diabetes. Some adult Americans consume less than the 50 to $200 \mu \mathrm{~g}$ of chromium considered the estimated safe and adequate daily dietary intake (ESADDI). This occurs largely because chromium-rich foods-brewer s yeast, broccoli, wheat germ, nuts, liver, prunes, egg yolks, apples with skins, asparagus, mushrooms, wine, and cheese-do not usually form part of the regular diet. Food processing also removes substantial chromium from foods. In addition, strenuous exercise and associated high-carbohydrate intake promote urinary chromium losses, thus increasing the potential for chromium deficiency. For athletes with chromium-deficient diets, dietary modification to increase chromium intake or prudent use of chromium supplements seems appropriate.

## Numerous Alleged Benefits

Touted as a fat burner and muscle builder, chromium is one of the most hyped minerals in the health food fitness literature. Supplemental intake of chromium, usually as chromium picolinate, often reaches $600 \mu \mathrm{~g}$ daily. This chelated picolinic acid combination supposedly yields better chromium absorption than the inorganic salt chromium chloride. Millions of Americans believe the unsubstantiated claims of health food faddists, television infomercials, and exercise zealots that additional chromium promotes muscle growth, curbs appetite, fosters body fat loss, and even lengthens life. Advertising targets chromium to bodybuilders and
other resistance-trained athletes as a safe alternative to anabolic steroids to favorably change body composition. Chromium supplements supposedly potentiate insulin action to increase amino acid anabolism in skeletal muscle. This belief persists despite data that chromium supplements exert no effect on glucose or insulin concentrations in nondiabetic individuals. ${ }^{5}$

Generally, studies suggesting beneficial effects of chromium supplements on body fat and muscle mass infer body composition changes from changes in body weight (or unvalidated anthropometric measurements). One study observed that supplementing daily with $200 \mu \mathrm{~g}(3.85 \mu \mathrm{~mol})$ of chromium picolinate for 40 days produced a small increase in FFM (estimated from skinfold thickness) and decrease in body fat in young men who resistance trained for 6 weeks. ${ }^{85}$ The researchers provided no data to show increased muscular strength. Another study reported increases in body mass without changes in strength or body composition in previously untrained female college students (no change in males) who received a daily $200-\mu \mathrm{g}$ chromium supplement during 12 weeks of resistance training compared with unsupplemented controls. ${ }^{119}$

Other research evaluated the effects of a chromium supplement of $200 \mu \mathrm{~g}$ daily on muscle strength, body composition, and chromium excretion in 16 untrained males during 12 weeks of resistance training. ${ }^{114}$ Muscular strength improved $24 \%$ for the supplemented group and $33 \%$ for the placebo group during training. No changes occurred in any of the body composition variables. The group receiving the supplement did show higher chromium excretion than controls after 6 weeks of training. The researchers concluded that chromium supplements provided no ergogenic effect on any measured variable. Furthermore, supplementing with $800 \mu \mathrm{~g}$ of chromium picolinate (plus 6 mg of boron) proved no more effective than a maltodextrin placebo to enhance lean tissue gain or promote fat loss during resistance training. ${ }^{4}$ Daily supplementation with $400 \mu \mathrm{~g}$ of chromium picolinate for 9 weeks did not promote weight loss in sedentary obese women; it actually caused weight gain during the treatment period. ${ }^{107}$

In support of chromium supplementation, greater body fat loss (no increase in FFM) occurred in subjects recruited from a variety of fitness and athletic clubs who consumed $400 \mu \mathrm{~g}$ of chromium daily over 90 days than in subjects who received a placebo. ${ }^{139}$ Hydrostatic weighing and DEXA techniques assessed body composition. However, body compositional data from hydrostatic weighing do not appear in the report, and the DEXA-derived analysis indicated average body fat values of $42 \%$ for both control and experimental subjects, an extraordinary level of obesity for members of fitness clubs. Collegiate football players who received daily $200-\mu \mathrm{g}$ supplements of chromium picolinate for 9 weeks showed no changes in body composition and muscular strength from intense weight training compared with controls receiving a placebo. ${ }^{52}$ Similar findings of no benefit on body composition and exercise performance emerged from a 14-week study of NCAA Division I wrestlers that compared combined chromium
picolinate supplementation with a typical preseason training program with identical training without supplementation. ${ }^{282}$

Loss of muscle mass commonly affects older individuals, so potential ergogenic effect on muscle from chromium supplementation should emerge readily in this age group. This did not occur for older men involved in high-intensity resistance training; a high chromium picolinate dosage ( $924 \mu \mathrm{~g} \cdot \mathrm{~d}^{-1}$ ) did not augment muscle size, strength, or power or FFM accretion above the unsupplemented condition. ${ }^{41}$ Obese personnel enrolled in the United States Navy s mandatory remedial physical-conditioning program who consumed an additional $400 \mu \mathrm{~g}$ of chromium picolinate daily showed no greater loss in body weight or percentage body fat or increase in FFM than a group receiving a placebo. ${ }^{261}$

A comprehensive double-blind study examined the effects of a daily chromium supplement ( 3.3 to $3.5 \mu \mathrm{~mol}$ as either chromium chloride or chromium picolinate) or a placebo for 8 weeks during resistance training in 36 young men. For each group, dietary intakes of protein, magnesium, zinc, copper, and iron equaled or exceeded recommended levels during training; subjects also maintained adequate baseline dietary chromium intakes. Supplementation increased serum chromium concentration and urinary chromium excretion equally regardless of its ingested form. Table 23.11 shows that compared with placebo treatment, chromium supplementation did not affect training-related changes in muscular strength, FFM, or muscle mass.

## Not Without a Potential Downside

Chromium competes with iron for binding to transferrin, the plasma protein that transports iron from ingested food and damaged red blood cells for delivery to tissues in need. The chromium picolinate supplement for the group whose data appear in Table 23.11 reduced serum transferrin (a measure of adequacy of current iron intake) compared with chromium chloride or placebo treatments. Conversely, other researchers observed that giving middle-aged men $924 \mu \mathrm{~g}$ of supplemental chromium daily as chromium picolinate for 12 weeks did not affect hematologic measures or indices of iron metabolism or iron status. ${ }^{40}$ We are unaware of studies that have evaluated the safety of long-term chromium supplementation or the ergogenic efficacy of supplementing in individuals with suboptimal chromium status. Concerning the bioavailability of trace minerals in the diet, excessive dietary chromium inhibits zinc and iron absorption. At the extreme, this could induce iron-deficiency anemia, blunt the ability to train intensely, and negatively affect exercise performance requiring high-level aerobic metabolism.

Further potential bad news emerges from studies in which human tissue cultures that received extreme doses of chromium picolinate showed eventual chromosomal damage. Critics contend that such high laboratory dosages would not occur with supplement use in humans. Nonetheless, one could argue that cells continually exposed to excessive chromium (e.g., long-term supplementation) accumulate this mineral and retain it for years.

TABLE 23.11 Effects of Two Different Forms of Chromium Supplementation on Average Values for Anthropometric, Bone, and Soft-Tissue Composition Measurements Before and After Resistance Training

|  | Placebo |  | Chromium Chloride |  | Chromium Picolinate |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Pre | Post | Pre | Post | Pre | Post |
| Age (y) | 21.1 | 21.5 | 23.3 | 23.5 | 22.3 | 22.5 |
| Stature (cm) | 179.3 | 179.2 | 177.3 | 177.3 | 178.0 | 178.2 |
| Weight (kg) | 79.9 | $80.5{ }^{\text {a }}$ | 79.3 | $81.1{ }^{\text {a }}$ | 79.2 | 80.5 |
| $\Sigma 4$ skinfold thickness (mm) ${ }^{\text {b }}$ | 42.0 | 41.5 | 42.6 | 42.2 | 43.3 | 43.1 |
| Upper-arm girth (cm) | 30.9 | $31.6^{a}$ | 31.3 | $32.0{ }^{\text {a }}$ | 31.1 | 31.4 |
| Lower-leg girth (cm) | 38.2 | 37.9 | 37.4 | 37.5 | 37.1 | 37.0 |
| FFMFM (kg) ${ }^{\text {c }}$ | 62.9 | $64.3{ }^{a}$ | 61.1 | $63.1{ }^{\text {a }}$ | 61.3 | $62.7^{a}$ |
| Bone mineral (g) | 2952 | 2968 | 2860 | 2878 | 2918 | 2940 |
| Fat-free body mass (kg) | 65.9 | $67.3{ }^{\text {a }}$ | 64.0 | $65.9{ }^{\text {a }}$ | 64.2 | $66.1{ }^{\text {a }}$ |
| Fat (kg) | 13.4 | 13.1 | 14.7 | 15.1 | 14.7 | 14.5 |
| Body fat (\%) | 16.4 | 15.7 | 18.4 | 18.2 | 18.4 | 17.9 |

From Lukaski HC, et al. Chromium supplementation and resistance training: effects on body composition, strength, and trace element status of men. Am J Clin Nutr 1996;63:954.
${ }^{a}$ Significantly different from pretraining value.
${ }^{b}$ Measured at biceps, triceps, subscapular, and suprailiac sites.
${ }^{c}$ Fat-free, mineral-free mass.

## Creatine

Meat, poultry, and fish provide a rich source of creatine, containing 4 to 5 g of creatine per kg of food. The body synthesizes only about 1 g of this nitrogen-containing organic compound daily from the nonessential amino acids arginine, glycine, and methionine in the kidneys, liver, and pancreas. The animal kingdom contains the richest creatine-containing foods, placing vegetarians at a distinct disadvantage for ready sources of exogenous creatine. Skeletal muscle contains approximately $95 \%$ of the bodys total 120 to 140 g of creatine.

Creatine sold in supplemental form as creatine monohydrate $\left(\mathbf{C r H}_{2} \mathbf{O}\right)$ comes as a powder, tablet, capsule, and stabilized liquid. Adding phosphate salts to the $\mathrm{CrH}_{2} \mathrm{O}$ molecule creates phosphocreatine ( PCr ), a less frequently used form of creatine supplementation. Supplements in this form produce the same training effects on body mass, muscular strength, and FFM (estimated from skinfolds) as creatine ingested in monohydrate form. ${ }^{195}$ Creatine can be purchased over-the-counter or mail order as a nutritional supplement (but without guarantee of purity). Ingesting a liquid suspension of creatine monohydrate at the relatively high dosage of 20 to 30 g per day for 2 weeks increases intramuscular concentrations of free creatine and PCr up to $30 \%$. These levels remain high for weeks after only a few days of supplementation. ${ }^{126,169}$ Sports governing bodies do not consider creatine an illegal substance.

## Important Component of High-Energy Phosphates

Creatine passes through the digestive tract unaltered for absorption into the bloodstream by the intestinal mucosa. Just about all ingested creatine incorporates into skeletal muscle (average
concentration, 125 mM [range 90 to 160 mM ] per kg dry muscle). About $40 \%$ exists as free creatine; the remainder combines readily with phosphate to form PCr . Type II, fast-twitch muscle fibers store about 4 to 6 times more PCr than ATP. As emphasized in Chapter 5, PCr serves as the cells energy reservoir to provide rapid phosphate-bond energy to resynthesize ATP (more rapid than ATP regenerated in glycogenolysis) in the reversible reaction:

$$
\mathrm{PCr}+\mathrm{ADP} \stackrel{\text { creatine kinase }}{\rightarrow} \mathrm{Cr}+\mathrm{ATP}
$$

PCr also shuttles intramuscular high-energy phosphate between the mitochondria and muscle filament cross-bridge sites that initiate muscle action. Maintaining a high sarcoplasmic ATP:ADP ratio by energy transfer from PCr plays an important role in maximum effort lasting up to 10 seconds. This exercise duration places high demands on ATP resynthesis that exceed energy transfer from intracellular macronutrient breakdown. Improved energy transfer capacity from PCr also lessens reliance on energy from anaerobic glycolysis with associated increase in intramuscular $\mathrm{H}^{+}$and decrease in pH from lactate accumulation. ${ }^{11}$ Because of limited intramuscular PCr , it seems reasonable that any PCr increase should accomplish the following:

1. Accelerate ATP turnover to maintain power output during short-term muscular effort.
2. Delay PCr depletion.
3. Diminish dependence on anaerobic glycolysis and decrease subsequent lactate formation.
4. Facilitate muscle relaxation and recovery from repeated bouts of intense, brief effort via faster ATP and PCr resynthesis; rapid recovery allows continued higher-level power output.

## TABLE 23.12 Selected Studies Showing Increases in Exercise Performance Following Creatine Monohydrate Supplementation

| Reference | Exercise | Protocol | Exercise Performance |
| :---: | :---: | :---: | :---: |
| d | Isokinetic, unilat, knee extensions ( $180 \cdot \mathrm{~s}^{-1}$ ) | 5 bouts of 30 ext, w/1-min rest periods | Less decline in peak torque production during bouts 2,3 , and 4 |
| e | Running | $4300 \mathrm{mw} / 4-\mathrm{min}$ rest periods | Improved time for final 300- and 1000-m runs |
|  |  | $4-1000 \mathrm{mw} / 3-\mathrm{min}$ rest periods | Improved total time for $41000-\mathrm{m}$ runs; reduction in best time for $300-$ and $1000-\mathrm{m}$ runs |
| a | $\begin{aligned} & \text { Cycle ergometry } \\ & \left(140 \mathrm{rev} \cdot \mathrm{~min}^{-1}\right) \end{aligned}$ | Ten 6 -s bouts w/1-min rest periods | Better able to maintain pedal frequency during second 46 of each bout |
| f | Cycle ergometry $\left(140 \mathrm{rev} \cdot \mathrm{min}^{-1}\right.$ ) | Five 6 -s bouts w/30-s recovery followed by one $10-\mathrm{s}$ bout | Better able to maintain pedal frequency near end of 10 -s bout |
| b | Cycle ergometry ( $80 \mathrm{rev} \cdot \mathrm{min}^{-1}$ ) | Three 30 -s bouts w/4-min rest periods | Increase in peak power during bout 1 and increase in mean power and total work during bouts 1 and 2 |
| c | Bench press | 1-RM bench press and total reps at $70 \% 1-\mathrm{RM}$ | Increase in 1-RM; increase in reps at $70 \%$ of 1-RM |
| g | Bench press | 5 sets bench press w/2-min rest periods | Increase in reps completed during all 5 sets |
| g | Jump squat | 5 sets jump squat w/2-min rest periods | Increase in peak power during all 5 sets |

${ }^{a}$ Balsom PD, et al. Creatine supplementation and dynamic high-intensity intermittent exercise. Scand J Med Sci Sports 1995;3:143.
${ }^{b}$ Birch R, et al. The influence of dietary creatine supplementation on performance during repeated bouts of maximal isokinetic cycling in man. Eur J Appl Physiol 1994;69:268.
${ }^{c}$ Earnest CP, et al. The effect of creatine monohydrate ingestion in anaerobic power indices, muscular strength and body composition. Acta Physiol Scand 1995;153:207.
${ }^{d}$ Greenhaff PL, et al. Influence of oral creatine supplementation on muscle torque during repeated bouts of maximal voluntary exercise in man. Clin Sci 1993;84:565.
${ }^{e}$ Harris RC, et al. The effect of oral creatine supplementation on running performance during maximal short-term exercise in man. J Physiol 1993;467:74P.
${ }^{f}$ Soderlund K, et al. Creatine supplementation and high-intensity exercise: influence on performance and muscle metabolism. Clin Sci 1994;87(suppl):120.
${ }^{g}$ Volek JS, et al. Creatine supplementation enhances muscular performance during high-intensity resistance exercise. J Am Diet Assoc 1997;97:765.
From Volek JS, Kraemer WJ, Creatine supplementation: its effect on human muscular performance and body composition. J Strength Cond Res 1996;10:200.

## Documented Benefits in Humans

Creatine supplementation received notoriety as an ergogenic aid when British sprinters and hurdlers used it in the 1992 Barcelona Olympic Games. Creatine supplementation at recommended levels exerts the following three effects:

1. Improves performance in muscular strength and power activities
2. Augments short bursts of muscular endurance
3. Provides for greater muscular overload to augment training effectiveness
No serious adverse effects from creatine supplementation for up to 4 years have been reported. ${ }^{232}$ Anecdotes indicate a possible association between creatine supplementation and cramping in multiple muscle areas during competition or lengthy practice in American football players. This effect may result from (1) altered intracellular dynamics because of increased levels of free creatine and PCr or (2) osmotically induced enlarged cell volume (greater cellular hydration) from the muscle fibers increased creatine content. Gastrointestinal tract disturbances (nausea, indigestion, and difficulty absorbing food) have been linked to exogenous creatine ingestion. It remains unclear whether the ergogenic effect differs in vegetarians and meat eaters. ${ }^{237}$

Creatine monohydrate supplements substantially increase muscle creatine content and performance in high-intensity exercise, particularly repeated intense muscular effort (Table 23.12). ${ }^{173,209,210,221,265,278}$ Figure 23.21 illustrates the ergogenic effects of creatine supplementation on total work accomplished during repetitive sprint cycling performance. Physically active but untrained males performed sets of maximal 6-second bicycle sprints interspersed with various recovery periods ( 24,54 , or 84 s ) to simulate sport conditions. Performance evaluations took place under creatine-loaded ( 20 g per day for 5 days) or placebo conditions. Supplementation increased muscle creatine ( $48.9 \%$ ) and $\mathrm{PCr}(12.5 \%)$, which produced a $6 \%$ increase in total work accomplished ( 251.7 kJ presupplement vs. 266.9 kJ creatine loaded) compared to the placebo group ( 254.0 kJ pretest vs. 252.3 kJ placebo). Creatine supplements have benefited an on-court ghosting routine of simulated positional play of competitive squash players. ${ }^{223}$ Supplementation also augments repeated sprint cycle performance after 30 minutes of constant load, submaximal exercise in the heat, without adversely affecting thermoregulatory dynamics. ${ }^{173}$

One research study evaluated a creatine dose of 30 g daily for 6 days in trained runners under two conditions: (1) four repeated $300-\mathrm{m}$ runs with a 4-minute recovery and (2) four 1000m runs with a 3 -minute recovery. ${ }^{117}$ Compared with placebo

$\square$ Pre-eading ПPost.loading
Figure 23.21 Effects of creatine loading versus placebo on total work accomplished during repetitive sprint-cycling performance. (From Preen CD, et al. Effect of creatine loading on long-term sprint exercise performance and metabolism. Med Sci Sports Exerc 2001;33:814.)
treatment, creatine supplementation improved performance under both conditions with the most impressive gains in repeated 1000-m runs. Supplementing with 20 g of creatine daily for 4 days also benefited anaerobic capacity in three 30 -second Wingate tests with a 5-minute rest between trials. For Division I football players, creatine supplementation with resistance training increased body mass, lean body mass, cellular hydration, and muscular strength and performance. ${ }^{21}$ Similarly, supplementation augmented muscular strength and size increases during 12 weeks of resistance training. ${ }^{287}$ The enhanced hypertrophic response with supplementation and resistance training possibly results from accelerated myosin heavy-chain synthesis. For resistance-trained men classified as responders to creatine supplementation (i.e., a creatine increase $\geq 32 \mathrm{mmol} \cdot \mathrm{kg}$ dry wt muscle ${ }^{-1}$ ), 5 days of supplementation increased body weight and FFM, and peak force and total force during repeated maximal isometric bench-presses. ${ }^{146}$ For men classified as nonresponders to supplementation (i.e., creatine increase $\leq 21 \mathrm{mmol} \cdot \mathrm{kg}$ dry wt muscle ${ }^{-1}$ ), no ergogenic effect occurred.

Figure 23.22 outlines possible mechanisms for enhanced exercise performance and training response by elevating intramuscular free creatine and PCr . Consuming a high dose of creatine helps replenish muscle creatine following intense exercise. This metabolic reloading promotes
recovery of muscle contractile capacity, enabling athletes to maintain repeated efforts of high-intensity exercise and training. A facilitated rate of muscle relaxation may also contribute to the ergogenic action of creatine supplementation. ${ }^{267}$ Besides benefiting weightlifting and bodybuilding, improved immediate anaerobic power output capacity aids sprint running, swimming, kayaking, cycling, jumping, football, and volleyball. Oral creatine supplementation combined with heavy-resistance training affects cellular processes in a manner that increase protein deposition within the muscle s contractile mechanism. ${ }^{287}$ This response could explain any increase in muscle size and strength associated with creatine supplementation.

Creatine supplementation does not improve cardiovascular and metabolic responses during continuous incremental treadmill running or performance that requires a high level of aerobic energy transfer. ${ }^{10,110}$

## Are There Risks?

Potential dangers of short-term creatine supplementation have been studied in healthy individuals, particularly on cardiac muscle and kidney function (creatine degrades to creatinine before excretion in urine). Creatine consumed 20 g per day for 5 consecutive days produced no detrimental effect on blood pressure, insulin action, plasma creatine, plasma CK activity, or renal function, measured by glomerular filtration rate, kidney permeability, and total protein and albumin excretion rates. ${ }^{153,175,185,200}$ Only limited information exists about the effects of long-term, high-dose supplementation with creatine. For healthy subjects, no differences in plasma contents and urinary excretion rates for creatinine, urea, and albumin emerged between control subjects and individuals who consumed creatine for up to 5 years. ${ }^{199}$ Glomerular filtration rate, tubular reabsorption, and glomerular membrane permeability also remained normal with long-term creatine use. Individuals with suspected renal malfunction should refrain from creatine supplementation because of the potential for exacerbating the disorder. ${ }^{205}$

## Age Effects Uncertain

Whether creatine supplementation augments the training response in older individuals remains equivocal. For 70-yearold men, a creatine supplementation loading phase ( 0.3 g per kg body mass for 5 days) followed by a daily maintenance phase ( 0.07 g per kg body mass) increased lean tissue mass, leg strength, muscular endurance, and average power of the legs during resistance training to a greater extent than a placobo. ${ }^{51}$ Similarly, creatine supplements benefit muscular performance in normally active older men. ${ }^{104}$ In contrast, no enhancement in resistance-training response to creatine ingestion occurred among sedentary and weight-trained older adults. ${ }^{24}$ These results were attributed to an age-related decline in creatine transport efficiency. Short-term creatine supplementation per se, without resistance training, does not increase muscle protein synthesis or FFM. ${ }^{191}$

Figure 23.22 Mechanisms to explain why increased intracellular creatine ( Cr ) and phosphocreatine ( PCr ) might enhance intense, shortterm exercise performance and the exercise-training response. (Modified from Volek JS, Kraemer WJ. Creatine supplementation: its effect on human muscular performance and body composition. J Strength Cond Res 1996;10:200.)


## Effects on Body Mass and Body Composition

Increases in body mass between 0.5 and 5.2 kg often accompany creatine supplementation, independent of changes in testosterone or cortisol concentrations. ${ }^{77,130,279}$ How much of the weight gain occurs from the anabolic effect of creatine on muscle tissue synthesis, retention of intracellular water from increased creatine stores, or other factors remains unclear.

Creatine intake during resistance training (4-d pretraining dosage, $20 \mathrm{~g} \cdot \mathrm{~d}^{-1}$, followed by $5 \mathrm{~g} \cdot \mathrm{~d}^{-1}$ during training) by young adult females increased maximal strength of trained muscles (20 25\%), maximal intermittent exercise capacity of the arm flexors (10 25\%), and FFM (6\%) compared with the placebo condition. ${ }^{264}$ Additional muscle water content could account for a portion of the FFM increase. A $2.42-\mathrm{kg}$ body mass gain associated with creatine supplementation and
resistance or agility training resulted partly from increases in fat- or bone-free body mass unrelated to an increase in total body water. ${ }^{152}$

Resistance-trained men matched for physical characteristics and maximal strength randomly received a placebo or creatine supplement. Supplementation consisted of 25 g daily followed by maintenance at 5 g daily. Both groups engaged in heavy resistance training for 12 weeks. Figure 23.23A shows the greater training-induced increase in body mass and FFM for the creatine-supplemented group compared with controls. Greater maximum bench press and squat strength increases occurred in the creatine group than in controls (Fig. 23.23B). Creatine supplementation induced greater muscle fiber hypertrophy with resistance training, indicated by greater enlargement in types I ( 35 vs . 11\%), IIA ( $36 \mathrm{vs} .15 \%$ ), and IIAB muscle fiber cross-sectional areas ( 35 vs. 6\%; Fig. 23.22C).


## $\square$ Creatine $\square$ Placebo

Figure 23.23 Effects of 12 weeks of creatine supplementation plus heavy-resistance training on changes in (A) body mass (BM), fat-free body mass (FFM), and body fat;
(B) muscular strength in the squat and bench press; and
(C) cross-sectional areas of specific muscle fiber types. The placebo group did identical training and received an equivalent quantity of powdered cellulose in capsule form.

* Change significantly greater compared to the placebo group. (From Volek JS, et al. Performance and muscle fiber adaptations to creatine supplementation and heavy-resistance training. Med Sci Sports Exerc 1999;31:1147.)

The larger volume of weight lifted during weeks 5 to 8 by the creatine supplement group suggests that higher quality training sessions mediated more favorable adaptations in FFM, muscle morphology, and strength performance.

## Creatine Loading

Many creatine users pursue a loading phase by ingesting 20 to 30 g of creatine daily for 5 to 7 days. Individuals who consume vegetarian-type diets show the greatest increase in muscle creatine levels because of their low dietary creatine content. Particularly large increases characterize individuals with normally low basal levels of intramuscular creatine. ${ }^{36,43}$ A maintenance phase follows the loading phase. During this time, the athlete supplements with as little as 2 to 5 g of creatine daily.

Practical questions for the athlete desiring to elevate intramuscular creatine levels concern the magnitude and time course of intramuscular creatine increase with supplementation, dosage needed to maintain the creatine increase, and rate of creatine loss or washout when supplementation ceases. To provide insight into these questions, researchers studied two groups of men. In one experiment, six men ingested 20 g of creatine monohydrate (approximately 0.3 g per kg of body mass) for 6 consecutive days and then stopped the supplementation. Biopsies assessed muscle creatine levels before supplement ingestion and at days 7, 21, and 35. Similarly, nine men took 20 g of creatine monohydrate daily for 6 consecutive days. Instead of discontinuing supplementation, they reduced dosage to 2 g daily (approximately 0.03 g per kg body mass) for an additional 28 days. Figure 23.24A shows that total muscle creatine concentration increased approximately $20 \%$ after 6 days. Without continued supplementation, muscle creatine content gradually declined to near baseline in 35 days. The group that continued to supplement with reduced creatine intake for an additional 28 days maintained muscle creatine at the higher level (Fig. 23.24B).

For both groups, the increase in total muscle creatine content during the initial 6-day supplementation period averaged about 23 mmol per kg of dry muscle; this represented about $20 \mathrm{~g}(17 \%)$ of total creatine ingested. A similar $20 \%$ increase in total muscle creatine concentration occurred with only a $3-\mathrm{g}$ daily supplement. However, the increase occurred more gradually and required 28 days rather than 6 days with the 6-g supplement.

A rapid way to creatine-load skeletal muscle requires ingesting 20 g of creatine monohydrate daily for 6 days; switching to a reduced 2-g per day dosage keeps these levels elevated for up to 28 days. If rapidity of loading is of little concern, supplementing with 3 g daily for 28 days achieves the same high levels.

Carbohydrate Ingestion Augments Creatine Loading. Consuming creatine with a sugar-containing drink increases creatine uptake and storage in skeletal muscle (Fig. 23.25). ${ }^{241}$ For 5 days, subjects received either 5 g of creatine four times daily or a 5 -g supplement followed 30 minutes later by 93 g of a high-glycemic simple sugar four times daily. The creatine-only group increased muscle $\mathrm{PCr}(7.2 \%)$, free creatine ( $13.5 \%$ ), and total creatine ( $20.7 \%$ ). Much larger increases occurred for the creatine-plus-sugar supplemented group ( $14.7 \%$ for $\mathrm{PCr}, 18.1 \%$ for free creatine, and $33.0 \%$ for total creatine). Creatine supplementation alone did not affect


Figure 23.24 A. Total muscle creatine concentration in six men who consumed 20 g of creatine for 6 consecutive days and then stopped the supplement. Muscle biopsies done before ingestion (day 0 ) and on days 7,21 , and 35 . B. Total muscle creatine concentration in nine men who ingested 20 g of creatine for 6 consecutive days and then ingested 2 g of creatine daily for the next 28 days. Muscle biopsies taken before ingestion (day 0 ) and on days 7,21 , and 35 . Values refer to averages per dry mass (dm). * Significantly different from day 0. (From Hultman E, et al. Muscle creatine loading in men. J Appl Physiol 1996;81:232.)
insulin secretion, whereas adding sugar elevated plasma insulin levels. More than likely, augmented creatine storage with a creatine-plus-sugar supplement resulted from insulinmediated glucose transport into skeletal muscle, which facilitated creatine transport into muscle fibers.

Stop Caffeine When Using Creatine. Caffeine negates the ergogenic effect of creatine supplementation. To evaluate the effect of preexercise caffeine ingestion on intramuscular creatine stores and intense exercise performance, subjects consumed either a placebo, a daily creatine supplement $\left(0.5 \mathrm{~g} \cdot \mathrm{~kg}^{-1}\right.$ body mass), or the same daily creatine supplement plus caffeine ( $5 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ body mass) for 6 days. ${ }^{263}$ Under each condition,


「 Cr ingestion
$\square \mathrm{Cr}+\mathrm{CHO}$ ingestion
Figure 23.25 Increases in dry muscle (dm) concentrations of phosphocreatine ( PCr ), creatine ( Cr ), and total creatine in one group after 5 days of Cr supplementation and in another group after 5 days of Cr and carbohydrate (CHO) supplementation. Values represent averages. * Significantly greater than creatine-only supplementation. (From Green AL, et al. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol 1996;271:E821.)
subjects performed maximal intermittent knee-extension exercise to fatigue on an isokinetic dynamometer. Creatine supplementation, with or without caffeine, increased intramuscular PCr (evaluated by nuclear magnetic resonance spectroscopy) between 4 and $6 \%$. Dynamic torque production also increased 10 to $23 \%$ with creatine compared with the placebo. Consuming caffeine totally negated creatine s ergogenic effect. To optimize creatines benefits, athletes should abstain from caffeinecontaining foods and beverages for several days prior to and during creatine loading, training, and competition.

## Some Research Shows No Benefit

Not all research confirms positive effects of creatine supplementation. Ergogenic effects may not emerge under the following seven conditions, but the reason for the discrepancies remains unknown:

1. In untrained subjects performing a single 15 -second bout of sprint cycling ${ }^{60}$
2. In trained subjects performing bouts of sport-specific physical activities such as swimming, cycling, and running ${ }^{37,88}$
3. In trained and untrained older adults ${ }^{131,290}$
4. In resistance-trained individuals ${ }^{250}$
5. In trained rowers ${ }^{71}$
6. During rapid weight loss ${ }^{187}$
7. When short-term supplementation does not increase muscle $\mathrm{PCr}^{88,183}$

## Lipid Supplementation with Medium-Chain Triacylglycerols

Do high-fat foods or lipid supplements elevate plasma fatty acid levels to increase energy availability from fat during prolonged aerobic exercise? Several factors affect the answer to this question. First, consuming triacylglycerols composed of predominantly long-chain fatty acids ( 12 to 18 carbons) delays gastric emptying. This negatively affects the rapidity of fat availability and slows fluid and carbohydrate replenishment, both crucial factors in intense endurance exercise. Second, after digestion and intestinal absorption (normally 3 to 4 h ), long-chain triacylglycerols reassemble with phospholipids, fatty acids, and a cholesterol shell to form fatty droplets called chylomicrons. These substances travel slowly to the systemic circulation via the lymphatic system. They eventually empty into the systemic venous blood in the neck region by way of the thoracic duct. Through the action of the enzyme lipoprotein lipase that lines capillary walls, chylomicrons in the bloodstream readily hydrolyze to provide free fatty acids and glycerol for use by peripheral tissues. The relatively slow rate of gastric emptying and subsequent digestion, absorption, and assimilation of long-chain triacylglycerols makes this energy source an undesirable supplement to augment energy metabolism during exercise.

Medium-chain triacylglycerols (MCTs) provide a more rapid source of fatty acid fuel. MCTs are processed oils, frequently produced for patients with intestinal malabsorption and tissue-wasting diseases. Marketing for the sports enthusiast hypes MCTs as fat burners, energy sources, glycogen sparers, and muscle builders. Unlike longer-chain triacylglycerols, MCTs contain saturated fatty acids with 8 to 10 carbon atoms along the fatty acid chain. During digestion, lipase in the mouth, stomach, and intestinal duodenum hydrolyzes MCTs to glycerol and medium-chain fatty acids (MCFAs). Their water solubility allows MCFAs to move rapidly across the intestinal mucosa directly into the bloodstream (portal vein) without first being transported as chylomicrons by the lymphatic system as long-chain triacylglycerols require. Once at the tissues, MCFAs move readily through the plasma membrane where they diffuse across the inner mitochondrial membrane for oxidation-they enter the mitochondria largely independent of the carnitine acyl-CoA transferase system. The speed of cellular uptake and mitochondrial oxidation contrasts with the relatively slower transfer and oxidation rate of long-chain fatty acids. MCTs do not usually store as body fat because of their relative ease of oxidation. Ingesting MCTs rapidly elevates plasma FFAs, making it plausible that these lipids might spare liver and muscle glycogen during aerobic exercise.

## Exercise Benefits Inconclusive

Consuming MCTs does not inhibit gastric emptying, as does common fat, but conflicting research supports their use in exercise. ${ }^{136,137,271,275}$ In early studies, subjects consumed 380 mg of MCT oil per kg of body mass 1 hour before exercising at 60 to $70 \%$ of $\mathrm{VO}_{2 \max }$ for 1 hour. ${ }^{66}$ Plasma ketone levels generally increased, but the exercise metabolic mixture did not change compared with a placebo trial or a trial after subjects consumed a glucose polymer. Catabolism of 30 g of MCTs (estimated maximal amount tolerated in the gastrointestinal tract) consumed before exercising contributed only 3 to $7 \%$ to the total exercise energy requirement. ${ }^{134}$

## INTEGRATIVE QUESTION

> Discuss the importance of the psychologic or placebo effect to evaluate claims for the effectiveness of particular nutrients, chemicals, or procedures as ergogenic aids.

Subsequent research investigated possible metabolic and ergogenic effects of consuming 86 g of MCT (surprisingly well tolerated by subjects). Six endurance-trained cyclists rode for 2 hours at $60 \%$ of $\mathrm{VO}_{2 \text { peak }}$ while ingesting 2 L of 4.3\% MCT emulsion, $10 \%$ glucose plus $4.3 \%$ MCT emulsion, or a $10 \%$ glucose solution during exercise. They then performed a simulated $40-\mathrm{km}$ cycling time trial. Figure 23.26 shows the effects of the different beverages on average speed in the time trials. Replacing the carbohydrate beverage with only MCTs produced an $8 \%$ decrement in performance (in agreement with another study), ${ }^{136}$ but the combined carbohydrate plus MCT solution consumed throughout exercise produced a $2.5 \%$ improvement in cycling speed compared with the two other conditions. This ergogenic effect occurred with reduced total carbohydrate oxidation at a given level of oxygen consumption, higher final circulating FFA and ketone levels, and lower final glucose and lactate concentrations.

The small ergogenic enhancement by MCT supplementation probably occurred because this exogenous source of fatty acids contributes relatively little to the total energy expenditure (and total fat oxidation) during sustained exercise. ${ }^{135}$ MCT ingestion does not stimulate release of bile, the gall bladder s fat-emulsifying agent. Thus, cramping and diarrhea often accompany excess intake of this lipid. It provides little ergogenic effect.

## Pyruvate

Ergogenic effects have been extolled for pyruvate, the threecarbon end product of the cytoplasmic breakdown of glucose in glycolysis. Exogenous pyruvate, as a partial replacement for dietary carbohydrate, supposedly augments endurance performance and promotes fat loss. Pyruvic acid, a relatively unstable chemical, causes intestinal distress, so various forms of the salt of this acid (sodium, potassium, calcium, or magnesium pyruvate) are manufactured in capsule, tablet, or powder form.


Figure 23.26 Effects of carbohydrate (CHO; 10\% solution), medium-chain triacylglycerol (MCT; 4.3\% emulsion), and carbohydrate + MCT ( $10 \%$ CHO $+4.3 \%$ MCT ) ingestion during exercise on simulated $40-\mathrm{km}$ time-trial cycling speeds after 2 hours of exercise at $60 \%$ of $\mathrm{VO}_{2 \text { peak }}$. * Significantly faster than 10\% CHO trials; ** Significantly faster than $4.3 \%$ MCT trials. (From Van Zyl CG, et al. Effects of medium-chain triglyceride ingestion on fuel metabolism and cycling performance. J Appl Physiol 1996;80:2217.)

Dosage recommendations range between a total of 2 and 5 g of pyruvate spread throughout the day and taken with meals. One capsule usually contains 600 mg pyruvate. The calcium form of pyruvate also contains approximately 80 mg of calcium with 600 mg of pyruvate. Some advertisements recommend dosage of one capsule per 20 pounds of body weight. Manufacturers also combine creatine monohydrate and pyruvate; 1 g of creatine pyruvate provides about 80 mg of creatine and 400 mg of pyruvate. Recommended pyruvate dosages range from 5 to 20 g per day. Pyruvate content in the normal diet ranges from 100 to 2000 mg daily. The largest dietary amounts occur in fruits and vegetables, particularly red apples ( 500 mg each), with smaller quantities in dark beer ( 80 mg per 12 oz ) and red wine ( 75 mg per 6 oz ).

## Endurance Performance

Several reports indicate beneficial effects of exogenous pyruvate on endurance performance. Two double-blind, crossover studies by the same laboratory showed that 7 days of daily supplementation of a $100-\mathrm{g}$ mixture of pyruvate $(25 \mathrm{~g})$ plus 75 g of dihydroxyacetone (DHA, another three-carbon compound of glycolysis) increased upper- and lower-body aerobic
endurance by $20 \%$ compared with exercise with a $100-\mathrm{g}$ supplement of an isocaloric glucose polymer. ${ }^{244,245}$ The pyruvate DHA mixture increased cycle ergometer time to exhaustion of the legs by 13 minutes ( 66 vs .79 min ), while upper-body arm-cranking exercise time increased by 27 minutes ( 133 vs. 160 min ). Exercising with the pyruvate DHA mixture reduced local muscle and overall body ratings of perceived exertion compared with the placebo condition. ${ }^{219}$

Proponents of pyruvate supplementation maintain that elevated extracellular pyruvate augments glucose transport into active muscle. Enhanced glucose extraction from the blood provides the important energy source to sustain highintensity aerobic exercise while conserving intramuscular glycogen stores. ${ }^{128}$ When the individual s diet contains a normal level of carbohydrate (approximately 55\% of total energy intake), pyruvate supplementation also increases preexercise muscle glycogen levels. ${ }^{245}$ Both of these effects-higher preexercise glycogen levels and facilitated glucose uptake and oxidation by active muscle-benefit endurance exercise similarly as preexercise carbohydrate loading and glucose feedings during exercise exert ergogenic effects.

## Body Fat Loss

Subsequent research by the same investigators who showed ergogenic effects of pyruvate supplementation indicates that exogenous pyruvate intake augments body fat loss when accompanied by a low-energy diet. Obese women in a metabolic ward maintained a liquid $1000-\mathrm{kCal}$ daily energy intake ( $68 \%$ carbohydrate, $22 \%$ protein, $10 \%$ lipid). Adding 20 g of sodium pyruvate plus 16 g of calcium pyruvate ( $13 \%$ of energy intake) daily for 3 weeks induced greater weight loss (13.0 vs. 9.5 lb ) and fat loss ( 8.8 vs .5 .9 lb ) than a control group on the same diet who received an equivalent amount of extra energy as glucose. ${ }^{246}$ These findings complement the researchers previous study with obese subjects that showed that adding DHA and pyruvate (substituted as equivalent energy for glucose) to a severely restricted low-energy diet facilitated body weight and fat loss (without increased nitrogen loss). ${ }^{247}$ The precise role of pyruvate in facilitating weight loss remains unknown. Consuming pyruvate may stimulate small increases in futile metabolic activity (metabolism not coupled to ATP production) with a subsequent wasting of energy.

Adverse side effects of a $30-$ to $100-\mathrm{g}$ daily pyruvate intake include diarrhea and gastrointestinal gurgling and discomfort. Until studies from independent laboratories reproduce existing findings for exercise performance and body fat loss, one should view the effectiveness of pyruvate supplementation with caution.

## Summary

1. The term ergogenic aid describes substances or procedures that improve physical work capacity, physiologic function, or athletic performance.
2. The strongest research studies apply a randomized, double-blind, placebo-controlled design.
3. Different levels of evidence permit grading the strengths of research studies.
4. Anabolic steroids compose a group of pharmacologic agents frequently used for ergogenic purposes. These drugs function like the hormone testosterone; they increase muscle size, strength, and power with resistance training in some individuals.
5. The $\beta_{2}$-adrenergic agonists clenbuterol and albuterol increase skeletal muscle mass and slow fat gain in animals to counter aging, immobilization, malnutrition, and tissue-wasting pathology. A negative finding showed hastened fatigue during shortterm, intense muscle actions.
6. Debate exists about whether administration of growth hormone to healthy individuals augments muscular hypertrophy when combined with resistance training. Health risks exist for those who abuse this chemical.
7. Dehydroepiandersterone (DHEA), a relatively weak steroid hormone synthesized from cholesterol by the adrenal cortex, steadily decreases throughout adulthood, prompting individuals to supplement, hoping to counteract the effects of natural aging. DHEA does not produce an ergogenic effect.
8. Research indicates no effect of androstenedione supplementation on basal serum concentrations of testosterone or training response for muscle size and strength and body composition.
9. No ergogenic effects exist for healthy subjects from chronic oral amino acid supplements on hormone secretion, training responsiveness, or exercise performance.
10. Hormonal dynamics from carbohydrate and/or protein supplementation immediately following a resistance-exercise workout suggests an ergogenic effect on training responsiveness.
11. Amphetamines, or pep pills, do not aid exercise performance or psychomotor skills, other than by a placebo effect. Adverse effects include drug dependency, headache, dizziness, confusion, and gastrointestinal distress.
12. Caffeine ingestion typically exerts an ergogenic effect by extending endurance in aerobic exercise from increased fat use for energy and conservation of glycogen reserves.
13. No compelling evidence supports ginseng supplementation to benefit physiologic function or exercise performance. Significant health risks accompany ephedrine use.
14. Concentrated buffering solutions consumed before exercise improve anaerobic exercise performance.
15. Further research must determine the benefits and risks of glutamine, phosphatidylserine, and $\beta$ hydroxyl $\beta$-methylbutyrate to provide a natural anabolic boost with resistance training.
16. The additional blood volume and increased red cell mass and concentration from red blood cell reinfusion contribute to a larger maximum cardiac output and an increase in the blood s oxygen-carrying capacity and $\mathrm{VO}_{2 \text { max }}$.
17. A physiologic rationale for why warm-up should enhance exercise performance includes benefits on muscle-shortening velocity and efficiency, enhanced oxygen delivery and use, and facilitated transmission of nerve impulses. Limited research supports the benefits of warm-up beyond a positive psychologic component.
18. Moderate warm-up proves beneficial immediately before sudden, strenuous exercise by reducing myocardial work and augmenting coronary blood flow when exercise begins.
19. Breathing hyperoxic gas during exercise extends endurance by increasing oxygen consumption, reducing blood lactate, and lowering pulmonary ventilation. Using this procedure before or after exercise provides no ergogenic effect.
20. Carbohydrate loading augments endurance in prolonged submaximal exercise. Athletes should be well informed about this procedure because of potential negative effects.
21. A modification of the classic loading procedure provides the same high level of glycogen storage without dramatic alterations in the diet and exercise routine.
22. No benefits emerge from chromium supplements on training-related changes in muscular strength, physique, or muscle mass for individuals with adequate dietary chromium intake.
23. Creatine supplements increase intramuscular creatine and PCr , enhance brief anaerobic power output capacity, and facilitate recovery from repeated bouts of intense effort.
24. Medium-chain triacylglycerols (MCTs) enhance fat oxidation and conserve glycogen during endurance exercise. This procedure does enhance performance by an additional $2.5 \%$.
25. Pyruvate supplementation purportedly augments endurance performance and promotes fat loss, but a definitive conclusion concerning its effectiveness requires research verification.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

World Anti-Doping Agency: Prohibited List www.wada-ama.org/en/prohibitedlist.ch2
Official website of the Olympic Movement www.olympic.org/
American College of Sports Medicine www.acsm.org/
U.S. Drug Enforcement Administration www.usdoj.gov/dea/
U.S. Drug Enforcement Administration:

Drug Abuse Prevention and Control www.usdoj.gov/dea/pubs/csa.html
U.S. Food and Drug Administration www.fda.gov


# Exercise Performance and Environmental Stress 

The true explorer does his work not for any hopes of reward or honor, but because the thing he has set for himself to do is a part of his being, and must be accomplished for the sake of the accomplishment. And he counts lightly hardships, risks, obstacles, if only they do not bar him from his goal.

## OVERVIEW

Admiral Robert E. Peary, Polar Explorer

Sport activities often take place at terrestrial elevations that impair oxygenation of blood flowing through the lungs and severely limit aerobic energy metabolism for exercise. At the other extreme, exploration beneath the waters surface poses a different challenge. Divers must transport their sea-level environment as a gas mixture compressed in a scuba tank carried on the back. Some diving enthusiasts use no external assistance, and the length of an underwater excursion becomes limited by two factors: (1) the quantity of air inhaled into the lungs just before the dive and (2) the buildup of arterial carbon dioxide during the dive. In both breath-hold diving and scuba diving, the environment provides unique challenges and dangers for the participant, often independent of the stress of exercise. Consideration also must focus on the thermal quality of the environment. On land, exercising in a hot, humid environment or extreme cold imposes severe stress. These environmental demands impair exercise capacity and pose a severe threat to health and safety.

Space exploration and accompanying short- and long-term exposures to near-zero gravity present a unique set of environmental stressors that impinge on physiologic function, structural mass, and exercise capacity both during flight and upon return to Earth.

The extent that each environmental stressor deviates from neutral conditions and the duration of the exposure determine the total impact on the body. The effect of several simultaneous environmental stressors (e.g., extreme cold exposure at high altitude) may exceed the simple additive consequence of each stressor imposed separately.

In the four chapters that follow, we explore the specific problems encountered at altitude, during exercise in hot and cold environments, and from prolonged exposure to microgravity. We also discuss the immediate physiologic adjustments and long-term adaptations as the body strives to maintain internal consistency despite an environmental challenge. The chapter on sport diving considers the unique problems associated with this increasingly popular form of sport and recreation.

# Interview With Dr. Barbara L. Drinkwater 



Education: BS (Douglass College, Rutgers University, New Brunswick, NJ); MEd (University of North Carolina, Greensboro, NC); PhD (Purdue University, West Lafayette, IN)

Current Affiliation: Retired May 1, 2000. Previously, Research Physiologist, Department of Medicine, Pacific Medical Center, Seattle, WA

Honors and Awards: See Appendix E, available online at http://thepoint.lww.com/mkk7e.

Research Focus: The response of women to exercise as mediated by environmental factors and aging. Special areas of interest have been the female athlete, her physical performance under environmental stressors such as heat and altitude, the effect of exercise-associated amenorrhea on bone health, and the role of exercise, calcium, and exercise in preventing osteoporosis.

Memorable Publication: Drinkwater BL. Bone mineral content of amenorrheic and eumenorrheic athletes. N Engl J Med 1984;311:277.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

In recognition of her distinguished scientific contributions as one of the foremost investigators of exercise and physiological issues pertaining to women, particularly with respect to the study of bone mineral content relative to menstrual function, pregnancy, physical activity, and calcium intake, and for her distinguished international leadership and professional contributions to exercise science and sports medicine.

Dr. Drinkwater began her well-known scientific work with a series of landmark studies, first on the aerobic capacity, training, and detraining characteristics of young women track athletes and then on the influence of air pollutants and thermal stress on the working capacity of humans. She has demonstrated a continuing interest in gender differences and aging on aerobic capacity, body composition, and thermal responses. Indeed, an anthology of the woman in sport would be incomplete without reference to her data-based studies and scholarly reviews of the physiological responses of women to exercise, particularly in reference to age, fitness, and heat stress.

Dr. Drinkwater has earned the respect of the international scientific community for her primary scientific contri-
bution, the interactions of menstrual function, estrogen, and exercise on bone mineral content. Her work has clarified the importance of adequate menstrual function on bone mineral density in young athletic women, the long term consequences of bone mineral losses following athletic amenorrhea, and the role of estrogen relative to physical activity for the prevention of bone mineral loss in menopause.

Second only to her scientific contributions, Dr. Drinkwater has demonstrated an exemplary commitment to professional leadership and development of beginning scholars and clinicians. She has served or chaired many of the vital committees of ACSM and was elected as Trustee, Vice President, and President. She remains a strong voice that brings an important message to the American College of Sports Medicine Foundation, where she serves on the Board of Directors. Dr. Drinkwater is an icon who represents unfailing support, nurturing, and challenging of beginning investigators and clinicians in exercise science and sports medicine.

Dr. Drinkwaters highly regarded contributions to the international scientific community, her professional leadership, and her commitment to the development of beginning scientists and clinicians form the basis of recognizing her with ACSMs highest distinction.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

> In 1965, I was teaching a methods course in track and field to physical education majors. One of them
asked me why women werent allowed to compete in the marathon and were restricted to running twice around the track. I decide to investigate the scientific rationale and found instead that myths and prejudice, not science, limited womens participation in sports. Several years later I had the opportunity to join the

Institute of Environmental Stress at the University of California, Santa Barbara. With the encouragement of the director, Steven M. Horvath, PhD, I began the series of studies that would demonstrate clearly that women of all ages could attain high levels of aerobic power and that cardiovascular fitness, not gender, accounted for the previous notion that women could not tolerate exercise in the heat.

## What influence did your undergraduate education have on your final career choice?

> My undergraduate degree was in physical education. I had an excellent program that emphasized science as well as sports skills and teaching methods. However, none of the female faculty members had a doctorate degree, and graduate education was never mentioned. The assumption in those days was that we majors would go directly into teaching. However, Im sure it was my love for sport and the excellent courses I had in physiology and kinesiology that later led me into the exercise science field.

## Who were the most influential people in your career, and why?

> Oddly enough, the most influential individual in my career was Ben Winer, PhD, who taught the statistics courses I took in the doctoral program at Purdue. He was an outstanding teacher, and the skills and knowledge of experimental design that I gained in his classes led to my unofficial role of statistician and advisor on study designs at the Institute of Environmental Stress. Obviously, I owe a great deal to Steve Horvath as well, who gave me the opportunity to work at the Institute. A career encompasses not only your research and teaching, but your professional contributions as well. Individuals such as Charles Tipton, John Sutton, Carl Gilsolfi, Peter Raven, Chris Wells, Toby Tate, and a multitude of others all enhanced that aspect of my career. Their support and encouragement had a tremendous impact on my career and me.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> The most enjoyable aspect of my scientific career has been the opportunity to encourage and open some doors for younger women on the road toward their own careers. That, plus the opportunity to speak to a wide variety of audiences about topics of importance to their health and well being, have given me a great deal of satisfaction. The least enjoyable aspect has been the constant need to search for funds to keep the research program going.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

> I would like to think that my most meaningful contribution to the field of exercise science has been to stimulate interest of other investigators in evaluating womens response to exercise, environmental stress, and aging. In terms of a specific area of research, I would have to select the area of the Female Athlete Triad, which demonstrates that the amenorrhea experienced by many female athletes can lead to irreversible bone loss. Until our 1984 paper in the New England Journal of Medicine, amenorrhea was assumed to be a benignand welcomeeondition by the athletes. When additional studies confirmed our results, athletes and those responsible for their health began to take the Triad seriously.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

> My advice to an undergraduate student would be to select as many science courses as possible in areas related to exercise science and work hard to get good grades. Your selection to the better graduate programs will depend largely on your grade point average and the recommendations of your professors. If you are not a serious student, you are not going to

have a successful career in research. In selecting a doctoral program, investigate thoroughly before applying. Not only will you be spending 4 to 5 years of your life in that department, but you will be depending on the reputation of that program and the faculty to secure a postdoctoral position. Among the factors to consider are the publications of the faculty and graduate students, ongoing research in your area of interest, laboratory facilities and equipment, success of graduates in obtaining postdoctoral positions, and the requirements for the PhD . If possible, talk with some recent graduates of the program and get their honest appraisal of their experience.

## What interests have you pursued outside of your professional career?

$>$ Sports, aviation, and animals. Ive been active in a number of sports, but am now totally involved with golfplaying several times a week and even taking my clubs over to Australia to play when not at an Olympic venue. When I was in Santa Barbara, I found time to get a commercial pilots license, an instrument rating, and an instrument instructors rating. I spent many hours in the air on trips throughout California and the Southwest. When I moved to Vashon in 1982, I had two dogs and one cat. Within 6 months, a puppy found at the dump and another 6 cats that had come out of the woods joined the family. At that point, I decided the island needed a humane society so I started one. Sixteen years later, the program is going strong and now includes a low-cost spay neuter program, a lost-and-found hotline, an adoption service, education programs in the schools, and medical surgical help as well.

## Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 20 years?

> The exercise science field is so diverse that it may be impossible to make a general statement regarding future directions. I do believe there will be increasing interest in the interaction of exercise and health. As our population continues to age, the rising cost of medical care will force an emphasis on lifestyle and other preventive measures. The Surgeon Generals Healthy People 2000 Report has made physical activity and fitness the number one priority for health promotion and disease prevention. The responsibility for providing data-based evidence that physical activity does indeed prevent or ameliorate disease states, as well as defining the optimum exercise program for each segment of the population, will be the responsibility of the exercise scientist who is challenged by studying integrated physiological systems.

## You have the opportunity to give a last lecture. Describe its primary focus.

> I cant even conceive of accepting an invitation to give a last lecture! The actual final lecture I give will be one that I probably accepted to give six months earlier, and in the interim Ive decided Ive said enough, I have nothing new to say, and its time to leave the stage to younger professionals with new and exciting data and insights. I hope I have the good sense to recognize that time when it comes.


## CHAPTER 24

## Exercise at Medium and High Altitude

## CHAPTER OBJECTIVES

> Outline the effects of increasingly higher altitudes on (1) partial pressure of oxygen in ambient air, (2) oxygen saturation of hemoglobin in pulmonary capillaries, and (3) $\mathrm{VO}_{2 \text { max }}$
> Describe and quantify the oxygen transport cascade at sea level and 4300 m
> Discuss immediate and longer term physiologic adjustments to altitude exposure
> Give symptoms, possible causes, and treatment for acute mountain sickness, high-altitude pulmonary edema, and high-altitude cerebral edema
> Describe the lactate paradox and possible causes for its occurrence
> Summarize factors that affect the time course for altitude acclimatization
>Graph the relationship between the decrease in $\mathrm{VO}_{2 \text { max }}$ (\% sea-level value) with increasing altitude exposure
> Discuss alterations in circulatory function that offset the benefits of altitude acclimatization on oxygen transport capacity
> Discuss whether altitude training produces greater improvement than sea-level training on sea-level exercise performance
> Describe the training concept of living high, training low

More than 40 million people live, work, and recreate at terrestrial elevations between $3048 \mathrm{~m}(10,000 \mathrm{ft})$ and 5486 m $(18,000 \mathrm{ft})$ above sea level. In terms of the Earths topography, these elevations encompass the range generally considered high altitude. High-altitude natives inhabit permanent settlements up to 5486 m in the Andes and Himalayas. Prolonged exposure of an unacclimatized person to this altitude causes death from the ambient airs subnormal oxygen pressure (hypoxia), even if the person remains physically inactive. The physiologic challenge of even medium-altitude exposure becomes readily apparent during physical activity. In the United States, in excess of 1 million people a year ascend Pikes Peak, Colorado ( 4300 m ) by train, car, or railroad, and thousands of others do so by climbing, cycling, and running. Millions more throughout the world ascend to high altitudes for mountaineering, trekking, tourism, business, and scientific and military excursions. Many newcomers to altitude do not take sufficient time to acclimatize to the physiologic challenge of the reduced partial pressure of oxygen $\left(\mathrm{PO}_{2}\right)$ in ambient air.

## THE STRESS OF ALTITUDE

Altitudes physiologic challenge comes directly from decreased ambient $\mathrm{PO}_{2}$, not from reduced total barometric pressure per se or any change in the relative concentrations (percentages) of gases in inspired (ambient) air. Figure 24.1 illustrates the barometric pressure, pressures of the respired gases, and percentage saturation of hemoglobin at various terrestrial elevations. Figure 24.2 shows changes that occur in oxygen availability (reflected by $\mathrm{PO}_{2}$ ) in ambient air, alveolar air, and arterial and mixed-venous blood as one ascends from sea level to Pikes Peak. The oxygen transport cascade refers to the progressive change in the environments oxygen pressure and in various body areas.

Air density decreases progressively with ascent above sea level. For example, barometric pressure at sea level averages 760 mm Hg ; at 3048 m , the barometer drops to 510 mm Hg. At an elevation of 5486 m , the pressure of a column of air at the Earths surface equals about one-half of its sea-level pressure. Dry ambient air at sea level and altitude contains

a) Lightheadedness, headache b) Insomnia, nausea, vomiting, pulmonary discomfort
c) Dyspnea, anorexia, GI disturbances d) Lethargy, general weakness e) Impending collapse

Figure 24.1 Changes in environmental and physiologic variables with progressive elevations in altitude ( $\mathrm{P}_{\mathrm{a}} \mathrm{O}_{2}$, partial pressure of arterial oxygen; $\mathrm{P}_{\mathrm{a}} \mathrm{CO}_{2}$, partial pressure of arterial carbon dioxide; $\mathrm{P}_{\mathrm{i}} \mathrm{O}_{2}$, partial pressure of oxygen in inspired air; $\mathrm{S}_{\mathrm{a}} \mathrm{O}_{2}$, oxygen saturation of hemoglobin).


「 Sea level $\square 4300 \mathrm{~m}$
Figure 24.2 Oxygen transport cascade from sea level to $4300 \mathrm{~m}(14,108 \mathrm{ft})$.
$20.93 \%$ oxygen, while the $\mathrm{PO}_{2}$ (density of the oxygen molecules) of air decreases directly with the fall in barometric pressure upon ascending to higher elevations $\left(\mathrm{Po}_{2}=0.2093 \times\right.$ barometric pressure). Thus, ambient $\mathrm{PO}_{2}$ at sea level averages 150 mm Hg , but only 107 mm Hg at 3048 m . At the summit of Mt. Everest ( $8848 \mathrm{~m} ; 29,028 \mathrm{ft}$ ), ambient air pressure usually ranges between 251 and 253 mm Hg with a concomitant alveolar $\mathrm{PO}_{2}$ of about 25 mm Hg (ambient air $\mathrm{PO}_{2}$ between 42 and $43 \mathrm{~mm} \mathrm{Hg}) .{ }^{102}$ This equals only about $30 \%$ of the oxygen available in air at sea level. Arterial hypoxia that accompanies the reduction in $\mathrm{PO}_{2}$ precipitates both the immediate physiologic adjustments to altitude and the longer term process of acclimatization. Following the recommendation of the International Union of Physiological Sciences (www.iups.org/), acclimatization refers to adaptations produced by changes in the natural environment, whether through a change in season or place of residence. In contrast, acclimation concerns adaptations produced in a controlled laboratory environment (in specialized chambers) that simulate high altitude or microgravity, hypoxic environments, and extremes of thermal stress.

## Oxygen Loading at Altitude

The S-shaped nature of the oxyhemoglobin dissociation curve (see Chapter 13, Fig. 13.4) indicates that only a small change occurs in hemoglobins percentage saturation with oxygen until an altitude of about 3048 m . At 1981 m ( 6500 ft ), for example, alveolar $\mathrm{PO}_{2}$ decreases from its sea-level value of 100 mm Hg
to 78 mm Hg , yet hemoglobin remains $90 \%$ saturated with oxygen. This relatively small arterial desaturation exerts little effect on a person during rest or performance of mild exercise but severely curtails performance in vigorous aerobic activities. The poorer performances of men and women in middle-distance and distance running and swimming during the 1968 Olympics in Mexico City (altitude 2300 m ; 7546 ft ) resulted from the small reduction in oxygen transport at this altitude. No new world records were established in events lasting longer than 2.5 minutes. Altitude does not impair the short-term anaerobic energy system at moderate altitude (e.g., glycogen storage, pathways of glycolysis and corresponding phosphorylase and phosphofructokinase enzyme activity) or success in sprint power activities such as sprint running, speed skating, track cycling, jumping, and discus. ${ }^{28,32}$ Performance in single bouts of such activities often improves because of lower air density (reducing air resistance or drag force) at altitude than at sea level. The lessened air resistance from a $24 \%$ reduction in air density at 2300 m should also improve performance in the shot put, hammer throw, and javelin. Impaired performance has been reported for repeated intervals of short-term power output (15-s training intervals) in elite athletes. ${ }^{13}$

In the transition from moderate altitude to higher elevations, values for alveolar (arterial) $\mathrm{PO}_{2}$ position on the steep part of the oxyhemoglobin dissociation curve. This dramatically reduces hemoglobin oxygenation and oxygen transport capacity and negatively affects even mild-intensity aerobic activities. At high elevations in the Andes and Himalayas, oxygen loading of hemoglobin decreases dramatically, and physical activity becomes at best difficult to sustain. Any small change in inspired $\mathrm{PO}_{2}$ (i.e., barometric pressure) greatly affects aerobic capacity at the summit of Mt. Everest. For well-acclimatized mountain climbers, breathing ambient air with a $\mathrm{PO}_{2}$ of 48.5 mm Hg produces a $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ of 1450 mL $\cdot \mathrm{min}^{-1}$. This declines to $1070 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ with only a $6-\mathrm{mm} \mathrm{Hg}$ decrease in inspired $\mathrm{PO}_{2}$ a-decrease of $63 \mathrm{~mL} \cdot \min ^{-1}$ in $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ for each 1-mm Hg drop in inspired $\mathrm{PO}_{2} .{ }^{101,102}$

Sudden exposure to an altitude of 4300 m reduces aerobic capacity by $32 \%$ compared with sea-level values. ${ }^{111}$ Permanent living becomes nearly impossible at altitudes above $5182 \mathrm{~m}(17,000 \mathrm{ft})$ and mountain climbing at that altitude frequently requires the aid of hyperoxic breathing mixtures. At $5486 \mathrm{~m}(18,000 \mathrm{ft})$, arterial $\mathrm{Po}_{2}$ averages 38 mm Hg , and hemoglobin maintains only $73 \%$ oxygen saturation. Amazingly, reports describe acclimatized mountaineers who lived for weeks at $6706 \mathrm{~m}(22,000 \mathrm{ft})$ breathing only ambient air. ${ }^{43}$ In fact, members of two Swiss expeditions to Mt. Everest remained at the summit for 2 hours without breathing equipment $!^{68}$ This represents an impressive feat considering that arterial $\mathrm{PO}_{2}$ averaged only 25 mm Hg with a corresponding arterial blood oxygen saturation of $58 \%$. An unacclimatized person becomes unconscious within 30 seconds under these conditions. For acclimatized men at simulated extreme altitudes that approach the summit of Mt. Everest, $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ decreases by $70 \%$ from 4.13 to $1.17 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, or from 49.1 to $15.3 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1} .{ }^{34}$ These low values reflect the sea-level aerobic capacity of a sedentary 80 -year-old man. In

## FOCUS ON RESEARCH

## High Altitude: A Hostile Environment

Pugh LGCE, et al. Muscular exercise at great altitudes. J Appl Physiol 1964;19:431.
> Since the first ascent of Mt. Everest ( $8848 \mathrm{~m} ; 29,028 \mathrm{ft}$ ) in 1953 by Sir Edmund Hillary and Tenzig Norgay, scientists have studied relationships among terrestrial elevation, partial pressure of oxygen in ambient air, arterial hemoglobin oxygen loading, and cardiovascular function to explain reduced exercise capacity at altitude. Early experiments at high altitude posed enormous scientific challenges owing to equipment limitations and lack of trained personnel with mountaineering experience. The experiments, carried out by the Himalayan Scientific and Mountaineering Expedition of 19601961 (sponsored by the publishers of World Book Encyclopedia, Chicago, and Medical Research Council, London, England), represent classic experiments in environmental physiology. Discoveries from this legendary scientific expedition provided the underpinnings to current understanding about physical work at high altitude. The research by L. G. C. E. Pugh and coworkers was part of the first series of studies to demonstrate that lung diffusion capacity, cardiac output, and the oxygen cost of extreme pulmonary ventilation limit exercise capacity at altitudes above $5800 \mathrm{~m}(19,000 \mathrm{ft})$.

The researchers used bicycle ergometer exercise to assess physical working capacity at sea level and at altitudes ranging from 4650 m to 7440 m (barometric pressure of 440 to 300 mm Hg ). They established a base station at 4650 m but used a prefabricated laboratory hut at 5800 m (barometric pressure of 380 mm Hg ) to conduct most of the research.

Subjects included eight men: six experienced mountaineers and one sportsman,all acclimatized to high altitudeand one high-altitude Sherpa guide. The scientists with the Himalayan Scientific Expedition were five of the seven lowland subjects. The Sherpa guide carried the bicycle ergometer ( 20 kg ) to the laboratory hut. Subjects pedaled at 50 RPM, with expired air collected by the Douglas bag method. A dry-gas meter measured expired air volumes with respiratory gas concentrations analyzed with a Lloyd Haldane chemical analyzer. The exercise protocol (preceded by a $10-\mathrm{min}$ warm-up) included 6 minutes of exercise ( 12 min at sea level) starting at $300 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ with increments of $300 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$. The test terminated when the subject would not exercise for at least 2 minutes at a given intensity. Oxygen consumption, pulmonary ventilation, heart rate, respiratory exchange ratio, and venous blood samples (not secured from all subjects) were obtained during the last 2 minutes at each exercise level.

Figure 1 presents the researchers original plot of $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ in relation to terrestrial elevation. Clearly, $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ decreased from sea level upward and declined steeply above 6000 m , to reach an average of $1.42 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at 7440 m .

Figure 2 shows pulmonary ventilation (STPD and BTPS) and heart rate in response to $\dot{\mathrm{V}} \mathrm{O}_{2}$ during exercise at different altitudes. The curves for pulmonary ventilation shift to the left and increase in slope during exercise at higher elevations, with submaximal effort requiring the greatest ventilation at the highest altitude. This altitude-related hyperventilation reflects the experience of mountain climbers at great altitude; any slight increase in mountain slope or snow conditions brings them to a halt with breathlessness. Only the highest altitude produced apparent impairment of maximum exercise ventilation. Heart rates remained elevated during submaximal exercise at altitude.


[^45]Figure 1 Oxygen consumption during submaximal (purple symbols; men climbing at their typical pace) and maximal (yellow and orange symbols) exercise in relation to ambient barometric pressure and terrestrial elevation. S.L., sea level

## FOCUS ON RESEARCH

## Continued

Figure 3 shows a tendency for a higher respiratory exchange ratio ( R ) at all exercise levels at 5800 m than at sea level. At $\dot{\mathrm{V}}{ }_{2}$ s above $2.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, R increased nearly vertically, a response consistent with the extreme hyper-

S.L. $\square 4600 \mathrm{~m} \square 5800 \mathrm{~m} \square 6400 \mathrm{~m} \square 7400 \mathrm{~m}$

Figure 2 Pulmonary minute ventilation (BTPS, STPD) and heart rate related to oxygen consumption at sea level and altitudes to $7400 \mathrm{~m}(24,440$ ft ). S.L., sea level.
ventilation at high altitude. Altitude exposure increased exercise blood lactate (not shown), which also contributed to hyperventilation. Finally, comparisons of data for the Sherpa guide with those from other subjects showed his superior work capacity, attributable to economy of ventilation with preservation of a normal blood pH and maintenance of a relatively higher arterial $\mathrm{Po}_{2}$. The guide also maintained a high pulmonary diffusing capacity for oxygen and high cardiac output relative to work intensity (measured in a separate experiment).

These pioneering studies demonstrated physiologic links to exercise limitations at high altitude and formed the foundation for expanding knowledge of human physical working capacity at extreme terrestrial elevations.


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\sea level \square 5800 m
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Figure 3 Respiratory exchange ratio during graded exercise at sea level and 5800 m (19,000 ft).
addition to impairment in oxygen transport capacity, highaltitude exposure impairs the homeostatic regulation of immune balance; this potentially could favor long-term immunological alterations and increase the risk of infections. ${ }^{26}$ Despite the considerable physiologic strain imposed by high altitude, mountaineer Tom Whittaker, age 50, became the first
amputee to reach Mt. Everests summit on his third attempt on May 27, 1998. Although remarkable performances at high altitude reflect exceptions and not the rule, they demonstrate the enormous adaptive capability of humans to survive and even work without external support at extreme terrestrial elevations (see Focus on Research.).

## INTEGRATIVE QUESTION

Respond to this question: If altitude has such negative effects on the body, why are certain track and field records broken during competition at higher elevations?

## ACCLIMATIZATION

During the many years that mountaineers attempted to climb the worlds highest peaks, they knew it required weeks to adjust to successively higher elevations. The term altitude acclimatization broadly describes adaptive responses in physiology and metabolism that improve tolerance to altitude hypoxia. Each adjustment to a higher elevation proceeds progressively, and full acclimatization requires an appropriate time period. Successful adjustment to medium altitude affords only partial adjustment to a higher elevation. Residents of moderate altitudes, however, show less decrement in physiologic capacity and exercise performance than lowlanders when both groups travel to a higher altitude. ${ }^{59}$

Table 24.1 reveals that compensatory responses to altitude occur almost immediately, while other adaptations take weeks or even months. The rapidity of the bodys response remains largely altitude dependent, yet considerable individual variability exists for both the rate and success of acclimatization. A person can retain many of the beneficial submaximal exercise responses with 16 days of acclimatization at 4300 m despite intermittent 8 -day sojourns to sea level. ${ }^{7}$ This suggests that certain aspects of acclimatization regress more slowly than their acquisition.

## Immediate Responses to Altitude Exposure

Arrival at elevations of 2300 m and higher initiates rapid physiologic adjustments to compensate for thinner air and accompanying reduction in alveolar $\mathrm{PO}_{2}$. The two more important responses include:

1. Increase in the respiratory drive to produce hyperventilation
2. Increase in blood flow during rest and submaximal exercise

## Hyperventilation

Hyperventilation from reduced arterial $\mathrm{PO}_{2}$ reflects the most important and clear-cut immediate response of the native lowlander to altitude exposure. Once initiated, this hypoxic drive increases during the first few weeks and can remain elevated for a year or longer during prolonged altitude residence. ${ }^{51}$

The aortic arch and branching of the carotid arteries in the neck contain peripheral chemoreceptors sensitive to reduced oxygen pressure. Reduced arterial $\mathrm{PO}_{2}$ that occurs at altitudes above 2000 m progressively stimulates these receptors. This modifies inspiratory activity to increase alveolar ventilation causing alveolar $\mathrm{PO}_{2}$ to rise toward the level in ambient air. Even small increases in alveolar $\mathrm{PO}_{2}$ with hyperventilation facilitate oxygen loading in the lungs and provide the rapid first line of defense against reduced ambient $\mathrm{PO}_{2}$. For females, variations in menstrual cycle phase do not affect ventilatory responses and exercise performance decrements during short-term altitude exposure compared with at sea level. ${ }^{8}$ Mountaineers who respond with a strong, hypoxic ventilatory drive to sudden but extreme altitude exposure perform exercise

TABLE 24.1 Immediate and Longer-Term Adjustments to Altitude Hypoxia

| System | Immediate | Longer Term |
| :---: | :---: | :---: |
| Pulmonary acid base | Hyperventilation | Hyperventilation |
|  | Bodily fluids become more alkaline due to reduction in carbon dioxide $\left(\mathrm{H}_{2} \mathrm{CO}_{3}\right)$ with hyperventilation | Excretion of base $\left(\mathrm{HCO}_{3}{ }^{-}\right)$via the kidneys and concomitant reduction in alkaline reserve |
| Cardiovascular | Increase in submaximal heart rate | Submaximal heart rate remains elevated |
|  | Increase in submaximal cardiac output | Submaximal cardiac output falls to or below sea-level values |
|  | Stroke volume remains the same or decreases slightly | Stroke volume decreases |
|  | Maximum cardiac output remains the same or decreases slightly | Maximum cardiac output decreases |
| Hematologic |  | Decreased plasma volume |
|  |  | Increased hematocrit |
|  |  | Increased hemoglobin concentration |
|  |  | Increased total number of red blood cells |
| Local |  | Possible increased capillarization of skeletal muscle Increased red blood cell 2,3-DPG |
|  |  | Increased mitochondrial density |
|  |  | Increased aerobic enzymes in muscle |
|  |  | Loss of body weight and lean body mass |

tasks more effectively (and reach higher altitude) than climbers with a depressed hypoxic ventilatory response. ${ }^{89}$

## INTEGRATIVE QUESTION

From a physiologic perspective, what represents a safe altitude for flight in an airplane with a nonpressurized cabin?

## Increased Cardiovascular Response

Resting systemic blood pressure increases in the early stages of altitude adaptation. In addition, submaximal exercise heart rate and cardiac output can rise to $50 \%$ above sea-level values, while the hearts stroke volume remains unchanged. The increased submaximal exercise blood flow at altitude largely compensates for arterial desaturation. For example, a $10 \%$ increase in cardiac output during rest or moderate exercise offsets a $10 \%$ reduction in arterial oxygen saturation in terms of total oxygen transported through the body. Figure 24.3 shows that the oxygen cost of submaximal exercise at 100 watts on a bicycle ergometer at sea level and high altitude remains unchanged at about $2.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, but the relative strenuousness of effort increases dramatically at altitude. In this example, submaximal exercise representing $50 \%$ of sea-level $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ equals $70 \%$ of $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ at 4300 m .

## Catecholamine Response

Sympathoadrenal activity progressively increases over time during rest and exercise with altitude exposure. ${ }^{60,63,64}$


[^46]Figure 24.3 Comparison of oxygen cost and relative strenuousness of submaximal exercise at sea level and high altitude.


## $\square$ Norepinephrine $\square$ Epinephrine

Figure 24.4 Generalized response for a short stay at a high altitude ( $4300 \mathrm{~m} ; 14,108 \mathrm{ft}$ ) on urinary norepinephrine and epinephrine in eight male sea-level residents. (Modified from Surks MJ, et al. Changes in plasma thyroxine concentration and metabolism, catecholamine excretion and basal oxygen uptake during acute exposure to high altitude [14,100 ft]. J Clin Invest 1966;45:1442.)

Increased blood pressure and heart rate at altitude coincide with the steady rise in plasma levels and excretion rates of epinephrine. Norepinephrine levels peak in women and men after 6 days of high-altitude exposure and then remain stable. ${ }^{62,109}$ Increased sympathoadrenal activity also contributes to regulation of blood pressure, vascular resistance, and substrate mixture (enhanced carbohydrate use) ${ }^{12}$ during short- and long-term hypobaric exposures. Figure 24.4 shows 24-hour urinary excretion of norepinephrine and epinephrine during control (sea-level) measurements and following 7-days exposure to $4300-\mathrm{m}$ altitude. Epinephrine changed little but norepinephrine excretion increased by the fourth day. Urinary norepinephrine levels remain elevated for approximately 1 week following return to sea level.

Table 24.2 shows metabolic and cardiorespiratory responses to moderate and maximal cycling exercise in young men at sea level and during brief exposure to simulated altitude of 4000 m . Despite the increase in pulmonary ventilation during submaximal exercise at altitude, arterial oxygen saturation decreased from $96 \%$ at sea level to $70 \%$ during all exercise intensities. In submaximal exercise, increased cardiac output entirely compensated for the bloods reduced oxygen content.
Greater blood flow occurred from a higher heart rate (stroke volume remained unchanged). With an increase in cardiac output, submaximal exercise oxygen consumption remained essentially identical at sea level and altitude. The greatest altitude effect on aerobic metabolism emerged during maximal exercise, when $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ decreased to $72 \%$ of the sea-level value.

TABLE 24.2 Cardiorespiratory and Metabolic Response During Submaximal and Maximal Exercise at Sea Level and Simulated Altitude of 4000 m (13,115 ft)

| Exercise Level | $\mathrm{VO}_{2}\left(\mathrm{~L} \cdot \mathrm{~min}^{-1}\right)$ |  |  |  | Ve (L $\cdot$ min $^{\mathbf{- 1}} \mathrm{BTPS}$ ) |  |  | Arterial Saturation (\%) |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Altitude, $m$ |  |  | 4000 |  | 0 |  |  | 0 |  | 4000 |
| $600 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ |  |  | 1.56 |  | 39.6 |  |  | 96 |  | 71 |
| $900 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ |  |  | 2.23 |  | 59.0 |  |  | 95 |  | 69 |
| Maximum |  |  | 2.50 |  | 123.5 |  |  | 94 |  | 70 |
| Exercise Level | Q (L $\cdot \mathbf{m i n}^{-1}$ ) |  |  | HR (B $\cdot \mathbf{m i n}^{-1}$ ) |  | SV (mL) |  |  | $\begin{gathered} \mathrm{a}-\mathrm{vO}_{2} \mathrm{Diff} \\ \left(\mathrm{~mL} \mathrm{O}_{2} \cdot \mathrm{dL}^{-1}\right) \end{gathered}$ |  |
| Altitude, $m$ |  | 4000 |  | 0 | 4000 | 0 | 4000 |  | 0 | 4000 |
| $600 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ | 13.0 | 16.7 |  | 115 | 148 | 122 | 113 |  | 10.8 | 9.4 |
| $900 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$ | 19.2 | 21.6 |  | 154 | 176 | 125 | 123 |  | 11.4 | 10.4 |
| Maximum | 23.7 | 23.2 |  | 186 | 184 | 127 | 126 |  | 14.6 | 10.8 |

From Sternberg J, et al. Hemodynamic response to work at simulated altitude 4000 m . J Appl Physiol 1966;21:1589.
$\dot{\text { Q }}$, cardiac output; HR, heart rate; SV, stroke volume; $\mathrm{A}-\mathrm{vO} \mathrm{O}_{2}$ Diff, arteriovenous oxygen difference.

With maximal exercise during short-term altitude exposure ( $\leq 7 \mathrm{~d}$ ), ventilatory and circulatory adjustments fail to compensate for the depressed arterial oxygen content. Figure 24.5 illustrates the relationship between pulmonary
ventilation and oxygen consumption up to maximum during bicycle exercise at sea level and simulated altitudes from 1000 to 4000 m. Each 1000-m increase in altitude proportionately increased exercise ventilation volume. When exercise

Figure 24.5 Effects of a progressive increase in simulated altitude from sea level (tracheal $\mathrm{PO}_{2}=149 \mathrm{~mm} \mathrm{Hg}$ ) to 4000 m (tracheal $\mathrm{PO}_{2}=87 \mathrm{~mm}$ Hg ) on the relationship between pulmonary ventilation and oxygen consumption during cycle ergometry. (Modified from strand PO. The respiratory activity in man exposed to prolonged hypoxia. Acta Physiol Scand 1954;30:343.)




Figure 24.6 Arterial desaturation as a function of increasing altitude and corresponding impairment ( $\downarrow$ ) in diverse sensory and mental functions. (Modified from Fulco CS, Cymerman A. Human performance and acute hypoxia. In: Pandolf KB, et al., eds. Human performance physiology and environmental medicine at terrestrial extremes. Carmel, IN: Cooper Publishing Group, 1988.)
oxygen consumption exceeded $2.0 \mathrm{~L} \cdot \min ^{-1}$, pulmonary ventilation increased disproportionately at progressively higher elevations.

## Fluid Loss

Ambient air in mountainous regions remains cool and dry, allowing considerable body water to evaporate as inspired air becomes warmed and moistened in the respiratory passages. This fluid loss often leads to moderate dehydration and accompanying dryness of the lips, mouth, and throat. Fluid loss becomes pronounced for physically active people because of their large daily total sweat loss and exercise pulmonary ventilation volumes (and hence water loss). These individuals should have access to water at all times.

Sensory Functions. Figure 24.6 shows deterioration in a variety of sensory and mental functions with decreases in arterial oxygen saturation at altitude. Neurologic alterations range from a 5\% decrease in sensitivity to light at 1524 m to a further $25 \%$ decrease in light sensitivity and $30 \%$ decrease in visual acuity when elevation doubles to 3048 m ; at 6096 m , a $25 \%$ deterioration occurs in coding task performance and simple reaction time.

Myocardial Function. Individuals with normal electrocardiograms at sea level including patients with stable chronic heart failure generally show no adverse changes to indicate myocardial ischemia (e.g., arrythmias, angina, ECG abnormalities) at simulated high altitudes, even during maximal exercise. ${ }^{2,78,92}$ On Mt. Everest, the hearts contractile function remains stable despite considerable arterial hypoxia. ${ }^{72}$ Little information exists about the effects of altitude on individuals with coronary artery disease, so such patients should avoid high-altitude exposure altogether.

## Longer-Term Adjustments to Altitude

Hyperventilation and increased submaximal exercise cardiac output provide a rapid and relatively effective counter to the short-term challenge of altitude exposure. Concurrently, other slower acting adjustments occur during a prolonged altitude stay. Three important longer term adjustments improve tolerance to the relative hypoxia of medium and high altitudes:

1. Regulation of acid base balance of body fluids altered by hyperventilation
2. Synthesis of hemoglobin and red blood cells and accompanying changes in local circulation and aerobic cellular function
3. Elevated sympathetic neurohumoral activity reflected by increased norepinephrine that peaks within 1 week

## Acid Base Readjustment

The beneficial effect of hyperventilation at altitude to increase alveolar $\mathrm{PO}_{2}$ produces opposite effects on the bodys carbon dioxide level. Ambient air contains essentially no carbon dioxide, so the increased breathing volumes at altitude dilute normal alveolar carbon dioxide concentrations. This creates a larger than normal gradient for diffusion (wash out) of carbon dioxide from the blood to the lungs, causing a considerable decrease in arterial $\mathrm{PCO}_{2}$. For example, exposure to 3048 m decreases alveolar $\mathrm{PCO}_{2}$ to about 24 mm Hg , in contrast to its usual 40 mm Hg sea-level value. Alveolar $\mathrm{PCO}_{2}$ decreases to 10 mm Hg during a prolonged high-altitude stay.

Carbon dioxide loss from body fluids in a hypoxic environment creates a physiologic disequilibrium. In Chapter 13, we point out that carbonic acid $\left(\mathrm{H}_{2} \mathrm{CO}_{3}\right)$ normally carries the largest quantity of carbon dioxide in the body. This relatively weak acid readily dissociates into $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}{ }^{-}$that move

## IN A PRACTICAL SENSE

## Identification and Treatment of Altitude-Related Medical Problems

Natives who live and work at high altitudes as well as newcomers risk a variety of medical problems associated with reduced arterial $\mathrm{PO}_{2}$. These problems usually remain mild and dissipate within several days, depending on the rapidity of the ascent and degree of exposure. Other medical complications compromise overall health and safety. Three medical conditions threaten those who ascend to high altitude:

1. Acute mountain sickness (AMS), the most common malady
2. High-altitude pulmonary edema (HAPE), which reverses if the person returns quickly to a lower altitude
3. High-altitude cerebral edema (HACE), a potentially fatal condition if not diagnosed and treated immediately

## ACUTE MOUNTAIN SICKNESS

Most people experience the discomfort of AMS during the first few days at altitudes of 2500 m and above. Factors that predispose to AMS include individual susceptibility, rapid rate of ascent, and lack of prealtitude exposure. ${ }^{88}$ Nonspecific symptoms include headache, nausea, dizziness, fatigue, insomnia, and peripheral edema. This relatively benign condition, which becomes exacerbated by exercise in the first few hours of exposure, ${ }^{76}$ possibly results from acute reduction in cerebral oxygen saturation. ${ }^{81}$ It occurs most frequently in those who ascend rapidly to a high altitude without benefiting from gradual and progressive acclimatization to lower altitudes.

## TABLE 1 Altitude-Related Medical Conditions and Symptoms

| Condition | Symptoms |
| :---: | :---: |
| Acute mountain sickness (AMS) | Severe headache, fatigue, irritability, nausea, vomiting, loss of appetite, indigestion, flatulence, generalized weakness, constipation, decreased urine output with normal hydration, sleep disturbance |
| High-altitude pulmonary edema (HAPE) | Debilitating headache and severe fatigue; excessively rapid breathing and heart rate; rales; ${ }^{a}$ cough producing pink frothy sputum; bluish skin color (from low blood $\mathrm{PO}_{2}$ ); disruption of vision, bladder, and bowel functions; poor reflexes; loss of coordination of trunk muscles; paralysis on one side of the body |
| High-altitude cerebral edema (HACE) | Staggered gait, dyspnea upon exertion, severe weakness/fatigue, persistent cough with pulmonary infection, pain or pressure in substernal area, confusion, impaired mental processing, drowsiness, ashen skin color, loss of consciousness |

${ }^{a}$ Excess mucus in the lungs, diagnosed as clicking sounds heard through a stethoscope.

Symptoms (TABLE 1) usually begin within 4 to 12 hours and dissipate within the first week. ${ }^{36,40,53}$ Headache, the most frequent symptom, probably results from increased cerebral hemodynamics from short-term hyperventilation. ${ }^{44}$ Most symptoms become prevalent above 3000 m . Rapid ascent to 4200 m almost guarantees some form of AMS.

Decreased thirst sensation and severe appetite suppression occur during the early stages, often resulting in a $40 \%$ reduction in energy intake and consequent body mass loss. Diets low in salt and high in carbohydrates are well tolerated during the early stay at high altitude. A potential benefit of maintaining carbohydrate reserves through dietary intake lies in the liberation of more energy per unit oxygen with carbohydrate oxidation than with fat ( 5.0 kCal vs. 4.7 kCal per L of oxygen). Also, high blood lipid levels following a high-fat meal may reduce arterial oxygen saturation. Benefits of maintaining a high-carbohydrate diet include:

## 1. Enhanced altitude tolerance

2. Reduced severity of mountain sickness
3. Lessened physical performance decrements during the early
stages of altitude exposure
Even moderate exercise becomes intolerable for persons who suffer the effects of AMS. Symptoms subside and often disappear as acclimatization progresses. Acclimatizing slowly to moderate altitudes below 3048 m , followed by a gradual progression to higher elevations (termed staged ascent) usually prevents AMS. Climbers should spend several nights at 2500 to 3000 m before going higher, and an extra night should be added for each additional 600 to 900 m climbed. Abrupt increases of more than 600 m in the altitude for sleeping should be avoided at 2500 m or above ( climb high-sleep low ). If acclimatization proves ineffective, a $300-\mathrm{m}$ descent usually alleviates symptoms; supplemental oxygen and the drug acetazolamide (Diamox) facilitate recovery.

## HIGH-ALTITUDE PULMONARY EDEMA

For unknown reasons, about $2 \%$ of sojourners to altitudes above 3000 m experience HAPE. Symptoms (Table 1) usually manifest within 12 to 96 hours following rapid ascent. Major predisposing factors for HAPE include level of altitude, rate of ascent, and individual susceptibility. ${ }^{5,6}$ Changes in pulmonary function test variables after rapid ascent to high altitude fail to predict susceptibility to HAPE. ${ }^{90}$

Fluid accumulates in the brain and lungs in this life-threatening condition. ${ }^{3,75}$ At first, symptoms do not seem severe, but the syndrome progresses to pulmonary edema and fluid retention by the kidneys. Chest examination reveals wheezy, raspy sounds known as rales. Even in well-acclimatized individuals, HAPE can develop with severe exertion at elevations above $5486 \mathrm{~m}(18,000 \mathrm{ft})$, probably the result of increased pulmonary artery pressure with damage to the blood gas barrier. ${ }^{103}$

TABLE 2 lists appropriate methods to avoid and treat HAPE. Treatment to prevent severe disability or even death requires immediate descent to lower altitude on a stretcher (or being flown to safety) because physical activity from walking potentiates complications. With proper treatment, symptoms subside within hours, with complete clinical recovery within days. HAPE poses no problem for healthy individuals who journey to and recreate without acclimatization at altitudes below 1676 m .

## IN A PRACTICAL SENSE

## HIGH-ALTITUDE CEREBRAL EDEMA

HACE is a potentially fatal neurologic syndrome that develops within hours or days in individuals with AMS. HACE occurs in about

## TABLE 2 Prevention and Treatment of High-Altitude Pulmonary EDEMA

## Prevention

1. Slow ascent for susceptible individuals (average increase in sleeping altitude of $300350 \mathrm{~m} \cdot \mathrm{~d}^{-1}$ above 2500 m )
2. No ascent to higher altitude with symptoms of AMS
3. Descent when AMS symptoms do not improve after a day of rest
4. Under circumstances of high risk: Avoid vigorous exercise when not acclimatized
5. Nifedipine: 20 mg slow-release formulation every 6 hours (or 3060 mg sustained-release formulation once daily) for susceptible individuals when slow ascent is impossible

Treatment

1. Descent by at least 1000 m (primary choice in mountaineering)
2. Supplemental oxygen: $24 \mathrm{~L} \cdot \min ^{-1}$ (primary choice in areas with medical facilities)
3. When 1 and/or 2 are not possible:

Administer 20 mg nifedipine slow-release formulation every 6 hours
Use a portable hyperbaric chamber (see Fig. 26.9)
Descend to low altitude immediately

Continued


#### Abstract

$1 \%$ of persons exposed to altitudes above 2700 m ; it involves increased intracranial pressure that causes coma and death if left untreated. The early symptoms (Table 1), similar to those of AMS and HAPE, progressively worsen as the altitude stay progresses. Cerebral edema probably results from cerebral vasodilation and elevations in capillary hydrostatic pressure that moves fluid and protein from the vascular compartment across the blood brain barrier. ${ }^{37}$ An enlarged cerebral fluid volume eventually distorts brain structures, particularly the white matter, which exacerbates symptoms and increases sympathetic nervous system activity. Tissue hypoxia caused by high-altitude exposure also initiates a series of local events that stimulate angiogenesis (new capillary vessel growth) in brain tissue. ${ }^{110}$ Immediate descent to a lower elevation is mandatory because of the difficulty in adequately diagnosing HACE at high altitude.


## Other Conditions

Chronic mountain sickness (CMS), prevalent in a small number of altitude natives, can develop after months and years at altitude. CMS relates to excessive polycythemia, perhaps from a genetically linked variation in the EPO response to hypoxic stress. ${ }^{67}$ CMS symptoms include lethargy, weakness, sleep disturbance, bluish skin coloring (cyanosis), and change in mental status. High-altitude retinal hemorrhage (HARH) affects virtually all climbers at altitudes above $6700 \mathrm{~m}(21,982 \mathrm{ft})$. HARH usually progresses unnoticed, with no specific treatment or means for prevention. Hemorrhage in the macula of the eyethe oval yellow spot region in the back of the eyeball close to the optic discproduces irreversible visual defects. Retinal bleeding probably results from surges in blood pressure with exercise that cause blood vessels in the eye to dilate and rupture from increased cerebral blood flow.
to the lungs in the venous circulation. The $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}^{-}$recombine in the pulmonary capillaries to form $\mathrm{H}_{2} \mathrm{CO}_{3}$, which in turn forms carbon dioxide and water; carbon dioxide diffuses from the blood into the alveoli and leaves the body. A decrease in carbon dioxide level with hyperventilation increases the pH from loss of carbonic acid, making bodily fluids more alkaline.

Hyperventilation represents a sustained and beneficial response to altitude exposure, with physiologic adjustments proceeding during acclimatization to minimize the accompanying negative disruption in acid base balance. Control of ventilatory-induced alkalosis advances slowly as the kidneys excrete base $\left(\mathrm{HCO}_{3}{ }^{-}\right)$through the renal tubules. In turn, restoration of normal pH increases the respiratory centers responsiveness to enable even greater hyperventilation with altitude hypoxia.

## Reduced Buffering Capacity and the Lactate

Paradox. Establishing acid base equilibrium with acclimatization occurs at the expense of a loss of absolute alkaline reserve. The pathways of anaerobic metabolism remain unaffected at altitude, yet the bloods capacity for buffering acid gradually decreases; this lowers the critical level for acid metabolite accumulation.

On immediate ascent to high altitude, a given submaximal exercise load increases blood lactate concentration compared with sea-level values. Greater reliance on anaerobic glycolysis with altitude hypoxia presumably increases lactate accumulation. Surprisingly, after several weeks of hypoxic exposure the same submaximal and maximal exercise with large muscle groups produces lower lactate levels (Fig. 24.7). ${ }^{19,104}$ This occurs despite a lack of increase in either $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ or regional blood flow in active tissues. A general depression in maximum lactate concentrations becomes apparent in maximal exercise above 4000 m . A question arises concerning this apparent physiologic contradiction, termed the lactate paradox: How is lactate accumulation reduced without a corresponding increase in tissue oxygenation, when the hypoxemia associated with high altitude should promote lactate accumulation? ${ }^{99}$

Research to resolve the lactate paradox points to reduced output of epinephrine, the glucose-mobilizing hormone, during chronic high-altitude exposure. ${ }^{10}$ Reduced glucose mobilization from the liver reduces capacity for lactate formation. Diminished intracellular ADP during long-term altitude exposure may also inhibit activation of the glycolytic pathway. In addition, depressed lactate formation during maximal exercise may partly reflect an overall reduced central nervous

Figure 24.7 The lactate paradox: Less oxygen equals less (not more) lactate. Maximal blood lactate concentration ([Lab]max) as a function of altitude in both acclimatized lowlanders and high-altitude residents. The solid line of best fit includes all the points above an altitude of 1 km , except the four from Operation Everest II shown by - (From Ceretelli P, Samaja M. Acid base balance at exercise in normoxia and in chronic hypoxia. Revisiting the lactate paradox. Eur J Appl Physiol 2003;90:431; West JB. Point: The lactate paradox does/does not occur during exercise at high altitude J Appl Physiol 2007;102:2398.

system drive, which reduces capacity for all-out physical effort. ${ }^{61}$ Interestingly, lower blood lactate accumulation at high altitude does not relate to decreased buffering capacity with high-altitude acclimatization. ${ }^{48}$

## Hematologic Changes

An increase in the bloods oxygen-carrying capacity provides the most important longer-term adjustment to altitude exposure. Two factors account for this adaptation:

1. Initial decrease in plasma volume followed by
2. Increase in erythrocytes and hemoglobin synthesis

Initial Plasma Volume Decrease. During the first several days of altitude exposure, the bodys fluid shifts from the intravascular space to the interstitial and intracellular spaces. The decrease in plasma volume within several hours of altitude exposure increases red blood cell concentration. ${ }^{86}$ After a week at 2300 m , for example, plasma volume declines by about $8 \%$, whereas red blood cell concentration (hematocrit) increases $4 \%$ and hemoglobin $10 \%$. A 1-week stay at 4300 m decreases plasma volume 16 to $25 \%$ along with increases in hematocrit ( $6 \%$ ) and hemoglobin ( $20 \%$ ) concentration. ${ }^{38}$ The rapid plasma volume reduction (and accompanying hemoconcentration) increases the oxygen content of arterial blood above values observed on arrival at altitude. Increased urine
output (diuresis) accompanies the fluid shift from plasma during acclimatization; this maintains balance in the fluid compartments despite a lower total body water content.

Red Blood Cell Mass Increases. Reduced arterial $\mathrm{PO}_{2}$ at altitude stimulates an increase in total number of red blood cells, or polycythemia. The erythrocyte-stimulating hormone erythropoietin (EPO), synthesized and released primarily from the kidneys in response to localized arterial hypoxia, initiates red blood cell formation within 15 hours after altitude ascent. In the weeks that follow, erythrocyte production in the marrow of the long bones increases and remains elevated throughout the altitude stay. ${ }^{35}$ The blood of a typical miner in the Andes contains $38 \%$ more erythrocytes than a lowlander. In some apparently healthy high-altitude natives, red cell count may reach levels $50 \%$ above normal 8 million cells per $\mathrm{mm}{ }^{3}$ compared with 5.3 million for the native lowlander! ${ }^{58}$ Climbers acclimatized at 6500 m during a 1973 Mt. Everest expedition showed a $40 \%$ increase in hemoglobin concentration and a $66 \%$ increase in hematocrit. ${ }^{18}$ Debate concerns the precise benefits of increased hematopoiesis with altitude exposure and whether an optimum exists for hemoglobin concentration at high altitude. ${ }^{73,98}$ Clearly, extreme erythrocyte packing increases blood viscosity and restricts blood flow and oxygen diffusion to the tissues.

## INTEGRATIVE QUESTION

> For their assault on Mt. Everest, elite mountaineers spend 3 months at camps at 4877 m $(16,600 \mathrm{ft}), 5944 \mathrm{~m}(19,500 \mathrm{ft}), 6492 \mathrm{~m}(21,300 \mathrm{ft})$, $7315 \mathrm{~m}(24,000 \mathrm{ft})$, and $7925 \mathrm{~m}(26,000 \mathrm{ft})$ before the final ascent. Explain the physiologic rationale for this stage ascent approach to mountaineering.

In general, altitude-induced polycythemia translates directly to an increase in the bloods capacity to transport oxygen. For example, the oxygen-carrying capacity of blood in high-altitude residents of Peru averages $28 \%$ above sea-level values. The blood of well-acclimatized mountaineers carries 25 to 31 mL of oxygen per deciliter of blood compared with 20 mL for lowland residents. ${ }^{69}$ Despite reduced hemoglobin oxygen saturation at altitude, the quantity of oxygen in arterial blood may approach or even equal sea-level values.

Figure 24.8A illustrates the general trend for increased hemoglobin and hematocrit during acclimatization for eight young women who lived and worked for 10 weeks at the 4267-m summit of Pikes Peak. Because the researchers previous work showed fewer hematologic changes during acclimatization in women than in men (possibly from inadequate iron intake), each woman received iron supplementation prior to, during, and on return from altitude. Red blood cell concentration increased rapidly upon reaching Pikes Peak. A reduced plasma volume within the first 24 hours at altitude produced hemoconcentration. Hemoglobin concentration and hematocrit continued to rise in the month that followed and then stabilized for the remainder of the stay. Prealtitude values reestablished within 2 weeks after return to Missouri.

Figure 24.8B shows that iron supplementation increased prealtitude values for hematocrit and hemoglobin. One might anticipate this finding because young women frequently suffer from mild dietary iron insufficiency with depressed iron reserves (see Chapter 2). Comparison of the acclimatization curves for the iron-supplemented women and another group of women not given additional iron showed greater hematocrit increase in the supplemented group. Iron supplementation enhanced hematocrit increases at altitude to a level equivalent to men at the same location. Athletes with borderline iron stores may not respond to acclimatization as effectively as individuals who arrive at altitude with iron reserves adequate to sustain increased erythrocyte production.

## Cellular Adaptations

Debate concerns whether extreme terrestrial hypoxia stimulates vascular and cellular adaptations in humans that improve local oxygen extraction and maximize oxidative functions. ${ }^{33,41,65,94}$ Animals born and raised at high altitude show more concentrated capillarization of skeletal muscle (number per $\mathrm{mm}^{2}$ ) than sea-level counterparts. ${ }^{97}$ Chronic


Figure 24.8 A. Effects of altitude on hemoglobin ( Hb ; yellow line) and hematocrit (Hct; red line) levels of 8 young women from the University of Missouri ( 213 m ) prior to, during, and 2 weeks after exposure to 4267 m at Pikes Peak, Colorado. (From Hannon JP, et al. Effects of altitude acclimatization on blood composition of women. J Appl Physiol 1968;26:540.) B. Hematocrit response of young women receiving supplemental iron [ +Fe ] prior to and during altitude exposure compared with male and female subjects receiving no supplemental iron. (Courtesy of Dr. J. P. Hannon.)
hypoxia can initiate remodeling of capillary diameter and length, with formation of new capillaries to increase oxygen conductance to neural tissues. ${ }^{11}$

Human residents of sea level also increase tissue capillarization during an altitude stay. ${ }^{66}$ A more prolific microcirculation reduces the oxygen diffusion distance between blood and tissues to optimize tissue oxygenation at altitude when arterial $\mathrm{PO}_{2}$ decreases. Muscle biopsy specimens from humans living at altitude indicate that myoglobin increases up to $16 \%$ after acclimatization. ${ }^{74}$ Additional myoglobin augments oxygen storage in specific fibers and facilitates intracellular oxygen release and delivery at a low tissue $\mathrm{PO}_{2}$. Researchers are unclear whether the small increase in mitochondrial
number and concentration of aerobic energy transfer enzymes with prolonged exposure ${ }^{56}$ (or when training under normobaric hypoxic versus normoxic conditions) ${ }^{65}$ reflects exercise training effects, the hypoxic environment, or the combination of both factors. ${ }^{42,83}$

High-altitude natives benefit from a slight shift to the right of the oxyhemoglobin dissociation curve at altitude. This effect decreases hemoglobins affinity for oxygen to favor more oxygen release to tissues for a given cellular $\mathrm{PO}_{2}$. Increased concentration of red blood cell 2,3-diphosphoglycerate (2,3-DPG; see Chapter 13) also facilitates oxygen release from hemoglobin with long-term altitude exposure. Increased $2,3-$ DPG coupled with more circulating hemoglobin (and red blood cells) favorably affects the long-term residents capacity to supply oxygen to active tissue during physical activity.

## Body Mass and Body Composition

Prolonged high-altitude exposure reduces lean body mass (muscle fibers atrophy by $20 \%$ ) and body fat, with the magnitude of weight loss directly related to terrestrial elevation. Six men participated in a 40-day progressive decompression to an ambient pressure of 249 mm Hg in a hypobaric chamber to simulate ascent of Mt. Everest. ${ }^{80}$ Daily caloric intake from depressed appetite decreased by $43 \%$ during the exposure period. Reduced energy intake reduced body mass 7.4 kg , predominantly from the muscle component of the fatfree body mass. In addition to depressed appetite and food intake during high-altitude exposure, efficiency of intestinal absorption decreases, compounding the difficulty in maintaining body weight. ${ }^{15,24,105}$ Basal metabolic rate increases upon arrival at altitude to further affect the tendency to lose weight. To some extent, one can override an accelerated metabolic rate and minimize weight loss by consciously increasing energy intake while at altitude. ${ }^{16}$

## Time Required for Acclimatization

The time required to acclimatize to altitude depends on terrestrial elevation. Acclimation to one altitude ensures only partial adjustment to a higher elevation. As a broad guideline, it takes about 2 weeks to adapt to altitudes up to 2300 m . Thereafter, each $610-\mathrm{m}$ altitude increase requires an additional week to fully acclimatize up to 4600 m . Athletes who desire to compete at altitude should begin intense training immediately during acclimatization. Rapid initiation of training minimizes detraining effects induced by the normal tendency to reduce physical activity in the first few days at altitude. Acclimatization adaptations dissipate within 2 or 3 weeks after returning to sea level.

## METABOLIC, PHYSIOLOGIC, AND EXERCISE CAPACITIES AT ALTITUDE

The stress of high altitude considerably restricts exercise capacity and physiologic function. Even at lower altitudes, exercise performance deteriorates because physiologic and
metabolic adjustments do not fully compensate for the reduced ambient oxygen pressure. Stroke volume and maximum heart rate acclimatize in a direction that reduces oxygen transport capacity and $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$. ${ }^{30,82}$

## Maximal Oxygen Consumption

Figure 24.9A depicts the relationship between the decrease in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ (\% of sea-level value) and increasing altitude or simulated exposures (i.e., hypobaric chambers or normobaric hypoxic gas breathing) reported in diverse civilian and military studies. Disparities in experimental design and procedures and physiologic differences among subjects help to explain the variation in the points about the orange line that depict the relationship. Small declines in $\dot{\mathrm{VO}}_{2 \text { max }}$ become noticeable at an altitude of 589 m . Thereafter, arterial desaturation decreases $\dot{V} O_{2 \max }$ by 7 to $9 \%$ per $1000-m$ altitude increase to 6300 m , where aerobic capacity declines at a more rapid, nonlinear rate. ${ }^{22,70}$ For example, aerobic capacity at 4000 m averages $75 \%$ of the sea-level value. At $7000 \mathrm{~m}, \dot{\mathrm{~V}} \mathrm{O}_{2 \max }$ averages one-half that at sea level. The $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ of relatively fit men atop Mt. Everest averages about $1000 \mathrm{~mL} \cdot \mathrm{~min}^{-1} ;{ }^{68}$ this corresponds to an exercise power output of only 50 watts on a bicycle ergometer.

Physical conditioning prior to altitude exposure offers little protection because the endurance athlete experiences a slightly greater percentage reduction in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ than an untrained person. In addition, large variability exists among individuals in the decrement in $\dot{\mathrm{V}}_{2 \text { max }}$ with altitude exposure. Men experience the largest decrease, particularly those with (1) large lean body mass, (2) large sea-level aerobic capacity, and (3) low sea-level lactate threshold. ${ }^{77}$ To some extent, arterial desaturation and decrease in $\dot{\mathrm{V}}_{2 \text { max }}$ become more pronounced in individuals with a depressed hyperventilation response to exercise in a hypoxic environment. ${ }^{29}$ Despite any unique effects of altitude exposure on aerobically fit individuals, a standard exercise task at altitude (i.e., a given absolute amount of exercise) still provides relatively less stress for well-conditioned women and men because they perform it at a lower percentage of their $\dot{\mathrm{V}}_{2 \text { max }}$. No change in exercise economy occurs in response to 4 weeks of intermittent altitude exposure. ${ }^{96}$

## Circulatory Factors

After several months of acclimatization to hypoxia, $\dot{\mathrm{V}}_{2 \text { max }}$ at altitude still remains below sea-level values, even with relatively rapid and pronounced increases in hemoglobin concentration. This occurs because reduced circulatory capacityeembined effect of lowered maximum heart and stroke volumeeffsets the hematologic benefits of acclimatization.

## Submaximal Exercise

The immediate altitude response to exercise increases submaximal cardiac output (Table 24.2), but this adjustment


Figure 24.9 A. Reduction in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ as a percentage of the sea-level value related to altitude exposure derived from 146 average data points from 67 different civilian and military investigations conducted at altitudes from 580 m (1902 ft) to 8848 m ( $29,021 \mathrm{ft}$ ). Altitude represents data from actual terrestrial elevations or simulated elevations with hypoxic chambers or hypoxic gas breathing. The orange curvilinear line is a database regression line drawn using the 146 points. B. Generalized trend in performance decrements related to altitude exposure for runners and swimmers, primarily during competition. (Modified from Fulco CS, et al. Maximal and submaximal exercise performance at altitude. Aviat Space Environ Med 1998;69:793.)
diminishes as acclimatization progresses and does not improve with prolonged exposure. ${ }^{49}$ A progressive decrease in the hearts stroke volume (associated with diminished plasma volume) during the altitude stay reduces exercise cardiac output.

With a lower cardiac output, submaximal oxygen consumption remains stable through an expanded $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference. To some extent, an increased submaximal heart rate offsets the decrease in stroke volume during submaximal exercise.

## Maximal Exercise

Maximum cardiac output decreases after about 1 week above 3048 m and remains lower throughout ones stay. Reduced blood flow during maximal exercise results from the combined effect of decreases in maximum heart rate and stroke volume, both of which continue to decrease with the length and magnitude of altitude exposure. This blunted cardiac response does not result from myocardial hypoxia as reflected by normal electrocardiographic and coronary blood flow measurements during vigorous exercise at high altitudes. ${ }^{39,82}$ Decreased plasma volume and increased total peripheral vascular resistance contribute to the reduced maximum stroke volume. Enhanced parasympathetic tone induced by prolonged altitude exposure reduces maximum heart rate. ${ }^{85}$

## INTEGRATIVE QUESTION

If altitude acclimatization improves endurance performance at altitude, why doesnt it improve similar performance immediately upon return to sea level?

## Exercise Performance

Seven days of intermittent (4 h per day) simulated altitude exposure, in combination with either rest or exercise training, improves time-trial performance and induces physiologic adaptations during constant-work rate exercise at 4300 m , consistent with chronic exposure to this altitude. ${ }^{9}$ Specific nonhematological adaptations to hypoxic exposure that improve sea-level performance include improved muscle efficiency at the mitochondrial level from a tighter coupling of intracellular bioenergetic and mitochondrial function, greater muscle buffering, and ability to tolerate lactic acid production. ${ }^{31}$ Figure 24.9B illustrates the generalized trend in exercise performance decrements primarily during competition for athletes at different altitude exposures. Altitude exerts no adverse effect on events lasting less than 2 minutes. For longer duration events, poorer performance occurs at higher elevations than at sea level. The threshold for decrements appears at about 1600 m for events of 2 to 5 minutes, while only a $600-$ to $700-\mathrm{m}$ altitude induces poorer performance in events longer than 20 minutes. For the 1 - and 3-mile runs, medium altitude ( 2300 m ) decreases performance by 2 to $13 \%$ for fit subjects. ${ }^{27}$ This coincides with the $7.2 \%$ increase in 2-mile run times for highly trained middledistance runners at the same altitude. ${ }^{1}$ After 29 days of acclimatization, high-altitude exposure still increases 3-mile run time, compared with sea-level runs. ${ }^{71}$ The small improvement in endurance during acclimatization, despite lack of concomitant increase in $\dot{\mathrm{V}}_{2_{\text {max }}}$, relates to three factors:

1. Increased minute pulmonary ventilation (ventilatory acclimatization)
2. Increased arterial oxygen saturation and cellular aerobic functions
3. Blunted blood lactate response in exercise (see Lactate Paradox, p. 601)

## Aerobic Capacity on Return to Sea Level

Sea-level exercise performance does not improve after living at altitude when $\dot{V} O_{2 \max }$ serves as the improvement criterion. ${ }^{45,55,66}$ An 18-day stay at 3100 m produced no change in the altitude-induced $25 \%$ reduction in aerobic capacity in young runners. ${ }^{35}$ Also, $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ remained at the same prealtitude value on return to sea level. Even in studies that reported small improvements in $\dot{\mathrm{V}}{ }_{2 \text { max }}$ or exercise performance at altitude and on return to sea level, the change often relates to increased physical activity (i.e., effects of training and/or repeated testing) during altitude exposure. ${ }^{23,50}$

## Possible Negative Effects

Several physiologic changes during prolonged altitude exposure negate adaptations that could improve exercise performance on return to sea level. For example, the residual effects of muscle mass loss and reduced maximum heart rate and stroke volume do not enhance sea-level performance. Any reduction in maximum cardiac output at altitude offsets benefits from an increase in the bloods oxygen-carrying capacity. A depressed circulatory capacity returns to normal after a few weeks at sea level, but so also do potentially positive hematologic adaptations. Within a physiologic context, the controversial use of blood doping (see Chapter 23) mimics the hematologic benefits of altitude exposure without the negative effects on maximum cardiovascular dynamics and body composition.

## ALTITUDE TRAINING AND SEA-LEVEL PERFORMANCE

Endurance training at altitude does not improve subsequent sea-level exercise performance. Altitude acclimatization improves capacity for exercise at altitude, particularly high altitude. The effect of altitude training on aerobic capacity and endurance performance immediately on return to sea level remains unclear. Altitude adaptations in local circulation and cellular metabolism, combined with compensatory increases in the bloods oxygen-carrying capacity, should improve subsequent sea-level performance. Also, positive pulmonary adaptations and responses during prolonged hypoxic exposure do not regress immediately upon descent from altitude. If tissue hypoxia provides an important training stimulus, altitude plus training should act synergistically, making the total effect exceed similar training only at sea level. Unfortunately, much of the exercise training altitude exposure research contains experimental design flaws that limit assessment of this possibility.

Researchers used equivalent groups to compare effectiveness of altitude training ( 2300 m ) and equivalent training at sea level. Six middle-distance runners trained at sea level for 3 weeks at $75 \%$ of sea-level $\dot{\mathrm{VO}}_{2 \max }$. Another group of six runners trained an equivalent distance at the same percentage $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ at 2300 m . The groups then exchanged training sites and continued to train for 3 weeks at the same relative intensity as the preceding group. Initially, 2-mile run times aver-


Group 1 (sea level-altitude) $\square$ Group 2 (altitude-sea level)

Figure 24.10 Maximal oxygen consumption of two equivalent groups during training for 3 weeks at altitude and 3 weeks at sea level. Group 1 trained first at sea level and continued training for 3 weeks at altitude. For group 2, the procedure reversed; they trained first at altitude and then at sea level. Aqua arrows indicate change in training site. (From Adams WC, et al. Effects of equivalent sea-level and altitude training on $\dot{\mathrm{VO}}_{2 \text { max }}$ and running performance. J Appl Physiol 1975;39:262.)
aged $7.2 \%$ slower at altitude than at sea level. Run times improved $2.0 \%$ for both groups during altitude training, but postaltitude performance at sea level remained similar to the prealtitude sea-level runs. Figure 24.10 shows that short-term altitude exposure decreased $\dot{\mathrm{V}} \mathrm{O}_{2 \max } 17.4 \%$ for both groups; it improved only slightly after 20 days of altitude training. When the runners returned to sea level after altitude training, aerobic capacity remained $2.8 \%$ below prealtitude sea-level values. Clearly, for these well-conditioned middle-distance runners, no synergistic effect emerged from combining aerobic training at medium altitude compared with equivalent sealevel training.

Other studies have duplicated these observations for $\dot{\mathrm{V}}{ }_{2 \text { max }}$ and endurance performance at moderate and higher altitudes in athletes from sea level. ${ }^{25,52}$ Highly trained male track athletes flew to Nunoa, Peru (altitude 4000 m ), where they continued to train and acclimatize for 40 to 57 days. ${ }^{93} \mathrm{~V}_{2 \text { max }}$ decreased $29 \%$ below sea-level values after the initial 3 days at altitude; after 48 days it still remained $26 \%$ lower. The 440yard, 880-yard, and 1- and 2-mile runs during a track meet with the altitude natives measured running performance after acclimatization. The times after acclimatization remained slower than prealtitude sea-level times, particularly for the longer runs. When the athletes returned to sea level, $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ and running performance did not differ from prealtitude measures. On no occasion did a runner improve his previous prealtitude run time. Running times in the longer events averaged $5 \%$ below prealtitude trials. In other studies, training in a hypobaric chamber provided no additional benefit to sea-level performance compared with similar training (albeit at a higher absolute exercise level) at sea level. As expected, the altitudetrained group showed better exercise performance at simulated altitude than sea-level residents.

## Altitude Natives May Respond Differently

For endurance athletes native to moderate altitude, total hemoglobin and blood volume synergistically increase by exercise training and altitude exposure compared to endurance
athletes from sea level. ${ }^{87}$ This adaptive response, unique to athletes born and living at altitude (e.g., Kenyan runners, Colombian cyclists, Mexican walkers) may contribute to their extraordinary endurance performance. Longer-term altitude acclimatized cyclists also show improved aerobic capacity and peak power output during sea-level exercise simulations. ${ }^{14}$

INTEGRATIVE QUESTION
Give your opinion (and rationale) about what effects a 2-week exposure to 3000 m would have on maximal exercise performance of 60 -second duration.

## Decrement in Absolute Training Level at Altitude

One must lower the absolute workload to perform aerobic exercise at the same relative intensity at altitude as at sea level. If not, anaerobic metabolism provides a larger portion of the energy for exercise at altitude (see Fig. 24.3) and fatigue develops. Exposure to 2300 m and above makes it nearly impossible to train at the same absolute exercise intensity as at sea level. Table 24.3 shows the reduction in exercise intensity for training relative to sea-level standards for six college athletes. At 4000 m , the runners could train only at the intensity equivalent to $39 \%$ of sea-level $\dot{\mathrm{V}}{ }_{2 \text { max }}$ compared with an intensity of $78 \%$ when training at sea level. The absolute exercise training level at altitude may become so reduced that an athlete cannot maintain peak condition for sea-level competition. In this regard, elite athletes benefit from periodically returning from altitude to sea level for intense training to offset detraining during a prolonged altitude stay (see next section). Returning to a lower altitude intermittently does not interfere with acclimatization and might benefit altitude performance. ${ }^{7,23,91}$ Regardless of the training model, athletes who train at altitude should include high-intensity speed work to maintain muscle power.

TABLE 24.3 Effect of Altitude on Training Exercise Intensity for Six Collegiate Athletes

|  | Altitude |  |  |  |
| :--- | :---: | :---: | :---: | :---: |
|  | 300 | $\mathbf{2 3 0 0}$ | $\mathbf{3 1 0 0}$ | $\mathbf{4 0 0 0}$ |
| Intensity of workout $\left(\% \dot{\mathrm{VO}}_{2 \max }\right.$ at 200 m$)$ | 78 | 60 | 56 | 39 |

From Kollias J, Buskirk ER. Exercise and altitude. In: Johnson WR, Buskirk ER, eds. Science and medicine of exercise and sports. 2nd ed. New York: Harper \& Row, 1974.

## COMBINE ALTITUDE STAY WITH LOW-ALTITUDE TRAINING

Research has focused on the optimal combination of highaltitude stay plus low-altitude training in competitive runners. Athletes who lived at 2500 m but returned regularly to lower altitudes ( 1000 to 1250 m ) to train at near sea-level intensity (i.e., live high train low) showed greater average increases in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ and 5000 -m run performance than athletes who lived and trained only at 2500 m or those who lived and trained only at sea level. ${ }^{54,100}$ Strategies that combine altitude acclimatization and maintenance of sea-level training intensity provide synergistic benefits to sea-level endurance performance. Regular training exposure to a near sea-level environment prevents the impaired systolic function (i.e., reduced maximum stroke volume and cardiac output) typically observed during altitude training. Such an approach to training also improves running economy and the hypoxic ventilatory drive of elite distance runners, along with the benefits of the hypoxia-induced increases in serum erythropoietin (EPO) and accelerated erythropoiesis. ${ }^{47,84,95,108}$ To remove the inconvenience and cost of the live high train low strategy, a modification applies supplemental oxygen during training at altitude. ${ }^{106}$ Compared with control trials, supplemental oxygen increases (1) arterial oxyhemoglobin saturation, (2) exercise oxygen consumption, and (3) average power output during high-intensity workouts at moderate altitude. This form of training allows athletes to live at altitude yet effectively train low with minimal travel expense and inconvenience, and without inducing additional free radical oxidative stress. ${ }^{107}$

Not all individuals benefit to the same degree from the living high, training low strategy. Within the group that showed physiologic and performance increases with this protocol, some individuals were responders, while others showed little positive adjustment. ${ }^{20}$ The nonresponders displayed a smaller increase in plasma concentration of the ery-throcyte-producing hormone EPO after 30 hours at altitude than the responders. Such individuals experience a depressed increase in hematocrit during acclimatization to altitude exposure. Three prerequisites are required to benefit from combining altitude living and lower altitude training:

1. The elevation must be high enough to raise EPO concentrations to increase total red blood cell volume and $\dot{\mathrm{V}}_{2 \text { max }}$.
2. The athlete must respond positively with increased EPO output.
3. Training must take place at an elevation low enough to maintain training intensity and exercise oxygen consumption at near sea-level values.

## INTEGRATIVE QUESTION

Respond to a person who suggests that periodic breath-holding while exercising at sea level should produce physiologic adaptations similar to training at altitude.

## At-Home Acclimatization

Application of the live high train low training model poses considerable practical and financial hurdles. Unfortunately, some endurance athletes use the banned (and dangerous) practices of either blood doping or EPO injections to increase hematocrit and hemoglobin concentration without the potential negative effects of an altitude stay

A more prudent approach makes use of the observation that altitudes beneficial effects on erythropoiesis and aerobic capacity may require relatively short-term exposures to hypoxia. For example, daily intermittent exposures of 3 to 5 hours for 9 days to simulated altitudes of 4000 to 5500 m in a hypobaric chamber increased endurance performance, red blood cell count, and hemoglobin concentration in elite mountain climbers. ${ }^{17,79}$ This approach also decreases the rate of lactate appearance during intense exercise. ${ }^{21}$ These effects may be time and protocol dependent because a 4 -week regimen of intermittent normobaric hypoxia at rest (5:5 min hy-poxia-to-normoxia ratio for $70 \mathrm{~min}, 5$ days a week) did not improve endurance or augment erythropoietic markers in trained runners. ${ }^{46}$ Intermittent hypoxic training under normobaric conditions provides an added bonus with clinical and cardioprotective implicationsit-augments trainings effect on selected metabolic and cardiovascular risk factors. ${ }^{4}$

In the absence of a hypobaric chamber, three approaches create an altitude environment where an athlete, mountaineer, or hot-air balloonist living at sea level spends a large enough portion of the day to stimulate an altitude acclimatization response

1. Gamow Hypobaric Chamber. A person rests and sleeps for about 10 hours each day. The chambers total air pressure decreases to simulate the barometric pressure of a preselected altitude. Reduced barometric pressure proportionately reduces the inspired airs $\mathrm{P}_{2}$ to simulate altitude exposure and induce physiologic adaptations.
2. Simulate altitude at sea level by increasing the nitrogen percentage of the air within an enclosure. Increased nitrogen percentage correspondingly reduces the airs oxygen percentage, thus decreasing inspired air $\mathrm{PO}_{2}$. Nordic skiers have applied this technique by living for 3 to 4 weeks in a house that provides air with only $15.3 \%$ oxygen rather than its normal concentration of $20.9 \%$. The system requires mixing nitrogen gas and carefully monitoring the breathing mixture. Interestingly, the Norwegian Olympic Organization has banned these altitude houses for its own athletes because they consider this practice grey-zone doping.
3. A suitcase-sized unit developed by two-time British Olympic cyclist Shaun Wallace continuously supplies air with an oxygen content of approximately $15 \%$ to simulate an altitude of 2500 m (Hypoxico
Altitude Tent, Fig. 24.11). The 70-lb unit consists of a portable tent that fits over a normal bed. A hypoxic generator (housed in an airline suitcase) continually feeds altitude-simulating hypoxic air into the tent. The porosity of the tents material limits the rate of diffusion of outside oxygen into the tent and maintains the $15 \%$ oxygen concentration. Equilibration of the tents environment at the 15\% oxygen level requires about 90 minutes.

## Summary

1. The progressive reduction in ambient $\mathrm{PO}_{2}$ with increasing altitude produces inadequate hemoglobin oxygenation in arterial blood. Arterial desaturation impairs aerobic physical activities at altitudes of 2000 m and above.
2. Altitude exposure does not adversely affect shortterm (anaerobic) sprint and power performances that depend almost entirely on energy from intramuscular high-energy phosphates and glycolytic reactions.
3. Reduced $\mathrm{PO}_{2}$ and accompanying hypoxia at altitude stimulate physiologic responses and adjustments that improve altitude tolerance during rest and exercise. Hyperventilation and increased submaximal cardiac output via elevated heart rate provide the primary immediate responses.
4. Medical problems ranging from mild to lifethreateningAMS, HAPE, and HACEeften emerge during altitude exposure. The potentially lethal conditions of HAPE and HACE require immediate removal to a lower altitude.


Figure 24.11 The Hypoxico Altitude Tent fits over a double or queen-size bed or can be constructed for in-home use as a semipermanent cubicle. Patches of breathable nylon allow ambient oxygen (at higher $\mathrm{PO}_{2}$ ) to diffuse into the tent (at lower $\mathrm{PO}_{2}$ ) to maintain the percentage of oxygen within the tent at about 15\%. A hypoxic generator (left of tent) continuously supplies air with oxygen content that equilibrates within the tent to near $15 \%$. The bottom inset shows the time course for equilibration of air within the tent to reach the $15 \%$ oxygen level. (Photo courtesy of Hypoxico Inc., www.hypoxico.com, Cardiff, CA.)
5. Acclimatization entails physiologic and metabolic adjustments that improve tolerance to altitude hypoxia. The main adjustments involve (1) reestablishment of acid base balance of the bodily fluids, (2) increased synthesis of hemoglobin and red blood cells, and (3) improved local circulation and cellular metabolism.
6. The rate of altitude acclimatization depends on the terrestrial elevation. Noticeable improvements occur within several days. The major adjustments require about 2 weeks, but acclimatization to high altitudes requires 4 to 6 weeks.
7. Alveolar $\mathrm{PO}_{2}$ averages 25 mm Hg at the summit of Mt. Everest. For acclimatized men, this reduces $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ by $70 \%$ to about $15 \mathrm{~mL} \mathrm{O}_{2} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}$.
8. Despite acclimatization, $\dot{\mathrm{VO}}_{2 \text { max }}$ decreases about $2 \%$ for every 300 m above 1500 m . A decrement in endurance-related exercise performance parallels reduced aerobic capacity.
9. Altitude-related declines in maximum heart rate and stroke volume offset any beneficial effects of acclimatization. This partly explains the inability to achieve sea-level $\dot{\mathrm{V}}{ }_{2 \text { max }}$ values at altitude, even after acclimatization.
10. Training at altitude provides no greater benefit to sea-level exercise performance than equivalent training at sea level.
11. Athletes benefit from periodically returning from altitude to sea level for intense training to offset any detraining from lower levels of exercise during a prolonged altitude stay.
12. The Gammow hyperbaric chamber and Hypoxico tent system represent two approaches to creating an altitude environment under sea-level conditions.

1) References are available online at http://thepoint.lww.com/mkk7e.

On the Internet
International Union of Physiological Sciences www.iups.org/
The Hypoxico Altitude Tent www.hypoxico.com


## CHAPTER 25

## Exercise and Thermal Stress

## CHAPTER OBJECTIVES

> Explain how the hypothalamus maintains thermal balance

- Explain the four physical factors that contribute to heat gain and heat loss
> Discuss how the circulatory system serves as a workhorse for thermoregulation
> List desirable clothing characteristics for exercising in cold and warm weather
> Describe how football equipment and the cycling helmet affect heat dissipation and thermoregulation in exercise
> Discuss factors that maintain cutaneous and muscle blood flow and blood pressure during exercise in the heat
> Describe the cardiac-output, heart-rate, and strokevolume response during hot-weather exercise
> Graph the relationship between core temperature and relative exercise intensity ( $\% \mathrm{~V}_{2 \text { max }}$ )
> Quantify fluid loss during hot-weather exercise, and indicate the consequences of dehydration on physiology and performance
> Describe the purposes of fluid replacement and proposed benefits of preexercise hyperhydration and glycerol supplementation during exercise in a hot environment
> Explain how acclimatization, training, age, gender, and body fat modify heat tolerance during exercise
> Give symptoms, possible causes, and treatment for heat cramps, heat exhaustion, and exertional heat stroke
> Describe factors that constitute the WB-GT index and the relative importance of each factor
> List six factors that reduce the insulatory properties of clothing
> Summarize the American College of Sports Medicine WB-GT recommendations for endurance running and cycling
> Discuss immediate and possible longer term physiologic adjustments to cold stress
> Explain the purpose of the wind-chill temperature index and factors that comprise it

Humans can tolerate a decline in deep body temperature of $10 \mathrm{C}(18 \mathrm{~F})$ but an increase of only $5 \mathrm{C}(9 \mathrm{~F})$. Temperature technically represents the mean kinetic energy of a substances atoms as they move. The potential for heat exchange between substances (e.g., blood to capillary walls) or objects (e.g., playing surface to participants body) reflects a functional definition of this term. Over the past 25 years, more than 100 football players have died from excessive heat stress during practice or competition, most of them unnecessarily. Hyperthermia and dehydration also contributed to the deaths of three apparently healthy collegiate wrestlers just before their competitive season, ${ }^{131}$ with numerous accounts worldwide of heat-related deaths during marathon runs and other endurance events. The people who organize and guide athletic events and physical activity programs bear most of the responsibility for helping to eradicate heat injuries. A proper understanding of thermoregulation and the best ways to support these mechanisms should prevent such tragedies.

## Part 1 MECHANISMS OF THERMOREGULATION

## THERMAL BALANCE

Figure 25.1 shows that temperature of the deeper central tissues or core represents a dynamic equilibrium between factors that add and subtract body heat. Integration of mechanisms that alter heat transfer to the periphery (shell) regulates evaporative cooling and varies the bodys heat production to sustain thermal balance. Core temperature rises if heat gain exceeds heat loss, as readily occurs during vigorous exercise in a warm, humid environment; in contrast, core temperature declines in the cold when heat loss exceeds heat production.

Table 25.1 presents thermal data for heat production and heat loss via sweating during rest and maximal exercise.


Figure 25.1 Contributing factors to heat gain and heat loss to regulate core temperature at about 37 C (98.6 F).


The chemical reactions of energy metabolism produce body heat gains that can reach considerable levels during muscular activity. From shivering alone, whole body metabolism increases three- to five-fold. ${ }^{130}$ Metabolism in elite athletes often rises 20 to 25 times above the resting level, to about $20 \mathrm{kCal} \cdot$ $\min ^{-1}$ during intense aerobic exercise; this theoretically can increase core temperature by $1 \mathrm{C}(1.8 \mathrm{~F})$ every 5 to 7 min utes. The body also absorbs heat from solar radiation and objects warmer than the body. Heat leaves the body via the physical mechanisms of radiation, conduction, and convection, and most importantly by water vaporization from the skin and respiratory passages. Under optimal conditions, evaporative cooling with maximal sweating accounts for a heat loss of about $18 \mathrm{kCal} \cdot \mathrm{min}^{-1}$.

Circulatory adjustments provide the fine-tuning for temperature regulation. Heat conservation occurs when blood shunts rapidly to the deep cranial, thoracic, and abdominal cavities and portions of the muscle mass. This optimizes insulation from subcutaneous fat and other components of the bodys shell. Conversely, increases in internal heat dilate peripheral vessels as warm blood flows to the cooler periphery. The drive to maintain thermal balance remains so strong that it readily triggers a sweating rate of $2.0 \mathrm{~L} \cdot \mathrm{~h}^{-1}$ in exercise in the heat, or an oxygen consumption of $1200 \mathrm{~mL} \cdot \mathrm{~min}^{-1}$ from shivering in severe cold.

## HYPOTHALAMIC TEMPERATURE REGULATION

The hypothalamus contains the central coordinating center for temperature regulation. This group of specialized neurons at the floor of the brain acts as a thermostatusually set and carefully regulated at $37 \mathrm{C} \pm 1 \mathrm{C}(98.6 \mathrm{~F} \pm 1.8 \mathrm{~F})-$ that continually makes thermoregulatory adjustments to deviations from a temperature norm. Unlike the home thermostat, the hypothalamus cannot turn off the heat; it can only initiate responses to protect the body from either a buildup or loss of heat.

Two ways activate the bodys heat-regulating mechanisms:

1. Thermal receptors in the skin provide input to the central control center.
2. Changes in the temperature of blood that perfuses the hypothalamus directly stimulate this area.

Figure 25.2 shows the diverse structures embedded within the skin and subcutaneous tissue. The inset on the right depicts the dynamics of sweat evaporation from the skin surface. Peripheral thermal receptors responsive to rapid changes in heat and cold exist predominantly as free nerve endings in the skin. The more numerous cutaneous cold receptors generally exist near the skin surface. Cold receptors play an important role in initiating regulatory responses to a cold environment. The cutaneous thermal receptors act as an éarly warning system that relays sensory information to the hypothalamus and cortex. This direct line of communication evokes appropriate heat-conserving or heat-dissipating physiologic adjustments, and the individual consciously seeks relief from the thermal challenge.

The central hypothalamic regulatory center plays the primary role in maintaining thermal balance. In addition to receiving peripheral input, cells in the anterior portion of the hypothalamus detect slight changes in blood temperature. These cells heightened activity stimulates other hypothalamic regions to initiate coordinated responses for heat conservation (posterior hypothalamus) or heat loss (anterior hypothalamus). In contrast to peripheral receptors in detecting cold, the temperature of the blood that perfuses the hypothalamus provides the primary monitoring system to assess body warmth.

## THERMOREGULATION IN COLD STRESS: HEAT CONSERVATION AND HEAT PRODUCTION

The normal heat transfer gradient flows from the body to the environment. Generally, core temperature regulation involves no physiologic strain. However, excessive heat loss can occur in extreme cold, particularly at rest. The bodys heat production in this case increases, while heat loss slows to minimize any decline in core temperature.

## Vascular Adjustments

Stimulation of cutaneous cold receptors constricts peripheral blood vessels, which immediately reduces the flow of warm blood to the bodys cooler surface and redirects it to the warmer core. For example, cutaneous blood flow averages $250 \mathrm{~mL} \cdot \min ^{-1}$ in a thermoneutral environment, yet with


Figure 25.2 Right inset. Schematic illustration of the skin and underlying structures. The inset enlargement of the skin surface shows the dynamics of conduction, convection, and sweat evaporation for heat dissipation from the body. Each 1 L of water evaporated from the skin transfers 580 kCal of heat energy to the environment.
severe cold stress this flow approaches zero. ${ }^{55}$ Consequently, skin temperature declines toward ambient temperature to maximize the insulatory benefits of skin, muscle, and subcutaneous fat. A person with excessive body fat who is exposed to cold stress greatly benefits from this heat-conserving mechanism. For a thinly clad person with normal body fat content, cutaneous blood flow regulation generally provides effective thermoregulation at ambient temperatures between 25 and 29 C (77 84 F ).

## Muscular Activity

Shivering generates metabolic heat, but physical activity provides the greatest contribution in defending against cold. Exercise energy metabolism sustains a constant core temperature in air as cold as $-30 \mathrm{C}(-22 \mathrm{~F})$ without reliance on a heavy, restrictive clothing barrier. Internal temperature, not the bodys heat production per se, mediates the thermoregulatory response to cold. Shivering still occurs during vigorous exercise if the core temperature remains low. As a result, cold stress often induces higher exercise oxygen consumptions from shivering compared to performing the same exercise in a warmer environment.

When exercise metabolism decreases (e.g., from fatigue), shivering alone may not prevent a decline in core temperature. To some extent, the variability among individuals in shivering response dictates the diverse outcomes for those caught unprepared for accidental wet cold exposures. General muscle fatigue induced by prior strenuous exercise does not depress the shivering response. ${ }^{128}$

## Hormonal Output

Two Ł́alorigenic adrenal medulla hormones, epinephrine and norepinephrine, increase heat production during cold exposure. Prolonged cold stress also stimulates release of thyroxine, the thyroid hormone that increases resting metabolism.

## THERMOREGULATION IN HEAT STRESS: HEAT LOSS

The bodys thermoregulatory mechanisms primarily protect against overheating. Dissipating heat efficiently becomes crucial during exercise in hot weather, when inherent competition exists between mechanisms that maintain a large muscle


Figure 25.3 Heat production within active muscle and its transfer from the core to the skin. Under appropriate environmental conditions, excess body heat dissipates to the environment to regulate core temperature within a narrow range. (From Gisolfi CV, Wenger CB. Temperature regulation during exercise: old concepts, new ideas. Exerc Sport Sci Rev 1984;12:339.)
blood flow and thermoregulatory mechanisms. Figure 25.3 illustrates the potential avenues for heat exchange during exercise. Body heat loss occurs by four physical processes:

1. Radiation
2. Conduction
3. Convection
4. Evaporation

## Heat Loss by Radiation

All objects, including humans, continually emit electromagnetic heat waves (radiant energy). Our bodies usually remain warmer than the environment, making the net exchange of radiant heat energy move through the air to solid, cooler objects in the environment. This form of heat transfer does not require molecular contact between objects; it provides the means for the suns warming effect on the Earth. A person can remain warm by absorbing radiant heat energy from direct sunlight or by reflection from snow, sand, or water, even in subfreezing air temperatures. The body absorbs radiant heat energy from the surroundings when an objects temperature exceeds skin temperature.

## Heat Loss by Conduction

Heat exchange by conduction involves direct heat transfer from one molecule to another through a liquid, solid, or gas. The circulation transports most body heat to the shell, but a small amount continually moves by conduction directly through the deep tissues to the cooler surface. Heat loss by conduction then involves warming air molecules and cooler surfaces that contact the skin.

The rate of conductive heat loss depends on two factors:

1. Temperature gradient between the skin and surrounding surfaces
2. Thermal qualities of the surfaces

For example, immersing the body in cool water can produce considerable heat loss. Placing one hand in roomtemperature water clearly illustrates this phenomenon. Why does the hand in water feel much colder than the hand in air, even though the water and air have identical temperatures? The answer is straightforward: Water absorbs several thousand times more heat than air and conducts it away from the warmer body part. Sitting in an indoor swimming pool with water at $28 \mathrm{C}(82.4 \mathrm{~F})$ provides more discomfort than sitting on the pool deck at the same temperature. Warm-weather hikers often gain considerable body heat when exercising in a warm environment. Lying on a rock shielded from the sun facilitates some body heat loss by conductance between the rocks cool surface and the hikers warmer surface.

## Heat Loss by Convection

The effectiveness of heat loss by conduction depends on how rapidly the air (or water) adjacent to the body exchanges once it warms. If air movement or convection proceeds slowly, the air next to the skin warms and acts as a zone of insulation that minimizes further conductive heat loss. Conversely, if cooler air continually replaces warmer air about the body on a breezy day, in a room with a fan, or when running, heat loss increases because convection continually replaces the zone of insulation. For example, air currents at 4 miles per hour are about twice as effective for body cooling as air currents at 1 mile per hour. The cooling effect of airflow forms the basis
of the wind chill temperature index (see p. 638). This index indicates the equivalent still-air temperature for a particular ambient temperature at different wind velocities. Convection also exerts an effect on thermal balance in water because the body loses heat more rapidly when swimming than when remaining motionless.

## Heat Loss by Evaporation

Water vaporizing from the respiratory passages and skin surface continually transfers heat to the environment. Heat loss is then further facilitated by convective airflow that moves the moist, humidified air from the skins surface. ${ }^{91}$ Each vaporized liter of water extracts 580 kCal from the body and transfers it to the environment.

The bodys surface contains approximately 2 to 4 million sweat glands. During heat stress, these eccrine glandscontrolled by cholinergic sympathetic nerve fiberssecrete large quantities of hypotonic saline solution ( $0.20 .4 \%$ NaCl ). Evaporation of sweat from the skin exerts a cooling effect. The cooled skin in turn cools the blood diverted from interior tissues to the surface. In addition to heat loss through sweat evaporation, about 350 mL of insensible perspiration seeps through the skin each day and evaporates to the environment. Also, about 300 mL of water vaporizes daily from the moist mucous membranes of the respiratory passages. This is seen as foggy breath in cold weather.

## Evaporative Heat Loss at High Ambient Temperatures

Evaporation provides the major defense against overheating. As ambient temperature increases, conduction, convection, and radiation decrease in their effectiveness to facilitate body heat loss. When ambient temperature exceeds body temperature, the body gains heat by these three thermal transfer mechanisms. In such environments (or when conduction, convection, and radiation cannot dissipate a large metabolic heat load), sweat evaporation from the skin and respiratory tract provide the only means for heat dissipation. Increases in ambient temperature generally induce proportionate increases in sweating rate.

## Heat Loss During High Humidity

Three factors influence the total amount of sweat vaporized from the skin and/or pulmonary surfaces:

1. Surface exposed to the environment
2. Temperature and relative humidity of the ambient air
3. Convective air currents about the body

Relative humidity represents the most important factor in determining the effectiveness of evaporative heat loss. Relative humidity refers to the ratio of water in ambient air at a particular temperature compared to the total quantity of moisture that air could contain expressed as a percentage. For example, $40 \%$ relative humidity means that ambient air contains only $40 \%$ of the airs moisture-carrying capacity at
that specific temperature. With high humidity, the ambient vapor pressure approaches that of moist skin (about 40 mm $\mathrm{Hg})$. In this case, evaporation greatly diminishes even though large quantities of sweat bead on the skin and eventually roll off. This form of sweating represents useless water loss that can produce dehydration and overheating. A dangerous rise in core temperature can occur in athletes who compete in mod-erate- to high-intensity sports that exceed 30 minutes duration in environments above $35 \mathrm{C}(95 \mathrm{~F})$ and $60 \%$ relative humidity. In a Practical Sense, p. 617, describes how to assess the heat quality of the environment, with accompanying recommendations concerning physical activity related to ambient temperature, radiant heat, and relative humidity.

Continually drying the skin with a towel while sweating, as some tennis players do between games and sets, thwarts evaporative cooling. Evaporation, not sweat, cools the skin. Individuals can tolerate relatively high environmental temperatures provided relative humidity remains low. Most persons find hot, dry desert climates more comfortable than cooler but more humid tropical climates.

## INTEGRATIVE QUESTION

In deciding on the starting time for an upcoming summer marathon, what prior meteorologic information would be most valuable and why?

## Integration of Heat-Dissipating Mechanisms

The mechanisms for heat loss remain the same whether the heat load originates internally (metabolic heat) or externally (environmental heat).

## Circulation

The circulatory system represents the workhorse to maintain thermal balance (see Focus on Research, p. 619). At rest in the heat, heart rate and cardiac output increase, while superficial arterial and venous blood vessels dilate to divert warm blood to the body shell. This manifests as a flushed or reddened face on a hot day or during vigorous exercise. With extreme heat stress, 15 to $25 \%$ of the cardiac output passes through the skin. Enhanced cutaneous blood flow greatly increases the thermal conductance of peripheral tissues. This favors radiative heat loss to the environment, particularly from the hands, forehead, forearms, ears, and tibial areas.

## Evaporation

Sweating begins within several seconds of the start of vigorous exercise. After about 30 minutes, it achieves equilibrium in direct relation to the exercise load. An effective thermal defense exists when evaporative cooling combines with a large cutaneous blood flow. The cooled peripheral blood then flows to the deeper tissues to absorb additional heat on its return to the heart.

## IN A PRACTICAL SENSE

## Assessing Heat Quality of the Environment: How Hot Is too Hot?

Seven important factors determine the physiologic strain imposed by environmental heat:

1. Air temperature and relative humidity
2. Individual differences in body size and fatness
3. State of training
4. Degree of acclimatization
5. Environmental influences such as convective air currents and radiant heat gain
6. Exercise intensity
7. Amount, type, and color of clothing

Several football deaths from heat injury occurred with air temperature below 23.9 C ( 75 F ) but with relative humidity above $95 \%$. Prevention is the most effective control of heat stress injuries. ${ }^{30}$ Most importantly, acclimatization minimizes the likelihood of heat injury. Another consideration requires evaluating the environment for its potential thermal challenge using the wet bulb globe temperature (WB GT) index. This index of environmental heat stress developed by the military provides important information to the National Collegiate Athletic Association to establish thresholds for increased risk of heat injury and exercise performance decrements.

The WB GT index depends on ambient temperature, relative humidity, and radiant heat as related in the following equation:

$$
\mathrm{WB} \mathrm{GT}=0.1 \times \mathrm{DBT}+0.7 \times \mathrm{WBT}+0.2 \times \mathrm{GT}
$$

where DBT represents the dry-bulb temperature (air temperature) recorded by an ordinary mercury thermometer, and WBT equals the wet-bulb temperature recorded by a similar thermometer except that a wet wick surrounds the mercury bulb (Fig. 1). With high relative humidity, little evaporative cooling occurs from the wetted bulb, so this thermometers temperature remains similar to the dry bulb. On a dry day, considerable evaporation occurs from the wetted bulb to maximize the difference between the two thermometer readings. A small difference between thermometer readings indicates high relative humidity, whereas a large difference indicates little air moisture and rapid evaporation. GT represents the globe temperature recorded by a thermometer with a black metal sphere enclosing its bulb. The black globe absorbs radiant energy from the surroundings to measure this source of heat gain. Most industrial supply companies sell this relatively inexpensive thermometer.

| WB-GT Range |  | Recommendations |
| :---: | :---: | :---: |
| ${ }^{\circ} \mathrm{F}$ | C |  |
| 80-84 | 26.5-28.8 | - Use discretion, especially if unconditioned or unacclimatized |
| 85-87 | 29.5-30.5 | - Avoid strenuous activity in the sun |
| >88 | >31.2 | - Avoid exercise training |


Black bulb thermometer (Radiant heat)
Dry-bulb thermometer (Air temperature)
Figure 1 Right. Apparatus to measure wet bulb globe temperature (WB GT). Top. Guidelines to reduce risk of heat injury for outdoor athletic activities by use of the WB GT and wet-bulb temperature (WBT). (Modified from Murphy RJ, Ashe WF. Prevention of heat illness in football players. JAMA 1965;194:650.)

## IN A PRACTICAL SENSE

The top portion of the inset table in Figure 1 presents WB GT guidelines to reduce the chance of heat injury in athletic activities. These standards apply to lightly clothed humans but do not consider the specific heat load imposed by uniforms or equipment. For American football, the lower end of each temperature range serves as the more prudent guide. One can assess ambient heat load from wet-bulb thermometer (WBT) because this reading reflects both air temperature and relative humidity. The bottom portion of the table presents heat stress recommendations based on WBT.

The American College of Sports Medicine proposes the following recommendations concerning risk for heat injury with continuous exercise based on the WB GT:

## WB GT RECOMMENDATIONS FOR CONTINUOUS ACTIVITIES SUCH AS ENDURANCE RUNNING AND CYCLING ${ }^{2}$

Very high risk: Above 28 C ( 82 F)Pestpone race.
High risk: 23 to 28 C ( 7382 F)Heat-sensitive individuals
(e.g., obese, low physical fitness, unacclimatized, dehydrated, previous history of heat injury) should not compete.
Moderate risk: 18 to $23 \mathrm{C}(6573 \mathrm{~F})$
Low risk: Below 18 C ( 65 F )
Without the WBT, but knowing relative humidity (local meteorologic stations or media reports), the heat-stress index (FIG. 2) evaluates the relative heat stress. The index should rely on data close to the actual sport site to eliminate potential error from meteorologic data some distance from the event.

Continued


Figure 2 The heat-stress index.

## Hormonal Adjustments

Sweating produces loss of water and electrolytes; this initiates hormonal adjustments to conserve salts and fluid. Fluid conservation makes urine more concentrated during heat stress. Concurrently, repeated days of exercise in the heat or just a single exercise bout stimulates adrenocortical release of the sodium-conserving hormone aldosterone to act on the renal tubules to increase sodium reabsorption. Aldosterone also reduces sweats osmolality. Thus, sweat sodium concentration decreases during repeated heat exposure to further conserve electrolytes. At the same time, exercise and/or hypohydration stimulates vasopressin (also called antidiuretic hormone) release from the neurohypophysis of the hypothalamus. Vasopressin increases permeability of the collecting tubules of the kidneys to facilitate fluid retention. The magnitude of aldosterone and vasopressin release depends on hypohydration severity and physical activity intensity. ${ }^{87}$

## EFFECTS OF CLOTHING ON THERMOREGULATION

Clothing insulates the body from its surroundings. It can reduce radiant heat gain in a hot environment or retard conductive and convective heat loss in the cold.


A progressive slowing of marathon running performance of men and women as the wet bulb globe temperature (WB GT) increased from 10 to $25 \mathrm{C}(5077 \mathrm{~F})$ with performance more negatively affected for slower runners. (From Ely MR, et al. Impact of weather on marathon-running performance. Med Sci Sports Exerc 2007;39:487.)

## FOCUS ON RESEARCH

## Heat Stress and Cardiovascular Dynamics in Exercise

Rowell LB, et al. Reductions in cardiac output, central blood volume, and stroke volume with thermal stress in normal men during exercise. J Clin Invest 1966;45:1801.

- The 1966 research by Rowell and colleagues constituted the first study of cardiac output $(\mathrm{CO})$ of unacclimatized men during heat stress and exercise. The data showed reduced CO at high ambient temperatures and exercise intensities, and helped explain an unacclimatized mans limited exercise capacity during environmental heat stress.

The researchers tested the hypothesis that maximum blood flow decreased during strenuous exercise in the heat in unacclimatized subjects (six men; mean age, 23 y ; mean body surface area, $1.97 \mathrm{~m}^{2}$; mean $\dot{\mathrm{VO}}_{2 \max }$ at 23.6 C [74.4 F], 3.80 $\mathrm{L} \cdot \mathrm{min}^{-1}$ ) by measuring CO seven times
during each of four exercise intensities at 25.6 C (78 F) and 43.3 $\mathrm{C}(109.9 \mathrm{~F}$ ) in the same subjects ( 56 CO determinations per subject). The men walked for 15 minutes on a motor-driven treadmill at 3.5 mph at $7.5,10,12.5$, and $15 \%$ grades. They rested for 15 to 20 minutes between walks.

The care given to accuracy of CO measurements represented a unique aspect of this research. Open-circuit spirometry measured oxygen consumption $\left(\dot{\mathrm{V}}_{2}\right)$. The indicator dilution method assessed CO by indocyanine green dye injected into the right atrium and sampled from the aortic arch. Detailed repeat measurements reduced withinsubject variability. Stroke volume (SV), arteriovenous oxygen differences ( $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff), heart rate (HR), and central blood volume ( CBV ) were also determined.

Figure 1 presents data for $\dot{\mathrm{V}} \mathrm{O}_{2}, \mathrm{SV}$, $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff, CBV, and HR at each work load at the two different temperatures.

$\square 25.6^{\circ} \mathrm{C} \square 43.3^{\circ} \mathrm{C}$

Figure 1 Central blood volume (CBV), oxygen consumption $\left(\mathrm{VO}_{2}\right)$, heart rate (HR), arteriovenous oxygen difference ( $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ diff), and stroke volume (SV) during exercise of increasing intensity at $25.6 \mathrm{C}(78 \mathrm{~F})$ and 43.3 C (109.9 F).

Exercise $\dot{\mathrm{V}} \mathrm{O}_{2}$ remained unaffected by ambient temperature, while HR increased markedly at $43.3 \mathrm{C}(109.9 \mathrm{~F})$. At the two lowest exercise intensities, CBV at 43.3 C ( 109.9 F ) remained $16 \%$ below control values at $25.6 \mathrm{C}(78 \mathrm{~F})$. Decrements in CBV paralleled the percentage decrease in SV (also 16\%). CVC and SV remained reduced at the two higher exercise intensities, but SV showed more pronounced reductions.

Figure 2 presents the average CO responses to exercise at $25.6 \mathrm{C}(78 \mathrm{~F})$ and $43.3 \mathrm{C}(109.9 \mathrm{~F})$ at each of the four intensities (indicated as percent grade on the right). Ambient air temperature exerted only a small effect on CO during the first two exercise intensities. With further increases in intensity ( 12.5 and $15 \%$ grades), CO decreased more markedly during heat stress. For example, CO averaged $1.1 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ lower at $12.5 \%$ grade at $43.3 \mathrm{C}(109.9 \mathrm{~F}$ ) than in the cooler environment. Three subjects attained near-maximal HRs at $12.5 \%$ grade. However, CO failed to increase at the most intense exercise level, although $\dot{\mathrm{V}}_{2}$ increased the expected amount because of a widened $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2}$ difference.

This important experiment demonstrated that heat dissipation during moderate-to-severe exercise at a high ambient temperature occurs by repartitioning of CO rather than by increasing it. The decrease in CBV and SV during exercise in heat stress suggests a redistribution of blood from the core to the periphery coincident with a more rapid circulation time. The study showed for the first time that failure of cardiac output to increase adequately during heat stress constituted an important contributory factor that limited unacclimatized mans capacity to exercise in the heat.

$\left\lceil 25.6^{\circ} \mathrm{C} \square 43.3^{\circ} \mathrm{C}\right.$
Figure 2 Average responses for cardiac output during different intensities (percent grade) of exercise at 25.6 C (78 F) and 43.3 C (109.9 F).

## Clothing Insulations (CLO Units)

The United States military has made a strong research commitment to develop standards for the insulatory properties of clothing to meet environmental challenges. The clo unit represents an index of thermal resistance. It indicates the insulatory capacity provided by any layer of trapped air between the skin and clothing, including the clothings insulation value. Assuming an environment with negligible air movement and body movement to disturb the insulatory layer of air about the body, a clo unit of 1 maintains a sedentary person at 1 MET indefinitely in an environment of $21 \mathrm{C}(68.8 \mathrm{~F})$ and $50 \%$ relative humidity.

An individuals metabolic rate at a given environmental temperature also affects the clo unit requirement. Data in Table 25.2 show six conditions of metabolic intensity from sleeping to heavy work (expressed in MET units) and three environmental temperatures ( $0 \mathrm{C},-20 \mathrm{C},-50 \mathrm{C}$ [32 F, $4 \mathrm{~F},-58 \mathrm{~F}]$ ). Note the inverse relationship between metabolic intensity and the insulation requirement (more

## TABLE 25.2 CLO Values Required to

 Maintain Core Temperature Related to Physical Activity Level and Ambient Temperature|  | Temperature, C |  |  |
| :--- | :---: | :---: | ---: |
| Activity | $\mathbf{0}$ | $\mathbf{2 0}$ | $\mathbf{5 0}$ |
| Heavy work, 6.0 METs | 1.0 | 1.6 | 2.2 |
| Moderate work, 3.0 METs | 1.6 | 2.8 | 4.2 |
| Light work, 2.0 METs | 2.6 | 4.0 | 6.2 |
| Very light work, 1.5 METs | 3.4 | 5.6 | 8.2 |
| Rest, 1.0 MET | 5.4 | 8.3 | 12.4 |
| Sleep, 0.8 METs | 6.7 | 10.6 | 15.5 |

clothing required for less work). At rest (1 MET) at 0 C ( 32 F ), the clo requirement is 5.4 , but when temperature drops to $-50 \mathrm{C}(-58 \mathrm{~F})$, the clo requirement increases by $130 \%$ to 12.4 .

Six factors affect the insulation (clo) value of clothing:

1. Wind speedfncreased speed disturbs the zone of insulation.
2. Body movementsPumping actions of arms and legs disturb the zone of insulation.
3. Chimney effectLeosely hanging clothing ventilates the trapped air layers away from body.
4. Bellows effect Vigorous body movements increase ventilation of air layers that conserve body heat.
5. Water vapor transfer Clothing resists the passage of water vapor and thus decreases heat loss by evaporative cooling.
6. Permeation efficiency factorHow well clothing absorbs liquid (sweat) by capillary action (wicking); wicking sweat away from the body surface reduces the cooling effect of evaporation, thus improving clothings effectiveness for conserving body heat.

Table 25.3 presents clo values for common garments. To determine the total insulatory value of what a person wears, add the individual clo values for each garment. Without wind penetration or air movement around the clothing, the clo value for a given weight of clothes equals 0.15 times the clothing weight in pounds. For example, wearing 10 pounds of clothes produces a clo value of $1.5(0.15 \times 10 \mathrm{lb})$.

## Cold-Weather Clothing

In providing insulation from the cold, the mesh of the cloth fibers traps air that then warms. This establishes a barrier to heat loss because the cloth and air conduct heat poorly; insulation becomes more effective with a thicker zone of trapped air above the skin. For this reason, several layers of light clothing, or garments lined with animal fur, feathers, or synthetic fabrics (with numerous layers of trapped air), provide

better insulation than a single bulky layer. The clothing layer against the skin should also wick moisture from the bodys surface to the next insulating clothing layer for subsequent evaporation. Wool or synthetics (e.g., polypropylene) that insulate well and dry quickly serve this purpose. A wool cap contributes considerably to heat conservation; nearly 30 to $40 \%$ of body heat dissipates through the highly vascularized head region that represents only about $8 \%$ of the bodys total surface area. Conversely, cooling the head during exercise in hot weather reduces symptoms of thermal discomfort. When clothing becomes wet, through either external moisture or condensation from sweating, it loses almost $90 \%$ of its insulating properties. This facilitates heat loss from the body because water conducts heat 25 times faster than air.

The thermoregulatory challenge when exercising in cold air arises not from inadequate insulation, but from metabolic heat dissipation through a thick air clothing barrier. Crosscountry skiers alleviate this problem by removing layers of clothing as the body warms. This practice maintains core temperature without reliance on evaporative cooling. The ideal winter garment in cold, dry weather blocks air movement but also allows water vapor from sweating to escape through the clothing.

## Warm-Weather Clothing

Dry clothing, no matter how lightweight, retards heat exchange more than the same clothing fully wet. Switching to a dry tennis, basketball, or football uniform in hot weather makes little sense for temperature regulation. Evaporative heat loss occurs only when the clothing becomes wet. A dry uniform simply prolongs the time lag between sweating and subsequent evaporative cooling.

Different materials absorb water at different rates. Cottons and linens readily absorb moisture. In contrast, heavy sweatshirts and rubber or plastic clothing produce high relative humidity close to the skin. This retards vaporization of moisture from its surface, blunting or even preventing evaporative cooling. Warm-weather clothing should fit loosely to permit free circulation of air between the skin and environment to promote convection and evaporation from the skin. Moisture-wicking garments (e.g., polypropylene, CoolMax , Dry-Lite ) optimally transfer heat and moisture from the skin to the environment, particularly during intense exercise in hot weather. They also benefit the individual during exercise in cold environments because dry clothing (in contrast to sweat-drenched clothing) reduces the risk for hypothermia. Color also exerts an influence; dark colors absorb light rays and add to radiant heat gain, whereas lighter-colored clothing reflects heat rays away from the body.

## Football Uniforms

Football uniforms and equipment present a considerable barrier to heat dissipation during environmental heat exposure. ${ }^{81}$ Even with loose-fitting porous jerseys, the wrappings, padding (with its plastic covering), helmet, and other objects
of ármor effectively seal off $50 \%$ of the bodys surface from the benefits of evaporative cooling. The 6 or 7 kg of equipment, frequently transported over a hot artificial playing surface adds to the players total metabolic load. The large size of many of the athletes further magnifies heat stress, particularly for offensive and defensive linemen with relatively small surface area body mass ratio and higher body fat percentage than smaller teammates at the other skill positions.

Figure 25.4 depicts the metabolic and thermal stress provided by the football uniform. The experiment tested nine men who ran for 30 minutes at $25.6 \mathrm{C}(78 \mathrm{~F})$ and $35 \%$ relative humidity. In one test, the men wore only shorts; in another, they wore the complete football uniform including helmet and plastic padding. In a third series, they wore shorts and carried a backpack that contained 6.2 kg , the exact weight of the uniform and equipment.

Wearing football gear while exercising produced higher rectal and skin temperatures during exercise and recovery than the other exercise conditions. Skin temperature directly beneath the padding averaged only $1 \mathrm{C}(1.8 \mathrm{~F})$ less than rectal temperature. This indicates that subcutaneous blood in these areas cooled by only about one-fifth as much as blood near the skin surface directly exposed to the environment. Rectal temperature remained elevated in recovery with uniforms, so a rest period offers limited value in normalizing thermal status unless the athlete removes the uniform. The yellow line shows that the weight of the uniform accounts for a large portion of the heat load. Not wearing the uniform (light green line) produced cooler skin temperatures and lower sweat rates. Without the uniform, evaporation from the skin progressed freely, whereas the uniform insulated the athlete and reduced the effective evaporative surface.

## The Modern Cycling Helmet Does Not Thwart Heat Dissipation

For cyclists, wearing a commercially available helmet provides vital protection against possible head trauma, but does the cycling helmet impede thermoregulatory processes in a hot dry or hot humid environment? Because the head provides an important avenue for heat loss during exerciseinduced hyperthermia, many competitive cyclists believe riding without a helmet reduces thermal strain and physical discomfort. This belief persists even though the design of the current commercial protective helmet retains aerodynamic and lightweight features with ventilation ports for convective and evaporative cooling. To evaluate physiologic and perceptual responses of wearing a helmet, 10 male and 4 female competitive cyclists pedaled for 90 minutes at $60 \%$ of $\dot{\mathrm{VO}}_{2 \text { peak }}$ in both hot dry ( $35 \mathrm{C}[95 \mathrm{~F}], 20 \%$ relative humidity) and hot humid ( 35 C [ 95 F ], $70 \%$ relative humidity) environments, with and without a protective helmet. ${ }^{18}$ The results for oxygen consumption, heart rate, core, skin, and head skin temperatures, rating of perceived exertion, and perceived thermal sensations of the head and body revealed that exercising in a hot humid environment produced greater thermal stress than exercising under thermoneutral conditions. Wearing the


Figure 25.4 Effects of full football uniform and its equivalent weight on (A) rectal temperature and (B) skin temperature during exercise. Subjects ran at $9.6 \mathrm{~km} \cdot \mathrm{~h}^{-1}$ for 30 minutes at 25.6 C (78 F) and $35 \%$ relative humidity. The uniform (orange line) caused the largest heat stress because of its effect in retarding evaporative cooling. This significantly elevated rectal and skin temperatures. (From Mathews DK, et al. Physiological responses during exercise and recovery in a football uniform. J Appl Physiol 1969;26:611.)
helmet, however, did not increase the riders heat strain or perceived heat sensation from the head or body.

## Summary

1. Exposure to heat or cold stress initiates thermoregulatory mechanisms that generate and conserve heat at low ambient temperatures and dissipate heat at high temperatures.
2. The thermostat for temperature regulation resides in the brains hypothalamus. This coordinating center initiates adjustments in response to input from thermal receptors in the skin and changes in the temperature of the blood that perfuses the hypothalamic region.
3. Heat conservation in cold stress results from vascular adjustments that shunt blood from the cooler periphery to the warmer deep tissues of the bodys core.
4. If vascular mechanisms prove ineffective during cold stress, shivering provides input of metabolic
heat. Prolonged cold stress stimulates release of hormones that elevate resting metabolism.
5. Heat stress diverts warm blood from the bodys core to the shell. Four factorsfadiation, conduction, convection, and evaporationeentribute to heat dissipation.
6. Evaporation provides the major physiologic defense against overheating at high ambient temperatures and intense exercise.
7. Effectiveness of evaporative heat loss diminishes dramatically in warm, humid environments, making a person vulnerable to dehydration and spiraling core temperature.
8. Practical heat-stress indices (e.g., wet bulb globe temperature index, heat-stress index) use ambient temperature, radiant heat, and relative humidity to evaluate the environments potential heat challenge.
9. Three factors influence sweat vaporization from the skin or pulmonary surfaces: surface exposure, ambient air temperature and relative humidity, and convective air currents.
10. Vigorous exercise generates metabolic heat to maintain core temperature in cold air environments, even if the person wears little clothing.
11. The clo index reflects thermal resistance from clothingthe insulatory capacity of air trapped between skin and clothing including the clothings insulation value.
12. Wearing several layers of light clothing traps a zone of air against the skin; this provides more effective insulation from cold than a single thick layer of clothing.
13. Wet clothing loses its insulating properties; this greatly facilitates heat flow from the body.
14. Ideal warm-weather clothing is lightweight, loose fitting, and light colored. Even with these characteristics, heat loss slows until the clothing becomes wet and allows evaporative cooling.
15. Football uniforms impose a barrier to heat dissipation because they effectively shield about $50 \%$ of the bodys surface from the beneficial effects of evaporative cooling.

## Part 2 THERMOREGULATION AND ENVIRONMENTAL HEAT STRESS DURING EXERCISE

## EXERCISE IN THE HEAT

The refrigerating mechanism of evaporative cooling dissipates metabolic heat during exercise, particularly in hot weather. This places a demand on the bodys fluid reserves and often produces relative hypohydration. Excessive sweating leads to more serious fluid loss and reduced plasma volume. This causes circulatory failure in the extreme, and core temperature rises to lethal levels.

## Circulatory Adjustments

The body encounters two competitive cardiovascular demands when exercising in the heat:

1. The muscles require delivery of arterial blood (oxygen) to sustain energy metabolism.
2. Arterial blood diverts to the periphery to transport metabolic heat for cooling at the skin surface; this blood cannot deliver its oxygen to active muscle.

Submaximal exercise produces similar cardiac outputs in hot and cold environments. ${ }^{108}$ However, the hearts stroke volume usually remains lower in the heat in proportion to the fluid deficit and reduced blood volume created in exercise. ${ }^{41,90}$ This translates to higher heart rates at all submaximal levels of exercise in the heat. In contrast, the reflex compensatory increase in heart rate in maximal exercise fails to offset the stroke volume decrease so maximal cardiac output decreases (see Focus on Research, p. 619).

## Vascular Constriction and Dilation

Maintaining adequate cutaneous and muscle blood flow during exercise under heat stress requires other tissues to temporarily compromise blood supply. For example, during environmental heat stress, compensatory constriction of the splanchnic vascular bed and renal tissues rapidly counteracts active vasodilation of the subcutaneous vessels responsible for 80 to $95 \%$ of elevated skin blood flow. ${ }^{54,78}$ A prolonged reduction in renal and visceral tissue blood flow probably contributes to liver and renal complications during exertional heat stress.

## Maintenance of Blood Pressure

Vasoconstriction in the viscera increases total vascular resistance. A balance between dilation and constriction maintains arterial blood pressure during exercise in the heat. In intense exercise (with accompanying dehydration), relatively less blood diverts to peripheral areas for heat dissipation. Reduced peripheral blood flow reflects the bodys attempt to maintain cardiac output in the face of diminishing plasma volume caused by sweating. Circulatory regulation and muscle blood flow take precedence over temperature regulation during exercise in the heat. When submaximal exercise progresses without excessive physiologic strain, a greater dependence still exists on anaerobic metabolism than in cooler conditions. ${ }^{139}$ This produces earlier accumulation of lactate, encroachment on glycogen reserves, and premature fatigue during prolonged moderate exercise. Two factors increase blood lactate accumulation:

1. Decreased lactate uptake by the liver from reduced hepatic blood flow
2. Reduced muscle catabolism of circulating lactate because heat dissipation diverts a large portion of the cardiac output to the periphery

## Core Temperature During Exercise

Heat generated by active muscles can raise core temperature to fever levels that would incapacitate a person if caused by external heat stress alone. Endurance runners, including champions, show no ill effects from rectal temperatures as high as $41 \mathrm{C}(105.8 \mathrm{~F})$ at the end of a 3-mile race. ${ }^{12}$ Aerobically fit subjects perform longer in uncompensably hot environments (environments where thermoregulatory mechanisms are inadequate) and tolerate higher levels of hyperthermia than less fit subjects. ${ }^{16}$ An abnormally high core temperature for trained and untrained subjects impairs exercise performance. Fatigue generally coincides with core temperatures between 38 and 40 C ( 100104 F ). This temperature range reflects a Éritical high body temperature that impairs muscle activation directly from a high brain temperature that decreases the central drive to exercise. In addition to the fatiguing effects of altered cerebral blood flow and depressed neuromuscular drive, a thermally induced exercise impairment may also result from reduced blood flow to specific
regions of the gastrointestinal tract to produce gastrointestinal barrier dysfunction and increased permeability. This effect allows endotoxins to enter the internal environment and contribute to fatigue. ${ }^{17,64}$

## Temperature Regulated at a Higher Level During Exercise

Within limits, the increase in core temperature with exercise does not reflect a failure of the heat-dissipating mechanisms or contribute to early fatigue. To the contrary, it represents a well-regulated response even during exercise in the cold. Figure 25.5A illustrates the relationship between esophageal (core) temperature and power output (oxygen consumption) for five men and two women of varying fitness levels during progressively more intense exercise. Core temperature increases to a higher level for all subjects as exercise intensity increases, although considerable intersubject variation occurs in temperature response. Note that the lines move closer together in Figure 25.5B, which plots core temperature related to exercise oxygen consumption expressed as a percentage of each persons $\stackrel{\vee}{ } \mathrm{O}_{2 \text { max }}$. This indicates that relative workload (i.e., the percentage of exercise capacity) determines the change in core temperature with exercise. More than likely, a modest rise in core temperature represents a favorable adjustment that optimizes physiologic and metabolic functions.

In general, exercise at $50 \% \dot{\mathrm{~V}}_{2 \text { max }}$ in a comfortable environment increases core temperature to a new steady level of about $37.3 \mathrm{C}(99 \mathrm{~F})$, whereas work at $75 \%$ of maximum elevates temperature to $38.5 \mathrm{C}(101 \mathrm{~F})$, regardless of the ab solute exercise oxygen consumption. This means that a fit person generates more total energy (heat) in exercise than a less fit person at the same percentage of $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, yet both maintain about the same core temperature. The extra metabolic heat for the trained person dissipates via a larger sweat
output. However, the trained person exercises with a lower core temperature than the untrained person at identical exercise levels (same absolute $\dot{\mathrm{V}}_{2}$ ).

INTEGRATIVE QUESTION
What mechanisms explain how improved aerobic fitness increases exercise tolerance in a warm, humid environment?

## Water Loss in the Heat: Dehydration

Dehydration refers to body water loss from a hyperhydrated state to euhydration or from euhydration downward to hypohydration. A moderate exercise workout over 1 hour generally produces a sweat loss of 0.5 to 1.0 L . Greater water loss occurs from several hours of intense exercise in a hot environment. Exercise performed in less challenging thermal environments (e.g., cross-country skiing or swimming) still produce sweating. For swimmers and divers, water immersion also stimulates fluid loss through increased urine production. Non exercise-induced water loss occurs when power athletes (wrestlers, boxers, weightlifters, and rowers) aggressively attempt to thake weight through rapid weight loss induced by common dehydration techniquesexternal heat exposure via sauna, steam room, hot whirlpool or shower, fluid and food restriction, diuretic and laxative use, and vomiting. Athletes often combine these techniques, hoping to accelerate weight loss. The risk of heat illness greatly increases when a person begins to exercise in a dehydrated state.

Fluid deficits in the intracellular and extracellular compartments (hypovolemia) with hypohydration can rapidly reach levels that reduce the bodys ability to dissipate heat and increase the rate of heat storage and cardiovascular strain owing to reductions in sweating rate and skin blood flow for a


Male $\square$ Female

Figure 25.5 Relationship between esophageal temperature and (A) oxygen consumption (absolute exercise intensity expressed as power output) and (B) oxygen consumption as a percentage of $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max. }}$. (From Saltin B , Hermansen L. Esophageal, rectal, and muscle temperature during exercise. J Appl Physiol 1966;21:1757.)
given core temperature. Reduced heat tolerance severely compromises cardiovascular function and exercise capacity with intense exercise in hot environments. ${ }^{89,115}$ Sweat remains hypotonic to other body fluids, so the hypovolemia from sweating correspondingly increases plasma osmolality.

In terms of exercise performance, rapid weight loss through dehydration does not impair muscular strength (effects on muscular endurance remain equivocal) or a single bout of anaerobic power performance up to 60-seconds duration. ${ }^{18,42,88,134}$ Losing body water rapidly before exercising even improves muscular power and strength on a relative basis (per kg body mass). ${ }^{53}$ When intense exercise lasts longer than 1 minute, dehydration profoundly impairs physiologic function and optimal ability to train and compete. A moderate hypohydration equivalent to $1.5 \%$ body mass produced poorer intermittent all-out exercise performance than similar exercise in the euhydrated state. ${ }^{77}$ Dehydration associated with a $3 \%$ decrease in body weight also slows gastric emptying rate, thus increasing epigastric cramps and feelings of nausea.

## Magnitude of Fluid Loss

For an acclimatized person, water loss by sweating reaches a peak of about $3 \mathrm{~L} \cdot \mathrm{~h}^{-1}$ an hour during intense exercise in the heat and totals nearly 12 L on a daily basis. Several hours of intense sweating can produce sweat-gland fatigue that ultimately interferes with core temperature regulation. Elite marathon runners frequently experience fluid loss in excess of 5 L during competition, a loss equivalent to 6 to $10 \%$ of body mass. For a slower paced ultramarathon, the average fluid loss rarely exceeds 500 mL per hour. Even in a temperate climate of $10 \mathrm{C}(50 \mathrm{~F})$, soccer players lose an average of 2 L during a 90 -minute game. ${ }^{74}$ Acclimatized humans sustain their exceptional potential for evaporative cooling only with adequate fluid replacement. Table 25.4 provides the predicted sweating rates for individuals of different body weights running at various speeds in cold temperate and warm weather conditions.

Sports other than distance running induce a large sweat output and accompanying fluid loss. Football, basketball, and
hockey players lose large quantities of fluid during competition. Before a change in certification standards, high school wrestlers often lost 9 to $13 \%$ of preseason body weight prior to certification; the greatest portion of this weight loss came from voluntarily reducing water intake and excessive sweating just prior to the weigh-in. Collegiate wrestlers, excluding heavyweights, regained an average of 3.7 kg during the 20 hours between weigh-in and competition. ${ }^{117}$ In their desire to thake weight, high school and collegiate wrestlers usually competed in a dehydrated state, with reduced blood and plasma volumes. ${ }^{1,138}$ Transient, reversible mood alterations and impaired short-term memory also accompanied rapid weight loss in collegiate wrestlers. ${ }^{20}$

## Significant Consequences of Dehydration

Almost any dehydration impairs physiologic function and thermoregulation. Even a modest fluid loss of $2 \%$ body mass adversely affects exercise performance. ${ }^{28,31,86,132}$ As dehydration progresses and plasma volume decreases, peripheral blood flow and sweating rate diminish, making thermoregulation progressively more difficult. Preexercise dehydration equivalent to $5 \%$ of body mass increases rectal temperature and heart rate and decreases sweating rate, $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, and exercise capacity; it also attenuates multisetmultirepetition resistance exercise performance compared with exercise under normal hydration. ${ }^{56,113,120}$ Reduced central blood volume lowers ventricular filling pressure and helps to explain the elevated heart rate and 25 to $30 \%$ stroke volume reduction in the dehydrated state. An increase in heart rate does not offset the reduced stroke volume; consequently, cardiac output and arterial blood pressure decline.

Fluid loss becomes most apparent during exercise in hot, humid environments because the high vapor pressure of ambient air thwarts evaporative cooling. Figure 25.6 shows the linear dependency between sweating rate during rest and exercise) and the airs moisture content reflected by wet-bulb temperature (see In a Practical Sense, p. 617). Ironically, excessive sweat output in high humidity contributes little to cooling because of minimal evaporation.
$\begin{array}{ll}\text { TABLE 25.4 } & \begin{array}{l}\text { Predicted Sweating Rates }\left(\mathrm{L} \cdot \mathrm{H}^{-1}\right) \text { for Running at } 8.5 \text { to } 15.0 \mathrm{Km} \cdot \mathrm{H}^{-1} \text { in } \\ \text { Cool/Temperate }\left(\mathrm{TDB}^{a}=18 \mathrm{C}\right) \text { and Warm }(T D B=28 \mathrm{C}) \text { Weather }\end{array}\end{array}$ Cool/Temperate (TDB ${ }^{a}=18 \mathrm{C}$ ) and Warm (TDB $=28 \mathrm{C}$ ) Weather

| Body Weight (kg) | Climate | $\begin{gathered} 8.5 \mathrm{~km} \cdot \mathrm{~h}^{-1} \\ (5.3 \mathrm{mph}) \end{gathered}$ | $\begin{gathered} 10 \mathrm{~km} \cdot \mathrm{~h}^{-1} \\ (6.3 \mathrm{mph}) \end{gathered}$ | $\begin{gathered} 12.5 \mathrm{~km} \cdot \mathrm{~h}^{-1} \\ (7.9 \mathrm{mph}) \end{gathered}$ | $\begin{gathered} 15 \mathrm{~km} \cdot \mathrm{~h}^{-1} \\ (9.5 \mathrm{mph}) \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 50 | Cool/temperate | 0.43 | 0.53 | 0.69 | 0.86 |
|  | Warm | 0.52 | 0.62 | 0.79 | 0.96 |
| 70 | Cool/temperate | 0.65 | 0.79 | 1.02 | 1.25 |
|  | Warm | 0.75 | 0.89 | 1.12 | 1.36 |
| 90 | Cool/temperate | 0.86 | 1.04 | 1.34 | 1.64 |
|  | Warm | 0.97 | 1.15 | 1.46 | 1.76 |

[^47]
$\square$ Exercise: $350 \mathrm{kCal} \cdot \mathrm{h}^{-1} \square$ Rest: $80 \mathrm{kCal} \cdot \mathrm{h}^{-1}$
Figure 25.6 Effect of humidity (wet-bulb temperature) on sweat rate during rest and exercise in the heat. Ambient drybulb temperature was 43.4 C (110 F). (From lampietro PF. Exercise in hot environments. In: Shephard RJ, ed. Frontiers of fitness. Springfield, IL: Charles C Thomas, 1971.)

## Physiologic and Performance Decrements

Physiologic mechanisms contributing to dehydrationmediated exercise performance degradation include augmented hyperthermia, increased cardiovascular strain, altered metabolic and central nervous system functions, and increased perception of effort. ${ }^{114}$ Reduced peripheral blood flow and increased core temperature in exercise relate closely to dehydration level. A fluid loss equivalent to only $1 \%$ of body mass increases rectal temperature compared with the same exercise and normal hydration. For each liter of sweatloss dehydration, exercise heart rate increases $8 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, with a corresponding $1.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ decrease in cardiac output. ${ }^{21}$ A large portion of water lost through sweating comes from blood plasma, so circulatory capacity progressively decreases as sweat loss progresses. Fluid loss coincides with the following five factors:

1. Decreased plasma volume
2. Reduced skin blood flow for a given core temperature
3. Reduced stroke volume
4. Increased near-compensatory heart rate
5. General deterioration in circulatory and thermoregulatory efficiency in exercise

For exercise performance, dehydration equal to $4.3 \%$ of body mass reduced walking endurance by $48 \%$; concurrently, $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ decreased by $22 \%$. $^{22}$ These same experiments showed decreased endurance performance $(-22 \%)$ and $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ ( $-10 \%$ ) when dehydration averaged only $1.9 \%$ of body mass. Clearly, even modest dehydration imposes adverse thermoregulatory effects during exercise that relate to progressive deterioration in sports skill performance. ${ }^{5,6}$

## Diuretics

Diuretic-induced dehydration draws a greater percentage of water from the plasma than body water lost through sweating. In addition, drugs that cause diuresis markedly impair neuromuscular function; this does not occur with comparable fluid loss through exercise. Chemicals that induce vomiting and diarrhea for sudden weight loss trigger dehydration and promote excessive mineral loss with accompanying muscle weakness and impaired neuromuscular function.

## MAINTAINING FLUID BALANCE: REHYDRATION AND HYPERHYDRATION

Fluid replacement must focus on maintaining plasma volume so circulation and sweating progress at optimal levels. Ingesting fluid during exercise increases blood flow to the skin for more effective cooling, independent of any change in plasma volume. Prevention of dehydration and its consequences, especially hyperthermia, occurs only with an adequate and strictly observed water replacement schedule. ${ }^{116}$ Meeting this requirement often presents difficulties, because some coaches and athletes believe that ingesting water hinders performance. Left on their own, most individuals voluntarily replace only about half of the water lost in exercise $\left(<500 \mathrm{~mL} \cdot \mathrm{~h}^{-1}\right)$.

## Optimal Goals for Fluid Intake When Exercising

Goal of prehydrating: Start the activity euhydrated and with normal plasma electrolyte levels. This should be initiated when needed, at least several hours before the activity to enable fluid absorption and allow urine output to return to normal levels.
Goal of drinking during exercise: Prevent excessive dehydration ( $>2 \%$ body weight loss from water deficit) and excessive changes in electrolyte balance to avert compromising performance and health. During exercise, consuming beverages containing electrolytes and carbohydrate generally provide benefits over water alone.

American College of Sports Medicine Position Stand. Exercise and fluid replacement. Med Sci Sports Exerc 2007;39:377.

Adequate hydration provides the most effective defense against heat stress. The ideal hydration protocol requires balancing water loss with water intake, not pouring water over the head or body. No evidence indicates that restricting fluid intake during training in some way makes an athlete better able to adjust to subsequent work in the heat. A well-hydrated athlete always functions at a higher level than one who exercises in a dehydrated state.

Ingesting Éxtra water ( hyperhydration) before exercising in the heat offers thermoregulatory protection.

Hyperhydration delays hypohydration from inadequate fluid replacement during exercise, increases sweating during exercise, and produces a smaller rise in core temperature in uncompensable heat stress, where evaporative cooling is inadequate to maintain thermal balance. ${ }^{65}$ A practical way to promote acute preexercise hyperhydration involves the following:

1. Consume at least 500 mL of water before sleeping the night before exercising in the heat.
2. Consume another 500 mL upon awakening.
3. Consume an additional 400 to 600 mL of cold water 20 minutes before exercise.

An extended, systematic regimen of hyperhydration ( $4.5 \mathrm{~L} \cdot \mathrm{~d}^{-1}$ ) 1 week before soccer competition by elite young soccer players in Puerto Rico increased body water reserves (despite greater urine output) and improved temperature regulation during a soccer match in warm weather. ${ }^{102}$ The structured sequence of preexercise hyperhydration produced a 1.1 L greater total body fluid volume than with the athletes normal daily $2.5-\mathrm{L}$ fluid intake.

Preexercise hyperhydration does not replace the need for continual fluid replacement during exercise. In this regard, fluid temperature may play an augmenting role. Compared with fluid at body temperature of 37 C , ingesting a cold drink $(4 \mathrm{C})$ before and during exercise in the heat attenuated the increase in rectal temperature and reduced physiologic strain during exercise, which resulted in a $23 \%$ improved endurance capacity. ${ }^{68}$ The benefits of hyperhydration usually subside if the individual remains euhydrated during exercise. In distance running, for example, matching fluid loss with fluid intake becomes virtually impossible because only 800 to 1000 mL of fluid empty from the stomach each hour. This rate of stomach emptying does not match a water loss that can average nearly 2000 mL per hour. Under these conditions, preexercise hyperhydration proves beneficial.

## Does Exogenous Glycerol Provide a Benefit?

The three-carbon glycerol molecule achieved clinical notoriety (along with mannitol, sorbitol, and urea) for its role in producing osmotic diuresis. The capacity to influence water movement within the body makes glycerol effective in reducing excess fluid accumulation (edema) in the brain and eye.

When consumed with 1 to 2 L of water, glycerol facilitates intestinal water absorption and extracellular fluid retention, mainly in the plasma and interstitial fluid compartments. ${ }^{37,133}$ An expanded body fluid volume potentially sets the stage for fluid excretion from increased renal filtrate and urine flow. Because proximal and distal kidney tubules reabsorb large amounts of glycerol, much of the fluid portion of the increased renal filtrate is also reabsorbed; this averts marked diuresis and promotes hyperhydration.

Proponents of glycerol supplementation maintain that its hyperhydration effect reduces overall heat stress in exercise as reflected by increased sweating rate; this leads to a lower exercise heart rate and body temperature and enhanced endurance performance. Reducing heat stress with augmented
hyperhydration before exercise using glycerol plus water supplementation increases the safety of the participant. One gram of glycerol per kilogram of body mass with 1 to 2 L of water is the typical recommended preexercise glycerol dose; its hyperhydration effect lasts up to 6 hours.

Not all research demonstrates meaningful thermoregulatory benefits from glycerol hyperhydration over preexercise hyperhydration with plain water. ${ }^{65}$ For example, exogenous glycerol diluted in 500 mL of water consumed 4 hours before exercise failed to promote fluid retention or ergogenic effects. ${ }^{50}$ Also, no cardiovascular or thermoregulatory advantages result from consuming glycerol with small volumes of water during exercise. ${ }^{93}$ Side effects of exogenous glycerol ingestion include headache, nausea, dizziness, bloating, and light-headedness. A definitive conclusion about thermoregulatory benefits of exogenous glycerol awaits further research.

## Adequacy of Rehydration

Changes in body weight indicate water loss and adequacy of rehydration during and following exercise participation. Voiding small volumes of dark yellow urine with a strong odor qualitatively indicates inadequate hydration. Wellhydrated individuals typically produce large volumes of lightcolored urine without a strong smell.

The ideal condition replaces water losses from sweating during exercise at a rate close to or equal to sweating rate. Athletes can be weighed before and after practice. Each pound of weight lost represents $450 \mathrm{~mL}(15 \mathrm{fl} \mathrm{oz})$ of dehydration. Periodic water breaks during activity deter fluid depletion. Coaches and trainers must urge athletes to rehydrate because the thirst mechanism imprecisely monitors dehydration or the bodys fluid needs (see American College of Sports Medicine Clarifies Indicators for Fluid Replacement [ www.acsm-msse. org/]). The elderly generally require a longer time to rehydrate after dehydration. ${ }^{59}$ If a person relied entirely on thirst for rehydration, it could take several days to reestablish fluid balance following severe dehydration. Alcohol-containing beverages generally impede restoration of fluid balance, particularly if the rehydration fluid contains $4 \%$ or more alcohol. ${ }^{121,122}$

## fyi

## Optimize Hydration

## PREEXERCISE

Drink approximately 17 to 20 ounces 2 to 3 hours before activity
Consume another 7 to 10 ounces after the warmup ( 10 to 15 minutes before exercise).

## DURING EXERCISE

Drink approximately 28 to 40 ounces every hour of exercise ( 7 to 10 ounces every 10 to 15 minutes).
Rapidly replace lost fluids (sweat and urine) within 2 hours after activity to enhance recovery by drinking 20 to 24 ounces for every pound of body weight lost through sweating.

## Electrolyte Replacement: Added Sodium May Benefit Rehydration

Restoration of water and electrolyte balance in recovery occurs more rapidly by adding moderate-to-high amounts of sodium (between 20 and $60 \mathrm{mmol} \cdot \mathrm{L}^{-1}$ ) to the rehydration drink or combining solid food with appropriate sodium content with plain water. ${ }^{75,109}$ Adding a small amount of potassium ( $25 \mathrm{mmol} \cdot \mathrm{L}^{-1}$ ) may enhance water retention in the intracellular space and reestablish any extra potassium excretion that accompanies sodium retention by the kidneys. ${ }^{23,112}$ The ACSM recommends that sports drinks contain 0.5 to 0.7 g of sodium per liter of fluid consumed during exercise lasting more than 1 hour. A beverage that tastes good to the individual also contributes to voluntary rehydration during exercise and recovery. ${ }^{104,137}$

To restore fluid balance, the volume of ingested fluid following exercise must exceed by 25 to $50 \%$ the exercise sweat loss, because the kidneys continually form some urine regardless of hydration status. Pure water absorbed from the gut rapidly dilutes plasma sodium. In turn, decreased plasma osmolality stimulates urine production and blunts the normal sodium-dependent stimulation of the thirst mechanism. These responses are counter to the goal of rehydration. Without sufficient sodium in the beverage, excess fluid intake merely increases urine output without fully benefiting rehydration. ${ }^{123}$ Maintaining a relatively high plasma sodium concentration by adding sodium to ingested fluid sustains the thirst drive,
promotes retention of ingested fluids (lower urine output), and restores lost plasma volume more rapidly.

Figure 25.7 illustrates the effect of a rehydration beverage with added sodium on ingested fluid retention in recovery. Six healthy men exercised in a warm, humid environment until sweating produced a $1.9 \%$ weight loss. They then ingested one of four test drinks ( 2045 mL ) with sodium concentrations of either $2,26,52$, or $100 \mathrm{mmol} \cdot \mathrm{L}^{-1}$ (typical §ports drinks contain 1025 mmol sodium; normal plasma sodium concentration ranges between 138 and 142 mmol ) over a $30-$ minute period beginning 30 minutes after stopping exercise. From the 1.5 -hour urine sample onward, urine volume inversely related to the rehydration beverages sodium content. At completion of the study period, a difference in total body water content of 787 mL existed between trials using drinks with the lowest and highest sodium content. The drink containing 100 mmol sodium contributed to the greatest fluid retention.

With prolonged exercise in the heat, sweat loss can deplete the body of 13 to 17 g of salt ( $2.33 .4 \mathrm{~g} \cdot \mathrm{~L}^{-1}$ of sweat) daily, about 8 g more than typically consumed. It seems prudent in this deficit situation to replace the lost sodium by adding about one-third teaspoon of table salt to 1 L of water. Moderate exercise generally produces a negligible potassium loss in sweat. Even at competitive physical activity levels, potassium loss in sweat ranges between 5 and 18 mEq , which poses little or no immediate danger. ${ }^{23}$ With heavy sweating, increasing the intake of potassium-rich citrus fruits and


[^48]Figure 25.7 Cumulative urine output during recovery from exercise-induced dehydration. The oral rehydration beverages were four test drinks (equivalent to 1.5 times body weight loss, or 2045 mL ) containing sodium (and matching anion) in a concentration of either 2, 26, 52 , or $100 \mathrm{mmol} \cdot \mathrm{L}^{-1}$. (From Maughan RJ, Leiper JB. Sodium intake and post-exercise rehydration in man. Eur J Appl Physiol 1995;71:311.)
bananas replaces most potassium losses. Minor adjustments in food intake and electrolyte conservation by the kidneys adequately compensate for mineral loss through sweating.

## Whole-Body Precooling

Cold treatments that periodically apply cold towels to the forehead and abdomen during exercise or a cold shower before exercising in the heat improve heat transfer at the bodys surface only slightly above the same exercise without skin wetting. Whole-body precooling (core temperature decrease of $0.7 \mathrm{C}[1.26 \mathrm{~F}]$ ) with up to 60 minutes immersion in water at $23.5 \mathrm{C}(74 \mathrm{~F})$, on the other hand, increases subsequent exercise endurance in a hot, humid environment. Time to exhaustion inversely related to initial body temperature (lowered via precooling) and directly related to the rate of heat storage. ${ }^{40}$ Precooling with cold-water immersion enhanced the rate of heat storage and caused less thermoregulatory strainattenuated rise in skin and rectal temperatures and heart ratesduring exercise ${ }^{10,136}$ In addition, whole-body precooling of the skin by 5 to $6 \mathrm{C}(910.8 \mathrm{~F})$ without reduction in core temperature reduced thermal strain and increased distance cycled in 30 minutes under warm, humid conditions. ${ }^{57}$ In contrast, whole-body precooling provided no thermoregulatory benefit during a simulated triathlon ${ }^{9}$ or on the physiologic responses to a 90-minute soccer-specific exercise protocol under normal environmental conditions. ${ }^{30}$

## FACTORS THAT MODIFY HEAT TOLERANCE

Five factors interact to improve physiologic adjustments and exercise tolerance during environmental heat stress:

1. Acclimatization
2. Training status
3. Age
4. Gender
5. Body fat level

## Acclimatization

Relatively easy tasks performed in cool weather become taxing if attempted on the first hot day of spring. The early stages of preseason training for warm-weather sports often pose the greatest hazards for heat injury because thermoregulatory mechanisms have not adjusted to the dual challenge of exercise and environmental heat. Repeated exposure to hot environments when combined with exercise improves exercise capacity, with less discomfort upon subsequent heat exposure. ${ }^{97,113}$

The term heat acclimatization describes the collective physiologic adaptive changes that improve heat tolerance. Data from a classic study in the early 1960s show that major acclimatization occurs during the first week of heat exposure, with full acclimatization thereafter (Fig. 25.8). The process


Figure 25.8 Average rectal temperature, heart rate, and sweat loss during 100 minutes of daily heat-exercise exposure for 9 days. On day 0 , the men walked on a treadmill at an exercise intensity of $300 \mathrm{kCal} \cdot \mathrm{h}^{-1}$ in a cool climate. Thereafter, they performed the same daily exercise in the heat at 48.9 C ( 26.7 F wet bulb). (From Lind AR, Bass DE. Optimal exposure time for development of acclimatization to heat. Fed Proc 1963;22:704.)
requires only 2 to 4 hours of daily heat exposure. The first several sessions in the heat should include 15 to 20 minutes of light-intensity physical activity. Thereafter, exercise sessions increase in duration and intensity.

## INTEGRATIVE QUESTION

Your Maine, U.S. based soccer team competes in Hawaii in early spring. Discuss how you would prepare the team to compete in this hot humid environment making all precompetition preparations (1) at your school or (2) elsewhere, if time, money, and travel were not considerations.

Table 25.5 summarizes the main physiologic adjustments during heat acclimatization. Optimal acclimatization requires adequate hydration. During exercise, larger quantities of blood flow to cutaneous vessels to facilitate heat transfer from the core to periphery. A more effective cardiac output distribution also helps stabilize blood pressure during exercise. A lowered threshold for sweating complements these ¿irculatory acclimatizations. Consequently, cooling begins before core temperature increases appreciably. Sweating capacity, the most significant factor for heat acclimatization, increases early and nearly doubles after 10 days of heat exposure; sweat also becomes more dilute (less salt lost) and distributes more evenly over the skin surface. Concurrently, heat acclimatization reduces sodium loss from the kidneys. Adjustments in circulation and evaporative cooling enable the heat-acclimatized person to exercise with lower skin and core temperatures and heart rates. A lower exercise core temperature requires diversion of less blood to the skin, thus freeing a larger percentage of the cardiac output for active muscles. Acclimatization also reduces carbohydrate use in exercise, a response consistent with acclimatization-induced plasma epinephrine reduction. ${ }^{36}$

The major benefits of acclimatization dissipate within 2 to 3 weeks after returning to a more temperate environment.

## Training Status

Exercise-induced ínternal heat stress in a cool environment induces adjustments in peripheral circulation and evaporative cooling qualitatively similar to training in hot ambient temperatures. These training adaptations facilitate elimination of metabolic heat generated by exercise and generally occur with an 8- to 12 -week training period at an exercise intensity above $50 \%$ of aerobic capacity. This makes well-conditioned men and women living in a temperate climate respond more effectively to sudden, severe heat stress than sedentary counterparts. ${ }^{4}$ Exercise training increases the sensitivity and capacity of the sweating response so that sweating begins at a lower core temperature, hence producing larger volumes of more-dilute sweat, which thus conserves a variety of minerals. ${ }^{19}$ This results partly from intrinsic adaptations in the sweat glands. Concurrently, a training-induced adjustment in cutaneous circulation provides greater skin blood flow at a given internal temperature or percentage of $\dot{\mathrm{V}}{ }_{2 \text { max }}$, independent of age. ${ }^{54}$ Plasma and extravascular fluid volumes also increase during the initial stages of aerobic training. ${ }^{70,76}$ Enhanced physical fitness also sustains better blood flow to the gastrointestinal tract. This maintains the normal barrier to endotoxin movement from the gut lumen into the plasma, blunting the potential for endotoxin-induced fever that could aggravate exercise hyperthermia. ${ }^{111}$ The thermoregulatory benefit for exercise training occurs provided the individual remains fully hydrated during exercise. ${ }^{113}$

Exercise heat conditioning in cool weather offers fewer benefits than acclimatization from similar hot weather exercise training. A physically active person cannot achieve full heat acclimatization without exposure to environmental heat stress. Athletes who train and compete in hot weather have a distinct thermoregulatory advantage over athletes who

TABLE 25.5 Physiologic Adjustments During Heat Acclimatization

## Acclimatization Response <br> Effect

Improved cutaneous blood flow
Effective distribution of cardiac output

Lowered threshold for start of sweating
More effective distribution of sweat over skin surface
Increased sweat output
Lowered salt concentration of sweat
Lower skin and core temperatures and heart rate for standard exercise Less reliance on carbohydrate catabolism during exercise

Transports metabolic heat from deep tissues (core) to shell
Appropriate circulation to skin and muscles to meet demands of metabolism and thermoregulation; greater blood pressure stability during exercise Evaporative cooling begins early in exercise

Optimum use of effective body surface for evaporative cooling Maximizes evaporative cooling Dilute sweat preserves electrolytes in extracellular fluid
Frees greater proportion of cardiac output to the active muscles Carbohydrate sparing


## $\square$ Young males $\square$ Old males $\square$ Young females $\square$ Old females

Figure 25.9 Heart rate during moderate exercise in the heat in young and older men and women. Dry-bulb ambient temperature was 33.5 C (92.3 F) and wet-bulb was 28.5 C (83.3 F). (Modified from Henshel A. The environment and performance. In: Simonsen E, ed. Physiology of work capacity and fatigue. Springfield, IL: Charles C Thomas, 1971.)
train in cool climates and only periodically compete in hot weather.

## Age

Debate concerns the effects of aging on tolerance and acclimatization to moderate heat stress. An early study exposed men and women ages 60 to 93 years to 70 minutes of heat stress during exercise at intensities that ranged from 2 to 5 METs. Figure 25.9 shows the relationship between heart rate and exercise intensity in the heat for these older subjects and young men and women. The less fit elderly subjects exercised at higher heart rates than young adults of the same gender. However, environmental heat imposed no greater physiologic strain for the older groups because body temperature increased an average of only $0.3 \mathrm{C}(0.54 \mathrm{~F})$, compared with $0.2 \mathrm{C}(0.36 \mathrm{~F})$ for the younger group. Testing elderly subjects in the spring and fall evaluated their extent of natural heat acclimatization during the summer months. After the summer, all subjects had lower heart rates during the standard thermal exercise stress.

Comparisons between young and middle-aged competitive runners indicate no age-related decrements in thermoregulation during marathon running. ${ }^{106}$ Thermoregulatory function was not impaired in trained 50 -year-old men compared with younger men. ${ }^{99}$ Likewise, sweating capacity for men ages 58 to 84 years adequately regulated body temperature during prolonged desert walks. ${ }^{26}$ Research that controls for body size and composition, aerobic fitness, hydration, degree of acclimatization, and chronological age shows little or no age-related decrements on thermoregulatory capacity or heat-stress acclimatization.

## Age-Related Differences Do Exist

Several age-related factors affect thermoregulatory dynamics despite equivalence between young and older adults in capacity to regulate core temperature during heat stress. Aging delays the onset of sweating and blunts the magnitude of the sweating response in one of three ways ${ }^{52,58}$ :

1. Modified sensitivity of thermoreceptors
2. Limited sweat gland output per se
3. Dehydration-limited sweat output with insufficient fluid replacement

Aging also alters the intrinsic structure and function of the skin and its vasculature. ${ }^{47,51,61,73}$ Aging impairs the mechanisms that mediate cutaneous vasodilation, which results in an attenuated vasodilation response. Age-related vascular changes include depressed peripheral sensitivity that impairs cutaneous vasodilation from two factors:

1. Smaller release of vasomotor tone
2. Less active vasodilation once sweating begins

Older athletes show a 25 to $40 \%$ lower skin blood flow with increased core temperature than do younger athletes. ${ }^{60}$

Contributing factors include the combined effects of a lower cardiac output and reduced blood distribution from the splanchnic and renal circulations. ${ }^{84}$ Older adults do not recover from dehydration as readily as do younger counterparts, because of a reduced thirst drive. This places these elderly individuals in a chronic state of hypohydration (with a less-than-optimal plasma volume), which could impair thermoregulatory dynamics. An altered thirst mechanism and shift in the operating point for control of body fluid volume and composition also decrease total blood volume in older individuals. ${ }^{24,72}$

## Children

Children sweat less and maintain higher core temperatures during heat stress than adolescents and adults, even though children possess a larger number of heat-activated sweat glands per unit skin area. ${ }^{7,34}$ A reduced sweating response likely results from underdeveloped peripheral mechanisms, including the sweat glands and their surrounding tissues, rather than a depressed central drive for sweating. ${ }^{119}$ The age difference in thermoregulation lasts through puberty; it generally does not limit exercise capacity except during extreme environmental heat stress. ${ }^{107}$ Sweat composition differs between children and adults; childrens sweat shows higher sodium and chlorine concentrations and lower concentrations of lactate, $\mathrm{H}^{+}$, and potassium. ${ }^{34,83}$ From a practical standpoint, exercise intensity should decrease for children exposed to a hot environment; they also require more time to acclimatize than older competitors.

## Gender

Early comparisons of thermoregulation in men and women indicated that men exhibited greater tolerance to environmental
heat stress during a standard bout of exercise. A major flaw in this research required that women exercise at a higher percentage of aerobic capacity than men. When researchers controlled for this factor and compared men and women of equal fitness (or exercised both at the same $\% \dot{\mathrm{~V}} \mathrm{O}_{2 \text { max }}$ ), thermoregulatory gender differences became less pronounced. ${ }^{29,49}$ In essence, women tolerate the thermal stress of exercise at least as well as do men of comparable aerobic fitness and level of acclimatization; both genders also acclimatize to the same degree.

## Sweating

Sweating represents the distinct gender difference in thermoregulation. Women sweat less prolifically than men, despite possessing more heat-activated sweat glands per unit skin area. Women start to sweat at higher skin and core temperatures and produce less sweat than men do with a comparable heat-exercise load, even after equivalent acclimatization.

Evaporative Cooling Versus Circulatory Cooling. Women tolerate heat much like men of equal aerobic fitness at the same exercise level, despite a lower sweat output. Women probably use circulatory mechanisms for heat dissipation, whereas men make greater use of evaporative cooling. Clearly, producing less sweat to maintain thermal balance protects women from dehydration during exercise at high ambient temperatures.

Ratio of Body Surface Area to Body Mass. The typically smaller female has a relatively large external surface per unit of a body mass exposed to the environment. This factor conveys favorable dimensional characteristic for heat dissipation. Under identical conditions of heat exposure, women tend to cool faster than men. Children also possess a similar geometric advantage during heat stress from their larger ratio of surface area-to-mass than adults.

Menstruation. Phases of the menstrual cycle influence cutaneous vascular control that alters skin blood flow and sweating response during rest and physical activity. ${ }^{15,127}$ For example, a higher core temperature threshold initiates sweating during the luteal phase at both $60 \%$ and $80 \%$ of aerobic capacity. ${ }^{63}$ An upward resetting of the thermoregulatory setpoint for sweating occurs during the luteal phase and probably reflects a unique feature of hormone dynamics throughout the cycle. ${ }^{46,127}$ An upward shift of approximately 0.4 C $(0.72 \mathrm{~F})$ in oral temperature persists for about 6 days during the luteal phase. The change in thermoregulatory sensitivity during this phase does not impair ability to exercise intensely. ${ }^{71}$ In addition, no changes in the level of exercise performance, lactate threshold, or ventilatory threshold are associated with the menstrual cycle. ${ }^{124}$

## Body Fat Level

Excess body fat represents a liability when exercising in the heat. Because the specific heat of fat exceeds muscle tissue,
fat increases the insulatory quality of the body shell and retards heat conduction to the periphery. The large, overly fat person also has a smaller ratio of body surface area-to-body mass for effective sweat evaporation than a leaner, smaller person with less body fat.

Excess body fat directly adds to the metabolic cost of weight-bearing activities. Compounding this effect by adding the weight of sports equipment (e.g., American football, ice hockey, or lacrosse gear), intense competition, and a hot, humid environment places the overly fat person at a distinct disadvantage for temperature regulation and exercise performance. ${ }^{98}$ Fatal heat stroke (see next section) occurs 3.5 times more frequently in excessively overweight young adults than in individuals of average body size.

## INTEGRATIVE QUESTION

> Describe the ideal physical and physiologic characteristics that minimize heat injury risk while exercising in the heat.

## COMPLICATIONS FROM EXCESSIVE HEAT STRESS

Nearly 400 people die each year in the United States from excessive heat stress, and about half of these are men and women aged 65 and older. If the normal signs of heat stress go unheededthirst, tiredness, grogginess, and visual disturbanceseardiovascular compensation begins to fail. This initiates a cascade of disabling complications collectively termed heat illness. Heat cramps, heat exhaustion, and heat stroke constitute the major heat illnesses in order of increasing severity. Heat-related disabilities occur more frequently among overweight, unacclimatized, and poorly conditioned individuals, including those who exercise when dehydrated. ${ }^{2,13,100}$ No clear-cut demarcation exists between maladies because symptoms often overlap; exercise-induced heat injury frequently results from the cumulative effects of multiple adverse interacting stimuli. ${ }^{126}$ TABLE 25.6 summarizes the salient features of the cardiovascular response patterns during three distinct stages of exercise hyperthermia. These stageseempensation, crisis, and failureapply to heat exhaustion and heat stroke. The response patterns are broadly classified as either central circulatory, peripheral, or central nervous system effects. With serious heat illness, only immediate corrective action reduces heat stress until medical help arrives. ${ }^{27}$

## Heat Cramps

Heat cramps (severe involuntary, sustained, and spreading muscle spasms) occur during or after intense physical activity, usually in the specifically exercised muscles. Core temperature often remains within normal range. An imbalance in the bodys fluid level and electrolyte concentrations produces this form of heat illness. Crampers tend to have high sweat rates

## TABLE 25.6 Cardiovascular Responses During the Three Stages of Exercise Hyperthermia


and/or high sweat sodium concentrations. With heat cramps, body temperature does not necessarily increase. Prevention involves two factors:

1. Providing plentiful water that contains salt
2. Increasing daily salt intake (e.g., adding salt to foods at mealtime) several days before heat stress

Sweating causes electrolyte loss during prolonged heat exposure. Failure to replenish these minerals often leads to muscle pain and spasm, most commonly in the abdomen and extremities. Drinking copious amounts of water and increasing daily salt intake several days before heat stress generally prevents this heat-related malady. ${ }^{32}$

## Heat Exhaustion

Heat exhaustion usually develops in unacclimatized persons during the first summer heat wave or with the first hard training session on a hot day. Exercise-induced heat exhaustion occurs from ineffective circulatory adjustments compounded by depletion of extracellular fluid, principally plasma volume from excessive sweating. Blood usually pools in the dilated peripheral vessels; this drastically reduces the central blood volume necessary to maintain cardiac output. Characteristics of heat exhaustion include a weak and rapid pulse, low blood pressure in the upright position, headache, dizziness, and general weakness. Sweating may decrease somewhat, but core temperature does not rise to dangerous levels (i.e., $>40 \mathrm{C}$, or $104 \mathrm{~F})$. A person who experiences symptoms of heat exhaustion
should stop exercising and move to a cooler environment. Intravenous therapy replenishes fluid most effectively.

## Heat Stroke

Heat stroke, the most serious and complex of the heatstress maladies, requires immediate medical attention. It reflects failure of the heat-regulating mechanisms from an excessively high core temperature and can affect seemingly healthy adults even in a relatively cool environment. ${ }^{3,33,101,105}$ The classic form of heat strokeeore temperature $>40.5 \mathrm{C}$ (105 F), altered mental status, absence of sweatingusually occurs during heat waves. It affects young children, the elderly, and those with chronic diseases. In classic heat stroke, environmental heat overloads the bodys heat-dissipating mechanisms. Severe heat stress also produces a continuum of potentially negative alterations in the immune system and in leukocyte adhesion and activation processes (unrelated to elevated catecholamine levels). ${ }^{44}$ One in three individuals who survive a near-fatal case of classic heat stroke remains permanently disabled with multisystem organ dysfunction. ${ }^{25}$

Exertional heat stroke is a state of extreme hyperthermia from the interactive effects of two factors:

1. Metabolic heat load in exercise
2. Challenge for heat dissipation from a hot humid environment

When thermoregulation fails, sweating diminishes, the skin becomes dry and hot, and body temperature rises to
41.5 C (106.7 F) and above. This places an inordinate strain on cardiovascular function. The often subtle symptoms compound the complexity of emergency hyperthermia. With intense exercise, usually by young, highly motivated individuals, sweating may progress but body heat gain overpowers the avenues for heat loss. Other predisposing factors for exertional heat stroke include poor fitness status, obesity, inadequate acclimatization, sweat gland dysfunction, dehydration, and infectious disease. If left untreated, the disability progresses rapidly and death ensues from circulatory collapse and damage to the central nervous system and other organ systems. While awaiting medical treatment, aggressive steps must be taken to lower core temperature because mortality relates to the magnitude and duration of hyperthermia. Immediate treatment includes fluid replacement and body cooling with alcohol rubs, application of ice packs to the neck area, and whole-body immersion in cold or even ice water, the gold standard for treating exertional heat stroke. ${ }^{14,92,94}$ No attempt should be made to slow the respiratory rate because a rapid rate of breathing compensates for metabolic acidosis. Prudent treatment also includes specific drug therapy to counter possible endotoxin effects precipitated by heat stroke pathology. ${ }^{43}$

## Oral Temperature Unreliable

Oral temperature inaccurately measures core temperature after strenuous exercise. Rectal temperature following a 14-mile race in a tropical climate averaged 39.7 C (103.5 F), while oral temperature surprisingly remained normal at 36.6 C (98 F). ${ }^{110}$ Part of the discrepancy lies in the effects on oral temperature of evaporative cooling of the mouth and airways during high levels of exercise pulmonary ventilation.

## Summary

1. Core temperature normally increases during exercise; the relative stress of exercise determines the magnitude of the increase. A well-regulated temperature increase creates a more favorable environment for physiologic and metabolic functions.
2. Excessive sweating compromises fluid reserves to create a relative state of dehydration.
3. Sweating without fluid replacement decreases plasma volume, which leads to circulatory dysfunction and a precipitous rise in core temperature.
4. Exercise in a hot, humid environment poses a considerable thermoregulatory challenge because the large sweat loss in high humidity contributes little to evaporative cooling.
5. Fluid loss of more than $4 \%$ of body weight impedes heat dissipation, compromises cardiovascular function, and diminishes exercise capacity.
6. Adequate fluid replacement maintains plasma volume so circulation and sweating progress optimally.
7. The ideal replacement schedule during exercise matches fluid intake to fluid loss, a process effectively monitored by changes in body weight.
8. The small intestine can absorb about 1000 mL of water each hour. A small amount of electrolytes in the rehydration beverage facilitates fluid replacement more than drinking plain water.
9. The diet generally replaces minerals lost through sweating. With prolonged exercise in the heat, adding a small amount of salt to the replacement fluid ( $1 \mathrm{tsp} \cdot \mathrm{L}^{-1}$ ) facilitates sodium and fluid replenishment.
10. Repeated heat stress initiates thermoregulatory adjustments that improve exercise capacity and reduce discomfort on heat exposure. Such heat acclimatization triggers favorable cardiac output distribution while increasing sweating capacity. Ten days of heat exposure promotes full acclimatization.
11. Aging affects thermoregulatory functions but does not appreciably alter temperature regulation during exercise or acclimatization to moderate heat stress.
12. Women and men show equivalent thermoregulation during exercise when controlled for levels of fitness and acclimatization. Women produce less sweat than men when exercising at the same core temperature.
13. Heat cramps, heat exhaustion, and heat stroke constitute the major heat illnesses. Heat stroke, a medical emergency, is the most serious and complex of these maladies.
14. Oral temperature after exercising inaccurately measures core temperature because of evaporative cooling of the mouth and airways with high levels of pulmonary ventilation during exercise and recovery.

## Part 3 THERMOREGULATION AND ENVIRONMENTAL COLD STRESS DURING EXERCISE

## EXERCISE IN THE COLD

Human exposure to extreme cold produces significant physiologic and psychologic challenges. Cold ranks high among the differing terrestrial environmental stressors for its potentially lethal consequences. Core temperature becomes further compromised during chronic exertional fatigue and sleep loss, inadequate nourishment, reduced tissue insulation, and a depressed shivering heat production. ${ }^{140}$ Table 25.7 presents the physiologic changes associated with hypothermia that ranges from mild to severe.

Water provides an excellent medium to study physiologic adjustment to cold because it conducts heat about 25 times faster than air at the same temperature. Consequently, immersion in cool water of only 28 to $30 \mathrm{C}(8286 \mathrm{~F}$ ) imposes a thermal stress that rapidly initiates an array of thermoregulatory adjustments. Persons frequently shiver if they remain inactive in a pool or ocean environment because of a large conductive heat loss to the water. Even when exercising at moderate intensity in cold water, exercise metabolism often

TABLE 25.7 Core Temperature and Associated Physiological Changes that Occur as Core Temperature Falls; Individuals Respond Differently at Each Level of Core Temperature

|  | Core Temperature |  |  |
| :--- | :---: | :---: | :--- |
| Stage | F | C | Physiological Changes |
| Normothermia | 98.6 | 37.0 | No noticeable effect |
| Mild hypothermia | 95.0 | 35.0 | Maximal shivering, increased blood pressure |
|  | 93.2 | 34.0 | Amnesia; dysarthria; poor judgment; behavior |
|  |  |  | change |
| Moderate hypothermia | 91.4 | 33.0 | Ataxia; apathy |
|  | 89.6 | 32.0 | Stupor |
|  | 87.8 | 31.0 | Shivering ceases; pupils dilate |
| Severe hypothermia | 85.2 | 30.0 | Cardiac arrhythmias; decreased cardiac output |
|  | 85.2 | 29.0 | Unconsciousness |
|  | 82.4 | 28.0 | Ventricular fibrillation likely; hypoventilation |
|  | 80.6 | 27.0 | Loss of reflexes and voluntary motion |
|  | 78.8 | 26.0 | Acid base disturbances; no response to pain |
|  | 77.0 | 25.0 | Reduced cerebral blood flow |
|  | 75.2 | 24.0 | Hypotension; bradycardia; pulmonary edema |
|  | 73.4 | 23.0 | No corneal reflexes; areflexia |
|  | 66.2 | 19.0 | Electroencephalographic silence |
|  | 64.4 | 18.0 | Asystole |
|  | 15.2 | Lowest infant survival from accidental hypothermia |  |
|  | 56.2 | 13.7 | Lowest adult survival from accidental hypothermia |

From American College of Sports Medicine Position Stand. Prevention of cold injuries during exercise. Med Sci Sports Exerc 2007;38:2012.
generates insufficient heat to counter the large thermal drain, especially during swimming because heat transfer by convection increases when water moves past the skin surface.

Light and moderate exercise in cold water produces higher oxygen consumptions and lower body temperatures than identical exercise in warmer water. ${ }^{79,129}$ For example, swimming at a submaximal pace in a flume at $18 \mathrm{C}(64 \mathrm{~F})$ requires 500 mL of oxygen more per minute than swimming at the same speed in $26 \mathrm{C}(79 \mathrm{~F})$ water. ${ }^{95}$ The additional oxygen consumption directly relates to the energy cost of shivering as the body combats heat loss in colder water. Shivering also serves an important role in recovering from hypothermia; it attenuates the typical postexercise decline in core temperature and facilitates core rewarming. ${ }^{39}$ The body shows remarkable flexibility in oxidative fuel selection during sustained cold exposure, but shifts occur in shivering substrate from lipid to carbohydrate with intense cold stress. ${ }^{45}$

## Body Fat, Exercise, and Cold Stress

Differences in body fat content among individuals influence physiologic function in the cold during rest and exercise. ${ }^{80,130}$ Successful ocean swimmers possess a larger amount of subcutaneous fat than highly trained non-ocean swimmers. The additional fat increases the effective insulation in cold water when peripheral blood diverts from the bodys shell to the core. With this advantage, athletes with
greater thermal insulation from fat accretion swim in cool ocean water with almost no decline in core temperature. For leaner swimmers, exercise does not generate sufficient heat to offset heat drain to the water, and the bodys core cools.

Consider the stress from $\mathfrak{E o l d}$ as highly relative. The physiologic strain from cold-water and cold-land environments depends on ones level of metabolism and the body fats resistance to heat flow. A person with excess body fat who rests comfortably immersed to the neck in 26 C (78.8 F) water may sweat about the forehead during vigorous exercise. For this person, $18 \mathrm{C}(64.4 \mathrm{~F})$ provides a more favorable water temperature for high-intensity exercise. For a lean person, water at $18 \mathrm{C}(64.4 \mathrm{~F})$ proves debilitating during rest and exercise. An optimum water temperature exists for each person and for each physical activity. For most persons, water temperatures between $26 \mathrm{C}(78.8 \mathrm{~F})$ and $30 \mathrm{C}(86 \mathrm{~F})$ allow effective heat dissipation in sustained exercise without compromising exercise capacity from large deviations in core temperature. Even colder water may optimize performance in shorter term, near-maximal exercise, particularly for fatter people. For some as yet unexplained reason, older adults do not withstand the challenge of cold during rest and lowintensity exercise as effectively as younger counterparts with similar aerobic capacities. ${ }^{35}$ Age-related variations in body composition or hormonal functions may provide part of the explanation.

## Children and Cold Stress

Cold water provides an exceptionally stressful thermoregulatory environment for children. A childs distinctly large ratio of body surface area-to-mass facilitates heat loss in a warm environment but becomes a liability during cold stress because body heat dissipates rapidly. During exercise in the less stressful cold-air environment, children rely on two mechanisms to compensate for their relatively large body surface area: ${ }^{125}$

1. Augmented energy metabolism
2. More effective peripheral vasoconstriction in the limbs

## ACCLIMATIZATION TO COLD

Humans possess much less capacity for adaptation to longterm cold exposure than to prolonged heat exposure. The basic response of Eskimos and Lapps involves avoiding the cold or minimizing its effects. To this end, their clothing provides a near-tropical microclimate; the temperature inside an igloo typically averages $21 \mathrm{C}(70 \mathrm{~F})$ despite freezing outside temperatures with gale-force winds or freezing rain.

## The Ama

Studies of the Ama, the women divers of Korea and southern Japan, indicate some human cold adaptation. ${ }^{48}$ These women tolerate daily prolonged exposure to diving for food in cold water that in winter averages $10 \mathrm{C}(50 \mathrm{~F})$. During the summer, when water temperature rises to $25 \mathrm{C}(77 \mathrm{~F})$, the Ama perform three bouts of diving, each 45 minutes long. In winter, they perform only one 15 -minute dive daily. The women generally remain in the water until oral temperature declines to about 34 C (93.2 F). Figure 25.10A shows skin and core temperature responses of the Ama relative to time in the water. Mean skin and mean body temperatures always remained lower during the winter dives. Figure 25.10B shows the relationship between water temperature and coldest water temperatures when at least $50 \%$ of the Ama and nondiving Korean women and men started shivering. The response curve for the Ama (light blue) shifted to the right, clearly indicating a blunted thermogenic response (higher shivering threshold) until water temperature reached about $28 \mathrm{C}(82.4 \mathrm{~F})$. An elevated resting metabolism may contribute to how the Ama tolerate extreme cold. In winter, resting metabolic rate increased by about $25 \%$ compared with nondiving women from the same country. Interestingly, the Ama and nondiving female counterparts had equivalent body fat percentages. This suggests that circulatory adaptations aid the Ama by retarding heat transfer from the core to the skin during cold-water immersion.

## Other Examples of Cold Adaptation

A type of general cold adaptation occurs with regular and prolonged cold-air exposure. In this situation, heat production does not balance heat loss, and the person regulates at a lower


Figure 25.10 A. Differences in rectal temperature, mean skin temperature, and mean body temperature related to water temperature during summer and winter in Ama divers upon resurfacing from a dive. (Modified from Kang DH, et al. Energy metabolism and body temperature of the Ama. J Appl Physiol 1965;18:483.) B. Shivering response in professional Ama divers compared with nondiving Korean men and women at different immersion temperatures. The point where the lines cross the horizontal yellow line at 50 indicates the water temperature when $50 \%$ of a group began to shiver (Modified from Hong SK. Comparison of diving and nondiving women of Korea. Fed Proc 1963;22:831.)
core temperature during cold stress. Some peripheral circulatory adaptations also reflect a form of acclimation with severe local cold exposure. ${ }^{66,69}$ Repeated cold exposure of the hands or feet increases blood flow through these tissues during cold stress. This commonly occurs in fishermen who routinely handle nets and fish in cold water. ${ }^{96}$ Local adaptations actually facilitate heat loss from the periphery but provide a selfdefense because a vigorous circulation of warm blood in exposed tissue thwarts tissue damage from localized hypothermia. Long-term cold exposure may also blunt the typical depression of immune responses with acute cold stress. ${ }^{62}$ Improved physical fitness (high aerobic capacity and relatively large muscle mass) enhances thermoregulatory defense against cold stress to produce a larger shivering response and earlier (more sensitive) onset of shivering with cold exposure. ${ }^{8}$

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## Acclimatization to Cold

Shivering occurs at a lower body temperature because more heat is generated without shivering Improved ability to sleep in the cold Changes in peripheral blood flow distribution that either conserve heat in the core or warm the extremities to prevent cold injury

## HOW COLD IS TOO COLD?

Cold injuries from overexposure continue to rise because of increased participation by the general population in ice skating, ice fishing, cross-country skiing, snowboarding, snowmobiling, and all-season walking, hiking, jogging, and cycling. Pronounced peripheral vasoconstriction during severe cold exposure causes dangerously low skin and extremity temperatures, particularly when compounded by marked increases in convective and conductive heat loss. Predisposing factors to frostbite include alcohol use, low physical fitness, fatigue, dehydration, and poor peripheral circulation. ${ }^{103}$ Early warning signs of cold injury include tingling and numbness in the fingers and toes or a burning sensation in the nose and ears. Overexposure from failure to heed these warning signs leads to frostbite; in the extreme, irreversible damage occurs that requires surgical removal of the damaged tissue. From military operations and occupational perspectives, application of external heat to the torso during cold exposure can overcome the local effects of environmental cold and maintain fingers and toes at a comfortable temperature for up to 3 hours with exposure to $-15 \mathrm{C}(5 \mathrm{~F}) .{ }^{11}$

## INTEGRATIVE QUESTION

What information contributes to predicting an individuals survival time during extreme cold exposure?

In severe cold stress (e.g., near drowning in prolonged cold-water submersion), the brain experiences significant decrements in temperature, which reduce its oxygen needs. The central nervous system also benefits from a redistribution of blood from tissues that compromise their supply for relatively long periods. Other responses include potential benefits from the mammalian dive reflex (see Chapter 26, p. 650) and possibly cold-induced changes in neurotransmitter release. ${ }^{38}$

## INTEGRATIVE QUESTION

Explain the greater likelihood for resuscitation and survival from cold-water drowning than from drowning in warmer water.

## The Wind-Chill Temperature Index

One dilemma in evaluating the thermal quality of an environment relates to the inadequacy of ambient temperature alone to assess coldness. Many of us have experienced the chilling winds of a spring day even though air temperature remained well above freezing. In contrast, a calm subfreezing day may feel comfortable. Wind makes the differenceair currents on a windy day magnify heat loss because the warmer insulating air layer surrounding the body continually exchanges with cooler ambient air.

The wind-chill temperature index, presented in Figure 25.11 has been used by the National Weather Service since 1973 and was modified in 2001. Based on advances in science, technology, and computer modeling, the 2001 revised formula provides a more accurate, understandable, and useful way to understand the dangers from winter winds and freezing temperatures and provides frostbite threshold values. ${ }^{85}$ For example, a $1 \mathrm{C}(30 \mathrm{~F})$ ambient air reading is equivalent to $12.7 \mathrm{C}(9 \mathrm{~F})$ with a wind speed of 25 mph , while a $12.2 \mathrm{C}(10 \mathrm{~F})$ reading equals $23.8 \mathrm{C}(-11 \mathrm{~F})$ at the same wind velocity. If a person runs, skis, or skates into the wind, the effective cooling increases directly with forward velocity. Thus, running at 8 mph into a $12-\mathrm{mph}$ headwind creates the equivalent of a $20-\mathrm{mph}$ wind speed. Conversely, running at 8 mph with a $12-\mathrm{mph}$ wind at ones back creates a relative wind speed of only 4 mph . The white zone in the left of the figure denotes relatively little danger from cold injury for a properly clothed person. In contrast, the yellow-, orange-, and red-shaded zones indicate frostbite threshold values; the danger to exposed flesh increases, especially for the ears, nose, and fingers, when moving to the right of the chart. In the red-shaded zone, the equivalent wind-chill temperatures pose serious risk of exposed flesh freezing within minutes.

## Respiratory Tract During Cold-Weather Exercise

Cold ambient air generally poses no special danger of damaging respiratory passages. Even in extreme cold, incoming air warms to between $26 \mathrm{C}(78.8 \mathrm{~F})$ and $32 \mathrm{C}(89.6 \mathrm{~F})$ as it


Figure 25.11 The wind-chill temperature index. The proper way to evaluate the coldness of an environment. Figure shows the wind chill temperatures for the relative risk of frostbite and the predicted times to freezing of exposed facial skin. Wet skin exposed to wind will cool even faster, and if the skin is wet and exposed to wind, the ambient temperature used for the wind-chill table should be $10^{\circ} \mathrm{C}(50 \mathrm{~F})$ lower than the actual ambient temperature. (From American College of Sports Medicine Position Stand. Prevention of cold injuries during exercise. Med Sci Sports Exerc 2006;38:2012.)
reaches the bronchi, although values as low as 20 C ( 68 F ) have been observed with breathing large volumes of cold, dry air. ${ }^{82}$ Warming an incoming breath of cold air greatly increases its capacity to hold moisture. Thus, humidification of inspired cold air produces considerable water and heat loss from the respiratory tract with large ventilatory volumes during exercise. Airway moisture loss during cold-weather exercise contributes to mouth dryness, a burning sensation in the throat, irritation of the respiratory passages, and general dehydration. Wearing a scarf or cellulose mask-type baklava that covers the nose and mouth and traps the water in exhaled air (and warms and moistens the next incoming breath) helps minimize uncomfortable respiratory symptoms.

## Summary

1. Water conducts heat about 25 times faster than air; immersion in water of only 28 to $30 \mathrm{C}(8286 \mathrm{~F}$ ) provides considerable thermal stress that initiates rapid thermoregulatory adjustments.
2. Heat production from shivering and physical activity offsets heat flux to a cold environment. Shivering increases the metabolic rate by 3 to 6 METs .
3. Subcutaneous fat provides excellent insulation against cold stress. It greatly enhances the
effectiveness of vasomotor adjustments so individuals with excess body fat retain a large percentage of metabolic heat.
4. Individuals exhibit much less physiologic adaptation to chronic cold stress than to prolonged heat exposure.
5. Wearing appropriate clothing enables humans to tolerate some of the coldest climates on Earth.
6. Ambient temperature and wind influence the coldness of an environment. The wind-chill index determines the winds cooling effect on exposed tissue.
7. Considerable water loss occurs from the respiratory passages during exercise on a cold day, but inspired air temperature generally does not pose a danger to respiratory tract tissues.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

Medicine \& Science in Sports \& Exercise http://www.acsm-msse.org/

## CHAPTER 26



## Sport Diving

## CHAPTER OBJECTIVES

> Outline the chronology of historical milestones in diving from antiquity to present
> Quantify, with examples, the relationship between depth underwater and gas pressure and volume
> Discuss the rationale for snorkel size and underwater breathing depth
> Describe factors that limit the depth of a breathhold dive
> Describe the effects of hyperventilation on breath-hold duration and potential risks before diving
> Outline evidence that supports a diving reflex" in humans
> Describe open-circuit and closed-circuit scuba systems
> List causes, symptoms, and treatment of air embolism, lung burst, pneumothorax, mask squeeze, aerotitis, nitrogen narcosis, decompression sickness, and oxygen poisoning
> Discuss the decompression schedule for diving with compressed air in terms of its purpose and influencing factors
> Outline the rationale for saturation diving, and describe the environment where the diver lives for prolonged dives to exceptional depths
> Give reasons for breathing helium oxygen mixtures at great depth and discuss limitations to deep diving with these mixtures
> Describe the closed-circuit, mixed-gas system used by the U.S. Navy in technical diving

An estimated 5 million scuba divers work and recreate in the United States, with an additional 500,000 divers trained each year. Unquestionably, safe diving requires thorough knowledge of diving physics and physiology. We emphasize the relationships among diving depth, pressure, and gas volume and the potentially toxic effects of various gases breathed at high pressures in diving. ${ }^{6,30,32}$

## DIVING HISTORYANTIQUITY TO THE PRESENT

Men and women have practiced breath-hold diving for centuries as they hunted for sponges and food, salvaged artifacts and treasures, repaired ships, observed marine life, and participated in military maneuvers. The 5th century historian Herodotus tells of the underwater exploits of the Greek patriot Scyllias against the Persians. When Scyllias, taken as prisoner aboard ship, learned that Xerxes planned to attack a Greek flotilla, he escaped by jumping overboard. The Persians presumed he had drowned. To the contrary, Scyllias used a hollow reed as a snorkel and remained undiscovered, surfacing at night to cut each enemy ship loose from its moorings-saving the Greek Navy from sure disaster. Understandably, each dive could last only a few minutes until the discovery of how to remain underwater for longer durations. Using longer snorkels" did not work because the diver could not inhale against water pressure at depths greater than several feet (see p. 645). Rebreathing from an air-filled bag submerged underwater also failed because the buildup of exhaled carbon dioxide caused the diver to lose consciousness.

The first solutions to these problems took place in the 1530s with the invention of diving bells supplied with surface air. The bell, positioned a few feet from the surface, had its bottom open to water with its top portion containing air compressed by water pressure. A diver in the bell with his head surrounded by air could then hold his breath, swim from the bell for a minute or two and return for a short while, repeating the process until the air remaining in the bell became toxic.

In England and France in the 16th century, diving suits made of leather allowed descent to depths of 60 feet. Manual pumps delivered fresh air from the surface to the diver. Soon metal helmets could withstand greater water pressures, and divers could descend still further. By the 1830s, perfection of the surface-supplied air helmet allowed extensive underwater salvage work.

Starting in the 19th century, two main avenues of investigation-one scientific and the other technologicaccelerated underwater exploration. Two scientists, Paul Bert (1833 1886) and John Scott Haldane (1860 1936), explained the physiologic effects of water pressure on body tissues and also defined safe limits for compressed air diving. Technologic improvements with compressed air pumps, carbon dioxide scrubbers, and demand-valve regulators allowed prolonged underwater explorations.

## Chronology of Selected Events in Diving History

The area of underwater diving has fascinated scientists and sport enthusiasts since antiquity with its history rich in legend and scientific discovery. We present a brief chronology of selected events in the area. The Historical Diving Society offers more in depth reading and references (http://www.hds.org/).

4500 BC: Archeologists unearth shells in Mesopotamia dated to this period that must have originated from the sea floor.

3200 BC: Archeologists discover mother-of-pearl (abalone) shell ornaments dated to this period from the Egyptian Theban VI dynasty.

2500 BC : Greek divers make sponges widely available in commerce; The Iliad and The Odyssey mention diving and sponges.

550 BC: Pearl diving documented in India and Ceylon.
500 BC: Scyllias demonstrates the practical use of breathhold diving in military exploits against the Persian Navy.

100 BC: The Ama, Japan s women breath-hold divers of antiquity and modern times, gather pearl oysters, shellfish, and edible seaweed.


Ama diver.
1500: Da Vinci designs the first snorkel" device and dive fins for the hands and feet.

1530: Invention of the first diving bell.
1650: First effective air pump developed by Von Guericke, which physicist Robert Boyle (1627 1691) makes use of in compression and decompression experiments with animals.

1667: Robert Boyle makes first recorded observation of decompression sickness, or the bends," by documenting a gas bubble in the eye of a viper that had been compressed and then decompressed.

1690: Sir Edmund Halley (1656 1742; of comet fame) patents a practical diving bell (lead-coated wood with glass top to allow light to enter), 60 cubic feet $\left(1.7 \mathrm{~m}^{3}\right)$ in volume and
connected by a pipe to weighted barrels of air replenished from the surface, which permits dives to 60 feet for 90 minutes.


Halley s diving bell used weighted barrels of air to replenish the bell s atmosphere (late 17th century).

1715: John Lethbridge constructs his diving engine" built from an oak cylinder and supplied with compressed surface air. The diver remained submerged for 30 minutes at 60 feet while protruding his arms (sealed by greased leather cuffs) into the water for salvage work.

1776: First confirmed submarine battle; David Bushnell s American Turtle against the HMS Eagle (British) in New York harbor.

1788: John Smeaton s popular diving bell uses a hand pump to supply fresh surface air and a one-way valve to prevent air from returning to the pump when it stops.

1808: Friederich von Drieberg invents a bellows-in-abox device (named Triton) worn on the diver s back that delivers compressed air from the surface. The device never worked successfully but nonetheless suggested compressed air could be used in diving, an idea conceived by Halley in the late 1690s.

1823: Smoke helmet" for fighting structural fires is patented by Charles Anthony Deane. Later modified for diving, the helmet fastened over the head with weights and received surface air through a hose. In 1828, Charles and his brother John market the helmet with a loosely attached diving suit" so the diver could perform salvage work, but only in the full vertical position to prevent water from entering the suit.

1825: First prototype for scuba invented by William James incorporates a cylindrical belt (air reservoir) around the diver s trunk that supplies air to a helmet at 450 psi (lb per $i n^{2}$ ) by a hand-operated valve and rubber tube. The diver inhales through the nose and exhales through a mouthpiece connected by a short tube to an escape valve in the helmet $s$ crown. With the reservoir charged to 30 atmospheres, James believed a diver would have enough air to last 60 minutes.


James s first practical self-contained diving apparatus, composed of a copper or leather helmet with a glass plate window attached to a waterproof tunic sealed at the waist and wrists by elastic bandages."


Siebe s early diving suit.

1837: Augustus Siebe, the father of diving, seals the Deane brothers diving helmet to a waist-length jacket to create a full, watertight rubber suit that received surface air. This suit served as the forerunner for modern hardhat diving gear.

1839: Siebe s diving suit is used during salvage of the British warship HMS Royal George, sunk in 1782 to a depth of 65 feet; divers report the first symptoms of decompression sickness.

1843: From experience salvaging the HMS Royal George, the British Royal Navy establishes the first diving school.

1865: Beno t Rouquayrol and Auguste Denayrouze patent their underwater breathing apparatus ( aerophore") that consisted of a steel tank of compressed air (250 350 psi ) worn on the back and connected through an automatic demand valve to a mouthpiece. This forerunner of modern scuba enabled the diver to disconnect from a tether that supplied surface air and swim freely with the tank for several minutes.

1873: Dr. Andrew H. Smith, surgeon to the New York Bridge Company (builders of the Brooklyn Bridge), reports about bends in workers who leave their pressurized caisson. Smith recommends chamber recompression for future projects but does not mention nitrogen bubbles as the cause of decompression sickness.

1878: First self-contained diving apparatus developed by Henry A. Fleuss uses compressed oxygen (not compressed air). Rope soaked in caustic potash absorbs carbon dioxide so the diver rebreathes exhaled air without bubbles entering the water. The apparatus provides divers up to 3 hours of bottom time."


Aerophore scuba apparatus patented in 1865 by Beno t Rouquayrol and Auguste Denayrouze.

1878: Paul Bert publishes La Pression Barom trique, which describes physiologic studies of pressure changes. Bert proves that nitrogen gas bubbles cause decompression sickness (the bends," or caisson disease), gradual ascent prevents the problem, and recompression relieves pain.

1908: John Scott Haldane, Arthur Boycott, and Guybon Damant publish The Prevention of Compressed-Air Illness," a landmark paper that describes staged decompression to combat decompression sickness. Based on this work, the British Royal Navy and United States Navy develop diving tables for compressed air diving up to 200 feet deep.


Fleuss s first practicable self-contained diving apparatus that employs the closed circuit principle.


Deep sea pearl diver (circa 1896).

1912: Sir Robert Davis designs the first pressurized submersible decompression chamber.

1917: The U.S. Bureau of Construction and Repair first introduces the Mark V diving helmet, which revolutionizes salvage operations in World War II.

1920s: U.S. researchers experiment with helium oxygen mixtures for deep dives.

1924: The U.S. Navy and Bureau of Mines conduct the first experiments with helium oxygen mixtures.

1930: William Beebe and Otis Barton descend 1426 feet in a $4^{\prime} 9^{\prime \prime}$ bathysphere attached to a barge by a steel cable.

1930s: Guy Gilpatric pioneers use of rubber goggles with glass lenses for skin diving. By the mid-1930s, face masks, fins, and snorkels are in common use.

1933: French Navy captain Yves Le Prieur modifies the Rouquayrol-Denayrouze aerophore" by combining a new demand valve with a 1500 psi high-pressure air tank without a regulator, to eliminate restricting effects of hoses and lines. The diver breathes fresh air by opening a tap, while exhaled air escapes under the edge of the diver s mask.

1934: William Beebe and Otis Barton descend 3028 feet in a bathysphere near Bermuda, setting a depth record that remained until 1948.

1935: French Navy adopts Le Prieur s scuba.
1936: Le Prieur establishes the world s first scuba diving club, called the Club of Divers and Underwater Life."

1938: Edgar End and Max Nohl make the first intentional saturation dive" in a Milwaukee hospital hyperbaric chamber ( 27 h at a 101 - ft depth). Decompression takes 5 hours, and Nohl suffers the bends.

1939: A new diving bell, the McCann Erickson Rescue Chamber, makes the first successful rescue of men aboard the submarine USS Squalus, a new 310-foot submarine sunk in 243 feet of water in the North Atlantic. The chamber fit over the submarine s escape hatch, which four men at a time entered under one atmosphere of pressure. The rescue involved attaching salvage pontoons along the sides of the submarine with chains slung under the hull. The boat was then lifted off the bottom and moved to shallower water where the pontoons were reset. The process was
repeated until Squalus was shallow enough to enter the river at Portsmouth. The subsequent rescue and salvage operations ushered in several new technologies. First, the use of the McCann Rescue Chamber, and second, the first operational use of helium diving by the U.S. Navy. Dr. Albert Behnke (see Chapter 28, Reference Man and Reference Woman"), helped to supervise the successful rescue efforts (www.cisatlantic.com/trimix/other/squalus.htm).

1941 1944: Italian divers, working out of midget submarines during World War II, use closed-circuit scuba to place explosives under British naval and merchant marine vessels. The British adopt this technology to sink the German battleship Tirpitz on November 12, 1944 (www.bismarckclass.dk/tirpitz/tirpitz_menu.html).

1942 1943: Jacques-Yves Cousteau (1910 1997; French naval lieutenant) and Emile Gagnan (engineer for a Parisian natural gas company) redesign a car regulator to supply compressed air to a diver in initiation of a breathing cycle. They attach their new demand valve regulator to hoses, a mouthpiece, and a pair of compressed air tanks, which they patent as the Aqua-Lung. Frederic Dumas descends to 210 feet in the Mediterranean Sea and experiences livresse des grandes profondeurs -the rapture of the great depths. Cousteau achieves worldwide acclaim for his underwater explorations, movies, books, and dedication to environmental causes (www.cousteau.org/).

1947: Frederic Dumas uses the AquaLung and dives to $94 \mathrm{~m}(307 \mathrm{ft})$ in the Mediterranean Sea.

1948: Otis Barton descends in a modified bathysphere to 1370 m ( 4500 feet) off the coast of California.

1950s: August and Jacques Picard develop the bathyscaphe (deep boat), a completely self-contained vessel. In 1954, the bathyscaphe sets a diving record of 4050 m (13,287 ft).

1959: The YMCA begins the first nationally organized course for scuba certification.

1960: Jacques Picard and Don Walsh descend to approximately $10,916 \mathrm{~m}(35,820 \mathrm{ft}, 6.78$ miles; water pressure $16,883 \mathrm{psi}$, temperature 3 C [ 37.4 F$]$ ) in the August Picard designed, Swiss-built, U.S. Navy owned bathyscaphe Trieste, to the bottom of the Mariana Trench (deepest known seafloor depression on Earth) in the Pacific Ocean.

1960s: As accident rates for scuba divers climb, the first national agencies form to train and certify divers; NAUI (National Association of Underwater Instructors) forms in 1960, and PADI (Professional Association of Diving Instructors) forms in 1966.

1962: Albert Falco and Claude Wesley spend 7 days under $10 \mathrm{~m}(33 \mathrm{ft})$ of water near Marseilles in an underwaterliving habitat named Diogenes.

1963 1965: Divers live and work in underwater habitats for a month at a time at 60 m .

1968: John J. Gruener and R. Neal Watson dive to 133 m, breathing compressed air.

1970s: Implementation of diving safety standards include the following: certification cards to indicate a minimum


Captain Jacques Cousteau.


Dumas with the 1943 AquaLung Cousteau Gagnan unit. Note the waist level control valve.
training level and as a requirement for tank refills, change from J-valve reserve systems to nonreserve K-valves, adoption of submersible pressure gauges, and use of the buoyancy compensator and single-hose regulators.

1980: Divers Alert Network is founded at Duke University as a nonprofit organization to promote safe diving.

1981: Record 686-m (2250-ft) dive" is made in a Duke Medical Center chamber. Stephen Porter, Len Whitlock, and Erik Kramer live in the 8 -foot chamber for 43 days, breathing a nitrogen, oxygen, and helium mixture.

1983: Introduction of the first commercially available dive computer (Orca Edge).

1985: Robert Ballard (www.ife.org) and Ralph White use a remote-controlled camera to explore the wreck of the Titanic (3810-m [12,500-ft] depth).

1990s: Estimated 500,000 new scuba divers certified yearly in the United States as this activity s popularity increases for recreational and commercial purposes. Numerous scientific experiments using submersibles explore worldwide deepdiving sites in the Atlantic and Pacific oceans. The journeys include probing deep sea vulcanism, deep geology, and searching for artifacts from sunken vessels including the Titanic and 2000-year-old shipwrecks in the Mediterranean Sea.

2003: Tanya Streeter, a world champion freediver, shattered the men $s$ and women $s$ variable ballast freediving world records by descending 400 feet ( 122 m in 3 min 38 s ) to capture the variable ballast record (she becomes the first person to break all four deep freediving world records).

2004 2005: Expansion of technical diving by nonprofessionals who use mixed gases, new propulsion systems, full face masks, underwater voice communication, and digital cameras.

Lo c Leferme (France) sets the no limits" freediving record (maximum depth reached by a diver on a weighted sled before being pulled to the surface by a lift bag that the diver inflates at depth) of 171 m on October 30, 2004.

As of June 2008, the world records (male and female) for the static apnea event (maximum breath-holding time submerged underwater, usually face down) are established by Tom Sietas (Germany: 10 min 12 s ) and Natalia Molchanova (Russia: 8 min 00 s ).

## PRESSURE VOLUME RELATIONSHIPS AND DIVING DEPTH <br> Diving Depth and Pressure

Water remains essentially noncompressible owing to its high density. Consequently, its pressure against a diver s body increases directly with the depth of the dive. Two forces produce increased external pressure (hyperbaria) in diving:

1. Weight of the column of water directly above the diver (hydrostatic pressure)
2. Weight of the atmosphere ( $a t a$, or bar) at the water s surface

Table 26.1 shows that a column of seawater exerts a force of 1 sea-level ata ( 760 mm Hg , or 14.7 psi ) for each $10-\mathrm{m}$ ( $33-\mathrm{ft}$ ) descent below the water s surface. Because freshwater is less dense than seawater, a depth of approximately 34 feet corresponds to 1 ata in freshwater diving. Thus, a dive to 33 feet in seawater exposes the diver to a pressure of 2 ata: 1 ata from the weight of ambient air at the surface and the other from the weight of the column of water itself. Diving from sea level to $20 \mathrm{~m}(66 \mathrm{ft})$ exposes a diver to an absolute external pressure of 3 ata ; the pressure is 4 ata at $30 \mathrm{~m}(99 \mathrm{ft})$, and so on. Clearly, considerable external pressure builds up when diving relatively short distances below the surface.

Water constitutes a large portion of the body s tissues, so they too remain noncompressible and not particularly susceptible to increased external pressure during diving. The body also contains air-filled cavities-notably the lungs, respiratory passages, and sinus and middle ear spaces. Volume and pressure in these cavities change considerably with any increase or decrease in diving depth. Pain, injury, and even death occur unless adjustments equalize the rapid and large changes in pressure that occur in a hyperbaric environment.

## Diving Depth and Gas Volume

Boyles law (formulated in 1662 by chemist/physicist Robert Boyle) states that at constant temperature, the volume of a

TABLE 26.1 Relationship of Depth in Water to External Pressure, Lung Volume, and Inspired Gas Pressures

| Depth |  | Pressure |  | Hypothetical Lung Volume <br> mL | Inspired Air (mm Hg) |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| ft | m | atm | mm Hg |  | $\mathrm{PO}_{2}$ | $\mathrm{PN}_{2}$ |
|  |  | 1 | 760 | 6000 | 159 | 600 |
| 33 | 10 | 2 | 1520 | 3000 | 318 | 1201 |
| 66 | 20 | 3 | 2280 | 2000 | 477 | 1802 |
| 99 | 30 | 4 | 3040 | 1500 | 636 | 2402 |
| 133 | 40 | 5 | 3800 | 1200 | 795 | 3003 |
| 166 | 50 | 6 | 4560 | 1000 | 954 | 3604 |
| 200 | 60 | 7 | 5320 | 857 | 1113 | 4204 |
| $300$ | 90 | $10$ | 7600 | 600 | 1590 | 6006 |
| $400$ | 120 | 13 | 9880 | 461 | 2068 | 7808 |
| $500$ | $150$ | $16$ | $12,160$ | 375 | $2545$ | $9610$ |
| 600 | 180 | 19 | 14,440 | 316 | 3022 | 11,412 |

given mass of gas varies inversely with its pressure. When pressure doubles, volume halves; conversely, reducing pressure by one-half expands any gas volume to twice its previous size. Figure 26.1 (and Table 26.1) shows that if divers fill their lungs with 6 L of air at the surface and then descend to $10 \mathrm{~m}(33 \mathrm{ft})$, the lung volume compresses to 3 L . Diving an additional 10 m to a depth of 20 m ( 65.6 ft ; external pressure now 3 ata) reduces the original 6-L lung volume by two-thirds, to 2 L . At 91 m ( 300 ft ), the lung volume compresses to 0.6 L , simply from the compressive force of water against the air-filled thoracic cavity. For most individuals, further increases in diving depth reduce the pulmonary air volume and seriously damage the chest wall and lung tissue. As the diver returns to the surface, the air volume reexpands to its original 6 - L volume. For the scuba diver who breathes pressurized air beneath the water, a $6-\mathrm{L}$ lung volume at a $10-\mathrm{m}$ depth expands to 12 L at the water s surface; this 6 -L volume at $50-\mathrm{m}$ depth occupies 36 L at sea-level pressure. Failure to permit the extra" air volume to escape through the nose or mouth during ascent ruptures lung tissue from the powerful force of expanding gases.

## SNORKELING AND BREATH-HOLD DIVING

Swimming at the water s surface with fins, mask, and snorkel provides a common form of recreation and sport for spear fishing and exploring shallow areas of clear water. A J-shaped tube, or snorkel, allows the swimmer to breathe continually with the face immersed in water. The swimmer periodically takes a full breath of air and dives to explore beneath the water s surface. After about 30 seconds, the carbon dioxide level in arterial blood increases, causing the diver to sense the need to breathe and surface quickly. Snorkeling is essentially an extension of swimming, with diving limited entirely by the swimmer $s$ breath-holding ability.

## Limits to Snorkel Size

Novice skin divers often speculate that if they had a longer snorkel, they could swim deeper in the water and still breathe ambient air through the top of the snorkel. Some neophytes believe they can sit at a pool bottom and breathe through a garden hose extending to the pool deck! The idea of a longer snorkel seems intriguing, but two factors limit snorkel length and volume:

1. Increased hydrostatic pressure on the chest cavity as one descends beneath the water
2. Increased pulmonary dead space by enlarging the snorkel s volume

## Inspiratory Capacity and Diving Depth

When breathing through a snorkel, the diver inspires air at atmospheric pressure. At a depth of about $3 \mathrm{ft}(1 \mathrm{~m})$, the compressive force of water against the chest cavity becomes so large that the inspiratory muscles cannot overcome external pressure and expand thoracic dimensions. This makes inspiration impossible without external air at sufficient pressure to counter the compressive force of water at the particular depth. This reality forms the basis for scuba discussed on page 650 of this chapter.

## Snorkel Size and Pulmonary Dead Space

In Chapter 12, we explain that not all inspired air enters the alveoli. Approximately 150 mL of each breath fills the nose, mouth, and other nondiffusible portions of the respiratory tract. The snorkel, an extension of the airways, adds to the volume of the anatomic dead space. Consequently, the ideal snorkel averages about 15 inches ( 38 cm ) in length, with an inside diameter of five-eighths to three-quarters of an inch to minimize the effects of added dead space and resistance to


Figure 26.1 Gas volume varies inversely with the pressure acting upon it. A 6-L volume, whether in an open bell or in the flexible thoracic cavity, compresses to 3 L in 33 feet ( 10 m ) of seawater ( fsw ) because of a doubling of the external water pressure. At 99 fsw , or 4 ata, the gas decreases to $25 \%$ of original volume, or 1.5 L . The inset figure graphically illustrates the curvilinear relation between lung volume at the surface and depth in seawater. The volume change per unit depth change is greatest nearest the water s surface.
breathing. ${ }^{34}$ Any further increase in snorkel size (volume) increases anatomic dead space volume, thus encroaching on alveolar ventilation.

## Breath-Hold Diving

The duration and depth of a breath-hold dive depends on two factors:

1. Breath-hold duration until arterial carbon dioxide pressure reaches the breath-hold breakpoint
2. Relationship between a diver stotal lung capacity (TLC) and residual lung volume (RLV)

A full inspiration of ambient air causes 1 L of oxygen to move into the respiratory passages and lungs. Upon breath hold, 650 mL of oxygen sustains metabolism before partial pressures of arterial oxygen $\left(\mathrm{PO}_{2}\right)$ and carbon dioxide $\left(\mathrm{Pco}_{2}\right)$ signal the need to renew breathing. ${ }^{8}$ With some practice, most persons can breath hold for up to 1 minute, and 2 minutes represents a typical upper limit. During this time, arterial $\mathrm{PO}_{2}$ drops to 60 mm Hg , whereas $\mathrm{PCO}_{2}$, the most important factor controlling breath holding, rises to 50 mm Hg , signaling an urgency to breathe. Physical activity greatly reduces breathholding time because oxygen consumption and carbon dioxide production increase with exercise intensity.


Basic tools for snorkeling and breath-hold diving.

## Hyperventilation and Breath-Hold Diving: Blackout

Hyperventilation before breath-hold diving extends the breath-hold period; at the same time, the risk to the diver greatly increases. Blackout, a sudden loss of consciousness, poses a serious danger in skin diving; it usually afflicts divers who try to extend the dive s duration beyond reasonable limits. A critical reduction in arterial $\mathrm{PO}_{2}$ causes blackout, a condition that contributes to a total relaxation of respiratory muscles.

The breakpoint for breath holding corresponds to an increase in arterial $\mathrm{PCO}_{2}$ to 50 mm Hg . Some persons can ignore this stimulus and continue breath holding until arterial carbon dioxide reaches levels that cause severe disorientation and even blackout. When hyperventilation precedes breath hold, arterial $\mathrm{PCO}_{2}$ decreases from its normal value of 40 mm Hg to 15 mm Hg . Lowering the body s carbon dioxide content before the dive extends the breath-hold duration until arterial $\mathrm{PCO}_{2}$ increases to a level that stimulates ventilation. For example, 313 seconds is the longest breath hold recorded while breathing air without prior hyperventilation. Breath holds of 15 to 20 minutes occur with hyperventilation followed by several deep breaths of pure oxygen. ${ }^{21}$

Combining hyperventilation, breath holding, and exercise in the underwater environment poses serious risks. Consider the following scenario: A skin diver hyperventilates at the surface before a dive to reduce arterial $\mathrm{PCO}_{2}$ to augment breath-hold duration. The diver now takes a full inhalation and descends beneath the water. Alveolar oxygen continually moves into the blood for delivery to active muscles. Owing to previous hyperventilation, arterial carbon dioxide levels remain low, freeing the diver from the urge to breathe. Concurrently, as the diver swims deeper, external water pressure compresses the thorax, increasing gas pressure within this cavity. Increased intrathoracic pressure maintains a relatively high alveolar $\mathrm{PO}_{2}$. Even though
absolute alveolar oxygen quantity decreases as oxygen moves into the blood during the dive, $\mathrm{PO}_{2}$ continually loads hemoglobin as the dive progresses. When the diver senses the need to breathe from carbon dioxide buildup and begins to ascend, reversals occur in intrathoracic pressure. As water pressure on the thorax decreases with ascent, lung volume expands and alveolar $\mathrm{PO}_{2}$ decreases to a level where no gradient exists for oxygen diffusion into arterial blood. This places the diver in a hypoxic state. Near the surface, alveolar $\mathrm{PO}_{2}$ reaches levels so low that dissolved oxygen diffuses from venous blood returning to the lungs and flows into the alveoli; this causes the diver to suddenly lose consciousness before surfacing.

Additional Considerations. Two additional risks from hyperventilation preceding a breath-hold dive include:

1. A normal quantity of arterial carbon dioxide maintains the blood s acid base balance, mediated by $\mathrm{H}^{+}$ release as carbonic acid forms from the union of carbon dioxide and water. By reducing the blood s carbon dioxide content through hyperventilation, $\mathrm{H}^{+}$ concentration decreases, thus increasing pH and alkalinity.
2. Normal arterial $\mathrm{PCO}_{2}$ stimulates dilation of arterioles in the brain. ${ }^{25,28}$ A decrease in arterial carbon dioxide with hyperventilation can reduce cerebral blood flow to produce dizziness or loss of consciousness.

## Depths Limits with Breath-Hold Diving: Thoracic Squeeze

Progressing deeper beneath the water subjects the body s air cavities to tremendous compressive forces. Generally, when the lung volume compresses below 1.5 to 1.0 L (i.e., to RLV), internal and external pressures fail to equalize and lung squeeze occurs. (The In a Practical Sense" feature on p. 649 provides equations to estimate RLV from age, stature, and body mass.) Excessive hydrostatic pressure on pulmonary air volume causes extensive damage to pulmonary tissues.

Commercial breath-hold diving generally does not exceed depths of 100 feet of salt water (fsw), and lung squeeze generally occurs at depths between 150 and 200 fsw. However, individuals show considerable variability in the safe depth for breath-hold diving without danger of lung squeeze. The world record for no limits" breath-hold diving depth following a single breath of air for men is an amazing 702 fsw ( 214 m ), a level below the typical cruising depth of nuclear submarines. Herbert Nitsch of Austria achieved this remarkable physiologic feat in 2007. The external water pressure against the diver s thoracic cavity at this depth would compress his chest girth to less than 20 inches. Tanya Streeter of the Cayman Islands in 2003 redefined the limits of achievement for a woman by setting the world record for no limits breath-hold diving when she reached 524 fsw, or 160 m .

## IN A PRACTICAL SENSE

## Estimating Residual Lung Volume from Age, Stature, and Body Mass

In breath-hold diving, RLV plays a significant role by affecting the depth a diver can achieve without danger of lung squeeze. In fact, the divers TLC RLV ratio at the surface generally determines the critical diving depth before lung squeeze.

Laboratory techniques of helium dilution, nitrogen washout, or oxygen dilution routinely measure RLV (see Chapter 12). Each procedure requires complicated and expensive laboratory equipment. An alternative but less valid approach estimates RLV with genderspecific prediction equations based on age, stature, and body mass. The standard error of estimate for predicting RLV ranges between 325 and 500 mL .

## RLV PREDICTION EQUATIONS

Variables: age (y); St, stature (cm); BM, body mass (kg).
Normal-weight males

$$
\begin{aligned}
\operatorname{RLV}(\mathrm{L})= & (0.022 \times \text { Age })+(0.0198 \times \mathrm{St}) \\
& -(0.015 \times \mathrm{BM})-1.54
\end{aligned}
$$

Normal-weight females (only age and stature used)

$$
\operatorname{RLV}(\mathrm{L})=(0.007 \times \text { Age })+(0.0268 \times \mathrm{St})-3.42
$$

Overweight males (\%fat 25) and females (\%fat 30)

$$
\begin{aligned}
\mathrm{RLV}(\mathrm{~L})= & (0.0167 \times \text { Age })+(0.0130 \times \mathrm{BM}) \\
& +(0.0185 \times \mathrm{St})-3.3413
\end{aligned}
$$

## EXAMPLES

1. Male: age: 21.0 y; body mass: 80 kg ; stature: 182.9 cm RLV $(L)=(0.022 \times 21)+(0.0198 \times 182.9)$
$-(0.015 \times 80)-1.54$
$=0.462+3.621-1.2-1.54$
$=1.34 \mathrm{~L}$
2. Female: age: 19 y; stature: 160.0 cm

RLV $(\mathrm{L})=(0.007 \times 19)+(0.0268 \times 160.0)-3.42$

$$
=0.133+4.288-3.42
$$

$$
=1.00 \mathrm{~L}
$$

3. Overweight male: age: 35 y ; body mass: 104 kg ; stature: 179.5 cm

$$
\begin{aligned}
\operatorname{RLV}(\mathrm{L})= & (0.0167 \times 35)+(0.0130 \times 104) \\
& +(0.0185 \times 179.5)-3.3413 \\
= & 0.5845+1.352+3.321-3.3413 \\
= & 1.39 \mathrm{~L}
\end{aligned}
$$

Grimby G, S derholm B. Spirometric studies in normal subjects, III: static lung volumes and maximum ventilatory ventilation in adults with a note on physical fitness. Acta Med Scand 1963;2:199.
Miller WCT, et al. Derivation of prediction equations for RV in overweight men and women. Med Sci Sports Exerc 1998;30:322.


The ratio of the divers TLC to RLV at the surface generally determines the critical diving depth before lung squeeze; this ratio typically averages $4: 1$ at the surface. For example, for a diver with a $6.0-\mathrm{L}$ TLC and a $1.5-\mathrm{L}$ RLV, Boyles law predicts that TLC would compress to RLV at 30 m , or 4 ata external pressure. No danger from lung squeeze exists if lung volume remains greater than RLV because sufficient air remains in the lungs and rigid respiratory passages to equalize pressure and prevent damage from compression. If TLC during a dive decreases below RLV (i.e., if TLV RLV ratio falls below 1.00), pulmonary air pressure becomes less than the external water pressure. The unequalized pressure creates a relative vacuum within the lungs. In severe cases of lung squeeze, blood literally spurts from the pulmonary capillaries through the alveoli and into the lungs. In this situation, divers drown in their own blood. Further increases in depth cause
compression fractures of the ribs as the chest cavity collapses from excessive external pressure.

In many instances, the TLV RLV ratio at the surface considerably underestimates the actual impressive depths achieved by trained breath-hold divers. Part of the explanation may relate to a reduced RLV as immersion progresses because of a shift toward greater intrathoracic blood volume. Consequently, a smaller RLV underwater increases the TLV RLV ratio, allowing the individual to increase maximal depth before reaching the critical ratio.

Other Problems. If pressures within internal air spaces do not continually equalize with external hydrostatic pressures, problems other than lung squeeze limit the depth of a breath-hold dive. For example, if air at ambient pressure remains trapped within the middle ear (from inflamed tissue or


Tanya Streeter.
a mucous plug) and cannot equilibrate with air in the lungs, external hydrostatic pressure forces the eardrum inward and it ruptures. A ruptured eardrum frequently occurs at relatively shallow depths.

The sinus cavities also present difficulty for skin divers. Air compressed in the lungs by the external force of water attempts to move into the paranasal sinuses. However, sinuses inflamed and irritated from infection provide extremely narrow openings that hinder sinus space equilibration with pressure changes in the respiratory tract. Failure to equilibrate creates a relative vacuum in the sinus cavities that distorts their tissues shape and causes intense sinus pain. With severe disequilibrium, fluid and blood move into the sinuses to fill the vacuum.

## Diving Reflex in Humans

Physiologic responses to immersion, collectively termed the diving reflex, enable diving mammals to spend considerable time underwater. These responses include (1) bradycardia, (2) decreased cardiac output, (3) increased peripheral vasoconstriction, and (4) lactate accumulation in underperfused muscle. A modified diving response also has been described for humans during face immersion, breath-hold face immersion, and dives to modest depths. ${ }^{1,13,17,22}$ The research has primarily documented increased vagal activity that induces bradycardia in humans during face immersion and diving, particularly in cool and cold water. Elevated blood lactate concentration during breath-hold dives to 65 m at energy expenditures only slightly above rest also suggests a diving-
mediated peripheral vasoconstriction that decreases blood flow (oxygen supply) to skeletal muscles. ${ }^{12}$

More recent data have expanded the findings on blood lactate concentration to include hemodynamic aspects of breath-hold diving in thermoneutral and cool water by elite divers to depths of 40 to 55 m . Figure 26.2A illustrates the responses for one diver during descent to 40 m , bottom stay, and ascent (depth indicated by green line) in water at 25 C and 35 C . The electrocardiographic tracing (Fig. 26.2B) shows the longest R R interval recorded during the coolwater dive. After an initial tachycardia, bradycardia rapidly ensued and became most pronounced in cool water, where heart rate decreased to $16 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ near the bottom. Because stroke volume did not change appreciably during the dive, lower heart rates reduced cardiac output (yellow line). Output decreased to a low of $3 \mathrm{~L} \cdot \min ^{-1}$ ( $25 \mathrm{C}[77 \mathrm{~F}]$ ) compared with the value of $6.4 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ at the surface. A large number of diverse arrhythmic beats, often more frequent than true sinus beats, accompanied bradycardia, mainly in the cool-water dives. Arterial blood pressure increased suddenly and dramatically, reaching 280/200 and $290 / 150 \mathrm{~mm} \mathrm{Hg}$ in two divers. This hypertensive response reflected overall peripheral vasoconstriction; the large increase in blood lactate concentrations reflected increased anaerobic metabolism.

The intense cardiovascular responses to breath-hold diving in elite divers resembles response patterns of diving mammals. The occurrence of arrhythmias and large increases in blood pressure probably reflects species differences and less perfect human adaptation.

## SCUBA DIVING

The discussion of snorkeling emphasized that at depths below 1 m , inspiratory muscle power cannot overcome the compressive force of water against the thoracic cavity. Air under pressure from an external source to promote inspiratory action counteracts the external hydrostatic force. The self-contained underwater breathing apparatus (scuba), principally developed in 1943 by French oceanographer/ecologist/researcher Jacques-Yves Cousteau and Emile Gagnan (1915 2003), is the most common apparatus to supply air under pressure for complete independence from the surface (sold commercially as Aqua-Lung). Sport divers should use only this form of scuba. The scuba system, strapped to the diver s chest or back, includes a tank of compressed air and a demand regulator valve that delivers air the diver needs at a particular depth with hose and mouthpiece or full face mask. Two basic scuba designs exist: (1) the common open-circuit system and (2) the closed-circuit system, used primarily for clandestine military operations and special applications that require mixed gases.

Underwater commercial operations frequently apply sur-face-demand diving techniques in operations below a $50-\mathrm{m}$ depth. This approach supplies air directly from a compressor at the surface to the diver via a direct reinforced hose.


Figure 26.2 A. Heart rate, stroke volume, and cardiac output for an elite breath-hold diver throughout a dive to 40 m (131 ft) in warm (35 C [95 F]) and cool (25 C [77 F]) water. Green line, diving depth in relation to time; yellow line, cardiac output throughout the dive; CTRL, control measures prior to dive. B. Electrocardiographic tracing (see Chapter 16, Fig. 16.2) showing longest R-R interval during the dive in 25 C water. (*), QRS complex during the dive. (From Ferrigno M, et al. Cardiovascular changes during deep breath-hold dives in a pressure chamber. J Appl Physiol 1997;83:1282.)

German-born British engineer/inventor Augustus Siebe (1788 1872) provided the original design for this system in 1819; it consisted of a copper helmet (hard hat) riveted to a leather jacket, with air delivered continuously from the surface. The excess supplied air and the diver s expired air bubbled out from the bottom of the jacket. If the diver moved substantially from the vertical position, water would rush in through the bottom of the jacket and fill the headpiece. Siebe modified this design in 1837 (see unnumbered figure on p. 643); he constructed a full waterproof diving suit bolted to a breastplate and helmet that allowed a diver to work in any position because the suit encapsulated the entire body. Valves admitted air through the diver s helmet as needed, and expired air exited the helmet also through valves. ${ }^{20}$ Siebe s closed" diving helmet allowed divers to dive safely to depths previously impossible to attain.

## Open-Circuit Scuba

Figure 26.3 illustrates the typical open-circuit scuba system for submerged swimming with neutral buoyancy in relatively shallow water. For most diving purposes, the steel or aluminum tanks (lightweight titanium that withstands high pressures also is used) contain $2000 \mathrm{~L}\left(7080 \mathrm{ft}^{3}\right.$ ) of air compressed to about

3000 psi; deeper and longer exposures require $3500 \mathrm{~L}\left(120 \mathrm{ft}^{3}\right)$ of compressed air. One tank supplies enough air for a 0.5 - to 1-hour dive to moderate depths. The start of inspiration creates a slight negative pressure. This opens the demand valve and releases air to the diver at a pressure nearly equal to the water s external pressure. The positive pressure created with exhalation closes the inspiratory valves and discharges the exhaled air into the water. The scuba gear contains gauges that continually monitor tank pressure and diving depth.

Open-circuit scuba presents several drawbacks. The air exhaled into the water generally contains approximately $17 \%$ oxygen, so the open-circuit system wastes" about $75 \%$ of the total oxygen in the tank. In addition, the diver requires a considerable mass of air at increased depths to provide tidal volume for adequate pulmonary ventilation. As an extreme example, inhalation of a 5-L volume at $300 \mathrm{fsw}(90 \mathrm{~m}$ ) requires the equivalent of 50 L of air at sea level! This dramatic effect of pressure on air volume greatly limits the time one can remain at great depth before depleting the scuba tank s air. Factors that influence the energy cost of swimming underwater (and thus pulmonary ventilation) include gender (lower in women than men), gear and number of tanks ( $25 \%$ higher with two tanks), fin type (flexible fin lower than rigid fin), and diver s experience (lower in advanced divers). ${ }^{27}$ Diving


Flexible breathing


Figure 26.3 General design of an open-circuit scuba unit. Compressed air flows through a two-stage regulator valve that reduces tank pressure to a near breathable pressure at a specific depth and releases air to the diver on demand at pressure equal to ambient" so the diver breathes without difficulty.
tanks contain moisture-free compressed air, making each breath produce heat and moisture loss as the inspired air warms and humidifies on its passage down the respiratory tract. This causes substantial body heat loss during prolonged diving. To counter heat loss, the diver breathes a heated gas mixture of compressed helium-oxygen to avoid hypothermia during deep diving (see p. 660).

Figure 26.4 shows the theoretical air time limits for a diver who performs similar work at various underwater depths. These time limits assume a completely filled standard compressed air tank and ascent and descent at 60 feet per minute. For example, a single aluminum tank that contains 80 $\mathrm{ft}^{3}$ of air compressed to 3000 psi normally sustains an 80minute dive near the surface. At a depth of 10 m , this tank supplies enough air for about 40 minutes, whereas at 3 ata (or 20 m ), dive duration decreases by one-third, to 27 minutes. These time limits vary with the diver s body size, type and intensity of physical activity, fitness level, and diving experience, all of which affect exercise energy cost and ventilatory volumes.

The wet suit, the most common protective garment worn by recreational scuba divers and surfers, counters cold stress during diving. This garment, constructed of air-impregnated rubber (usually foam neoprene), traps water against the diver s skin, which warms to body temperature to provide the insulatory boundary. The suit, filled with thousands of tiny gas bubbles, provides insulation. Wet suits generally furnish sufficient thermal protection for relatively short dives, even in ice water. For longer dives in moderately cold water (17 18.5 C [63 65 F$]$ ), a full wet suit offers insufficient thermal protection. ${ }^{4}$ Compression of the wet suit as the diver descends progressively diminishes the suit s insulating properties.

The modern dry suit-made from foam neoprene, crushed neoprene, vulcanized rubber, or heavy-duty nylon with laminated waterproof materials, and often worn over insulating garments-maximizes protection from cold stress. This protective clothing ensemble keeps the diver dry, has seals at the neck, wrists, and ankles and a waterproof zipper to prevent water from entering the suit. Dry-suit underwear traps a layer of air between the diver and the water for additional insulation. Layering of underwear adjusts insulation to water temperature.


Figure 26.4 Theoretical air time for a single tank containing 80 cubic feet of air. The yellow line includes the time spent descending at a rate of $60 \mathrm{ft} \cdot \mathrm{min}^{-1}$ plus time on the bottom; dashed line, indicates only bottom time."

## Closed-Circuit Scuba

The need for shallow diving maneuvers during World War II produced a new diving form that used rebreathing of pure oxygen and absorption of carbon dioxide within a closed system. The closed-circuit underwater breathing apparatus operates similarly to the closed-circuit spirometer described in Chapter 8. A small cylinder feeds pure oxygen into a bellows or bag from which the diver breathes. The breathing bag acts as a pressure regulator. Valves in the breathing mask direct the exhaled gas through a carbon dioxide absorbing canister that contains soda lime; the carbon dioxide free gas, then passes back to the diver. The oxygen cylinder replenishes the oxygen consumed in energy metabolism, allowing the diver to continually rebreathe oxygen, the only gas removed from the breathing bag. Thus, only a small oxygen cylinder sustains the submerged diver for 3 hours or longer. Because no expired air releases into the water, the system provides a near-silent and bubble-free operation for clandestine activities. Figure 26.5 illustrates a closed-circuit scuba design currently used by the U.S. Navy that requires only a single bottle of compressed oxygen. The other type of closed-circuit system uses mixed gas: one bottle of pure oxygen and a second bottle of a mixed gas containing helium and oxygen (heliox) or nitrogen and oxygen (nitrox; see pp. 660 663).

The closed-circuit system requires a high level of proficiency for safe use. Two main problems exist with closed-circuit scuba. First, a serious medical emergency occurs if carbon dioxide output exceeds its rate of absorption or if absorption fails altogether. With a faulty rebreathing system, the diver may not receive warning symptoms and can drown from becoming anesthetized by arterial carbon dioxide buildup. Second, high concentrations of inspired oxygen, particularly when breathed under high pressures beneath the water, produce a variety of adverse effects on physiologic functions, particularly those related to the central nervous system. These


Figure 26.5 General design of a closed-circuit scuba system used by the U.S. Navy. A small cylinder of pure oxygen feeds into a bellows or bag from which the diver breathes. The breathing bag acts as a pressure regulator. Valves in the breathing mask direct the exhaled gas through a $\mathrm{CO}_{2^{-}}$ absorbing canister containing soda lime; the $\mathrm{CO}_{2}$-free gas then passes back to the diver. The oxygen cylinder replenishes oxygen consumed in metabolism. Arrows indicate direction of airflow.

| TABLE 26.2 | U.S. Navy Recommended Depth Time Limits Breathing Pure Oxygen During Working Dives ${ }^{a}$ |  |
| :---: | :---: | :---: |
| Normal Operations |  |  |
| Depth |  | Time (min) |
| (ft) | (m) |  |
| 10 | 3.0 | 240 |
| 15 | 4.6 | 150 |
| 20 | 6.1 | 150 |
| 25 | 7.6 | 75 |
| Exceptional Operations |  |  |
| Depth |  |  |
| (ft) | (m) | Time (min) |
| 30 | 9.2 | 45 |
| 35 | 10.7 | 20 |
| 40 | 12.2 | 10 |

problems remain minimal if the depth time limits do not exceed the recommendations in Table 26.2. Closed-circuit oxygen breathing generally should not exceed a maximum depth of 25 fsw and definitely should not exceed 50 fsw because oxygen poisoning produces high risk of central nervous system seizures. Minimal risk usually exists in military diving because most clandestine operations require swimming underwater in relatively shallow depths to avoid detection at night. Decompression sickness does not pose a problem because no inert gas absorption occurs when rebreathing pure oxygen. The increased resistance to breathing and the generally large dead space common with the closed-circuit system limit intense physical work.

## SPECIAL PROBLEMS WITH BREATHING GASES AT HIGH PRESSURES

Henrys law (first proposed in 1803 by English chemist William Henry [1734 1816]) states that the quantity of gas dissolved in a liquid at a given temperature varies directly with the (1) pressure differential between the gas and the liquid and (2) gas solubility in the liquid. Underwater breathing systems must supply air, oxygen, or other gas mixtures at sufficient pressure to overcome the force of water against the diver s thorax. For example, at 3 ata ( $20-\mathrm{m}$ depth) the respired gas requires delivery at approximately $2280 \mathrm{~mm} \mathrm{Hg}(3 \times 760 \mathrm{~mm} \mathrm{Hg})$, whereas gas delivery at 60 m requires a pressure of 5320 mm Hg . The following sections consider the specific dynamics of breathing gases at high pressures and their effects on physiologic


Figure 26.6 Scuba diving hazards from failure to equalize internal and external gas pressures.
functions. We also examine the physical responses of a gas to abrupt changes in pressure. Figure 26.6 summarizes the main hazards of scuba diving posed by improper equalization of pressure within the body s air spaces (and diving mask) to changes in external pressure.

## Air Embolism

An air volume breathed underwater expands in direct proportion to the reduction in external pressure as the diver ascends to the surface. Air breathed at a depth of 10 m doubles in volume if brought to the surface. If normal breathing continues during ascent, the expanding air vents freely through the nose
and mouth. However, if a diver takes a full breath at 10 m but fails to exhale while ascending, the rapidly expanding gas eventually ruptures the lungs before the diver reaches the surface. Lung burst becomes a real possibility in scuba diving. Many inexperienced divers react to a perceived underwater danger by filling their lungs and then holding their breath while swimming rapidly to the surface. This particular diving hazard does not necessarily require a deep dive. Accidents caused by breath-hold ascent with scuba frequently occur in shallow dives; changes in pressure exert the greatest effect on the expanding lung volume near the water surface (see inset box in Fig. 26.1). Inhaling a full breath of compressed air in 6 feet of water causes serious overdistension of lung tissue if the
diver fails to exhale during ascent. Fatal air embolism can occur in swimming pools as shallow as 8 feet for an inexperienced scuba diver. Air embolism from pulmonary barotrauma ranks second only to drowning as a cause of death among recreational scuba divers.

If expansion of air in the respiratory tract causes lung tissue to rupture during ascent from underwater-from either breath holding or pulmonary obstruction (bronchospasm, excessive pulmonary secretions, or bronchial inflammation)air bubbles (emboli) enter the pulmonary venous system. Emboli then flow to the heart and enter the systemic circulation. Because the diver usually maintains a head-up, vertical position on ascent, the bubbles move upward in the body. Eventually, they lodge in the small arterioles or capillaries and restrict blood supply to vital tissue. General symptoms of air embolism include confusion, weakness, dizziness, and blurred vision. Severe blockage of pulmonary, coronary, and cerebral circulation causes collapse, unconsciousness, and frequently death. Effective treatment for air embolism requires rapid decompression to reduce bubble size and force them into solution to open the plugged vessels. Even with rapid, expert treatment, $16 \%$ of air embolism victims die.

## Pneumothorax: Lung Collapse

Air forced through the alveoli when lung tissue ruptures sometimes migrates laterally to burst through the pleural sac that covers the lungs. In about $10 \%$ of cases of this form of pulmonary barotrauma, an air pocket forms in the chest cavity outside the lungs, between the chest wall and lung itself. Continued expansion of trapped air during ascent collapses the ruptured lung (pneumothorax). Pneumothorax treatment often requires surgical intervention with a syringe to extract the air pocket.

To eliminate the danger of air embolism and pneumothorax, instructors teach divers to ascend slowly and breathe normally when using scuba gear. The diver s lungs must remain free from any disease that could lead to air trapping (e.g., chronic obstructive pulmonary disease). Air trapping creates difficulty equalizing alveolar pressure and external pressure during ascent.

## Mask Squeeze

Air in a facemask or goggles before a dive equals ambient air pressure at the surface. As the diver progresses deeper, a considerable pressure differential develops between the inside and outside of the mask to create a relative vacuum within the mask. For example, wearing swimming goggles to improve vision and protect the eyes from irritants during a dive beneath the water can cause the eyes to bulge or squeeze from their sockets. This leads to capillary rupture and hemorrhage of the eyes and surrounding soft tissue. The squeeze effect occurs because most goggles are constructed from rigid materials. Consequently, displacement of the eye and surrounding soft tissue into the air space between the eye and the goggles provides the only means to equalize the difference in air pressure between the goggle
space and external water pressure during breath-hold diving. As newer pools with separate diving areas reach depths of 14 feet $(4.3 \mathrm{~m})$, goggles pose a distinct risk to swimmers who dive to this depth.

Breath-hold diving with a facemask that covers the eyes and nose represents a somewhat different situation than diving with only swim goggles. Air pressure within the mask that covers the eyes and nose readily equalizes to external water pressure as air flows freely between the nasal passages and the lungs relatively large air volume. In breath-hold diving, air in the lungs compresses and passes through the nose to equalize mask pressure. With scuba, inspired air automatically adjusts to the external water pressure. Therefore, periodically exhaling through the nose into the mask balances pressures on both sides of the face mask.

## Aerotitis: Middle-Ear Squeeze

Divers often encounter problems equalizing pressure within the air space of the Eustachian tubes, the passages that connect the middle ear with the back of the throat. ${ }^{36}$ These relatively narrow, mucus-lined channels generally resist air flow. In healthy individuals, the tubes remain clear enough so that changes in external pressure against the eardrum equalize by pressure changes transmitted from the lungs through the Eustachian tubes. In skin and scuba diving (and air travel in nonpressurized aircraft), middle-ear pressure equalizes with external pressure by blowing gently against closed nostrils. Swallowing, yawning, or moving the jaws from side to side also helps to pop" the ears.

In upper-respiratory tract infection, the Eustachian tube membranes swell and produce mucus that can plug cranial air passages. The greatest difficulty involves equalizing middle-ear pressure during descent because an equal force from the ear canal does not readily match the pressure change against the eardrum s outer surface. The magnitude of pressure changes in diving considerably exceed those experienced in air travel. Divers can suffer severe pain only a few feet underwater because the eardrum stretches and moves inward toward the plugged canal. Further pressure disequilibrium creates a relative vacuum in the middle ear that hemorrhages tissues. Complete blockage of the Eustachian tubes can rupture the eardrum, forcing water into the middle ear as pressure equalizes.

Never Use Earplugs. Never wear earplugs while diving. During a dive, the external water pressure pushes the earplug deep into the external ear canal. A pocket of ambient air trapped between the plug and eardrum can rupture the eardrum outward during descent.

## Aerosinusitis

Inflamed, congested sinuses prevent air pressure in these cavities from equalizing during diving. Sinus air pressure that does not equalize during descent remains at atmospheric pressure while external pressure increases. This relative vacuum creates sinus squeeze," causing sinus membranes to bleed as blood occupies the space to equalize the pressure differential. ${ }^{26}$

## Nitrogen Narcosis: Rapture of the Deep

The total pressure of the respired gas during diving increases in direct proportion to diving depth. Likewise, the partial pressure of each gas in the breathing mixture increases, so at 10 m the nitrogen partial pressure doubles the sea-level value to 1200 mm Hg. With each additional $10-\mathrm{m}$ depth, nitrogen partial pressure increases by 600 mm Hg -inspired $\mathrm{PN}_{2}$ equals 4200 mm Hg at a $60-\mathrm{m}$ depth. At each successive depth, the gradient increases for the net flow of nitrogen across the alveolar membrane into the blood and eventually into all tissue fluids for equilibration. At 20 m , all tissues eventually contain three times as much nitrogen as before the dive. Tissue perfusion, tissue solubility coefficients, body composition, and temperature all influence nitrogen uptake at the tissue level.

Three-hundred fsw generally sets the limit for compressed air diving because dissolved nitrogen accumulation in the bodys fluids and tissues renders all but the most experienced divers incapable of accomplishing meaningful work. The U.S. Navy sets the maximum operating depth at 190 fsw for breathing compressed air. In 1935, Dr. Albert Behnke (see Chapter 28) and coworkers discovered for the first time that the increase in inspired nitrogen pressure while breathing compressed air during diving produced a narcotic effect characterized by a general state of euphoria similar to alcohol intoxication, termed rapture of the deep. Dissolved nitrogen at a depth of 30 m (98 $\mathrm{ft})$ produces effects similar to those felt after consuming alcohol on an empty stomach. Divers often speak of Martini s Law." This well-known dictum states that every 50 feet (15.2 m ) of seawater produces effects equal to 1 dry martini on an empty stomach. As a rough estimate, this would mean a diver at 200 feet ( 61 m ) experiences intoxication from pressurized nitrogen equal to 4 martinis! Eventually, high nitrogen levels produce a numbing, anesthetic effect on the central nervous system. The term nitrogen narcosis, or inert gas narcosis," collectively describes these mimicking effects of intoxication. The term was first coined by Jacques Cousteau (1910 1997; www.cousteau.org/) in his 1953 book, The Silent World. Cousteau s partner Frederic Dumas was diving to about 240 feet in the Mediterranean Sea. The following quote from Dumas was the first widely read description of the intoxicating effect of breathing nitrogen under pressure.

I $m$ anxious about that line, but I really feel wonderful. I have a queer feeling of the beatitude. I am drunk and carefree. My ears buzz and my mouth tastes bitter. The current staggers me as though I had too many drinks. I [have] forgotten Jacques and the people in the boats. My eyes are tired. I lower on down, trying to think about the bottom, but I can t . I m going to sleep, but I can $t$ fall asleep in such dizziness.

At the extreme, mental processes deteriorate so that a diver may feel that the scuba serves little purpose and remove it or swim deeper instead of toward the surface.

Nitrogen diffuses slowly into body tissues so the narcosis effect depends on dive depth and duration. Considerable individual variation exists for nitrogen sensitivity, but a mild narcosis usually appears after an hour or more at 30 to 40 m
( 98131 ft )-the maximum recommended depth for recreational scuba divers. Treatment requires that the diver ascend to a shallower depth, where complete recovery usually occurs rapidly. The precise role of body fatness in nitrogen narcosis remains controversial.

## Decompression Sickness

With rapid ascent, the external pressure against the diver s body decreases dramatically. Excess dissolved nitrogen in the body tissues begins to separate from the dissolved state; it eventually forms bubbles in the tissues, an effect not unlike the appearance of carbon dioxide bubbles when removing the cap from a carbonated beverage bottle. With the cap in place, the gas remains dissolved under pressure. Removing the cap suddenly reduces pressure above the fluid, causing bubbles to form. Decompression sickness occurs when dissolved nitrogen moves out of solution and forms bubbles in body tissues and fluids. It results from ascending to the surface too rapidly following a deep, prolonged dive, often made possible with double and triple air tanks. Nitrogen reaches equilibrium slowly in many tissues, particularly fatty tissues, so it leaves the body slowly. ${ }^{18,38}$ This means that women (with a greater average percentage body fat than men) and obese men face greater risk for decompression sickness. Figure 26.7 compares nitrogen elimination after a simulated dive" by two dogs that differed in fat content. The relatively fat dog (yellow line) eliminated considerably more nitrogen over the 4 -hour decompression than the leaner dog.

The term bends, a synonym for decompression sickness, was coined during construction of piers for the Brooklyn Bridge (1869 1883) to reflect the bent-over position of limping workers who emerged from the caisson. The following


## $\square$ Low body fat $\square$ High body fat

Figure 26.7 Nitrogen elimination from body tissues of a relatively lean dog and one higher in body fat during decompression in a chamber. (Courtesy of Dr. A. R. Behnke.)
poignantly describes the time course and fatal consequences of decompression sickness in an early history of this malady: ${ }^{37}$

In 1900, for example, a Royal Navy diver descended to 150 fsw in 40 minutes, spent 40 minutes at depth searching for a torpedo, and ascended to the surface in 20 minutes without apparent difficulty. Ten minutes later, he complained of abdominal pain and fainted. His breathing was labored, he was cyanotic, and he died after 7 minutes. An autopsy the next day revealed the organs to be healthy, but gas was present in the liver, spleen, heart, cardiac veins, venous, subcutaneous, and cerebral veins and ventricles.

## Nitrogen Elimination: Zero Decompression Limits

Diving at a depth of $30 \mathrm{~m}(98 \mathrm{ft})$ for up to 30 minutes represents the time limit before sufficient nitrogen dissolves to pose danger from decompression sickness. About 18 minutes is the limit at $40 \mathrm{~m}(131 \mathrm{ft})$, and one can spend almost an hour at 20 m without danger from decompression sickness. If a diver exceeds the depth duration recommendations for compressed air diving shown in Figure 26.8, the ascent to the surface must progress in a preestablished manner. With this approach, a recreational or commercial diver ascends at a prescribed, relatively slow rate designed not to require stops. This rate of ascent enables all excess dissolved nitrogen to diffuse from the tissues into the blood and escape through the lungs without bubbles forming. Contrary to conventional wisdom, exercise before diving or during decompression does not increase the number of bubbles or magnify the risk of decompression sickness. ${ }^{10}$ In fact, a period of mild continuous exercise ( $30 \% \dot{\mathrm{VO}}_{2 \max }$ ) during a 3-minute decompression period may reduce postdive formation of gas bubbles. ${ }^{9}$ Stage decompression requires the diver to make one or more stops on ascent to the surface. The time required for the slowest tissue compartment to lose sufficient nitrogen to allow ascent to the next depth determines the duration of such pauses (termed stage-decompression stops). For example, a dive to 30 m ( 98 ft ) for 50 minutes requires one 2-minute decompression stop at $6 \mathrm{~m}(20 \mathrm{ft})$ and a 24 -minute stop at $3 \mathrm{~m}(10 \mathrm{ft})$. Surface
stage decompression involves transfer of the diver from the water (after several in-water stops) to a decompression chamber at the surface. The judicious use of a hyperoxic breathing mixture facilitates recompression.

A conservative approach recommends that the sport diver not exceed a $20-$ to $25-\mathrm{m}$ ( 6682 ft ) depth ( $30-\mathrm{m}[98 \mathrm{ft}]$ maximum). During single or repetitive dives, the diver should never approach the time limits indicated by the decompression tables. The recommendations in Figure 26.8 assume a single dive, with a minimum of 12 hours between dives. For repeated dives within 12 hours, the diver must consult the appropriate repetitive dive decompression schedules. ${ }^{34}$ These recommendations account for the residual nitrogen remaining in the body at the start of the next dive if it occurs within the 12 -hour period. Interestingly, air travel within 24 hours of scuba diving increases risk of decompression sickness because commercial airlines usually pressurize cabins to an equivalent altitude of 7000 feet. This further reduction in ambient atmospheric pressure may initiate bubble formation from excess nitrogen dissolved in body tissues during the prior preflight dive(s). ${ }^{19}$

## Consequences of Inadequate Decompression

Bubbles within the vascular circuit initiate complications from decompression injury. ${ }^{5,11,24}$ With the exception of bubbles in central nervous tissue that cause lesions in the brain and spinal cord and damage intravertebral disks, ${ }^{14}$ the primary bubbles form in the venous and arterial vascular bed. Symptoms of decompression sickness usually appear within 4 to 6 hours following a dive. Severe violation of decompression procedures (e.g., diver runs out of air and ascends too rapidly) initiates symptoms immediately; these symptoms progress to paralysis within minutes. Indications of inadequate decompression include dizziness, itchy skin, and aching pain in the legs and arms, particularly in tight tissues such as ligaments and tendons (the classic and most common characteristic). The degree of injury depends on the size of the bubbles and where they form. Bubbles in the lungs cause choking and asphyxia;


Figure 26.8 Zero decompression limits. Any single dive that falls on the left side of the curve requires no decompression provided the rate of ascent does not exceed 60 ft per minute ( $\mathrm{m}=\mathrm{ft} \times 0.34048$ ). Dives on the right side of the line require the decompression period specified in standard decompression tables. ${ }^{35}$
bubbles in the brain and coronary arteries block blood flow and deprive these vital tissues of oxygen and nutrients, to produce cellular damage and death. Central nervous system bends occurs with some frequency; failure to provide immediate treatment leads to permanent neural damage.

Treatment. Treatment for the bends involves lengthy recompression in a hyperbaric chamber. This specialized device elevates external pressure to force nitrogen gas back into solution. Gradual decompression then follows to provide time for the expanding gas to leave the body as the diver returns to the surface." Immediate recompression offers the best chance for success; any delay decreases the prognosis for complete recovery. Figure 26.9 shows a collapsible, lightweight, transportable chamber for rapid deployment during transport of the diver to an appropriate facility to treat decompression accidents. The chances are slim for a sport diver to have ready access to such a recompression chamber. This makes it imperative that divers adhere strictly to recommendations for diving depth and duration.

Higher Prevalence with a Patent Foramen Ovale. Decompression sickness sometimes occurs after uneventful dives, without any reported errors in recommended decompression procedures. Divers with lesions localized in the high cervical spinal cord and brain areas show a higher prevalence of patent foramen ovale ( PFO ) of the myocardium than divers who experience decompression sickness that localizes in the lower spinal cord. ${ }^{15} \mathrm{PFO}$ consists of an interatrial septum channel that forms a functional valve between the right and left


Figure 26.9 Portable, collapsible recompression chamber ( 50 kg [110 lb]) for diving in remote locations. A compressed air cylinder provides a working pressure differential of 2.1 ata (bars), or 70 fsw , between the chamber environment and ambient conditions; the diver receives oxygen via a breathing mask. The tube is constructed from para-aramid fiber (like Kevlar) in a matrix of silicone rubber. This provides flexibility (can fold when not in use) and considerable strength under pressure (burst pressure approximately 14 ata differential pressure). (Manufactured by SOS Limited, London, England; photo courtesy of John Selby of SOS Hyperlite of Douglas, Isle of Man.)
atria. This channel could cause localized decompression sickness because nitrogen bubbles that the pulmonary vasculature normally filters pass through the PFO into the arterial circulation. The bubbles then migrate preferentially into the carotid and/or vertebral arteries. Divers should be evaluated for PFO with unexplained decompression sickness but with symptoms suggesting cerebral or high spinal localization. ${ }^{16}$

## Oxygen Poisoning

Inspiring a gas with a $\mathrm{PO}_{2}$ above 2 ata $(1520 \mathrm{~mm} \mathrm{Hg})$ greatly increases a diver s susceptibility to oxygen poisoning, particularly at elevated metabolic rates during physical activity. ${ }^{2}$ For this reason, closed-circuit scuba that uses pure oxygen severely restricts both diving depth and duration (Table 26.3). At depths greater than 25 fsw ( 7.6 m ), the diver should not rebreathe pure oxygen except in extraordinary circumstances. A decreased vital capacity strongly indicates impaired pulmonary function under hyperoxic conditions. ${ }^{7}$

Breathing high pressures of oxygen negatively affects bodily functions in three ways:

1. Irritates respiratory passages and eventually induces bronchopneumonia if exposure persists
2. Constricts cerebral blood vessels at pressures above 2 ata and alters central nervous system function
3. Depresses carbon dioxide elimination

For carbon dioxide elimination, an elevated inspired $\mathrm{PO}_{2}$ may force sufficient oxygen into solution in the plasma to supply the diver s metabolic needs. In this case, oxygen remains combined with hemoglobin (oxyhemoglobin) as blood returns to the pulmonary capillaries. This causes carbon dioxide buildup because deoxygenated hemoglobin normally transports considerable carbon dioxide as carboaminohemoglobin from the tissues (see Chapter 13). Treatment for oxygen poisoning consists of breathing air at sea-level pressure.

## Carbon Monoxide Poisoning

Potentially lethal carbon monoxide gas combines some 200 times more readily with hemoglobin than does oxygen.

TABLE 26.3 Representative Depth Time Limits for Closed-Circuit Diving with 100\% Oxygen

| Depth (fsw) | Maximum Time (min) |
| :---: | :---: |
| 25 | 240 |
| 30 | 80 |
| 35 | 25 |
| 40 | 15 |
| 50 | 10 |

Adapted from United States Navy diving manual, vol 2. Mixed gas diving, rev 3. NAVSEA publ 0994 LP-001-9020. May 1991.

Consequently, only a small quantity of carbon monoxide in the inspired mixture induces tissue hypoxia. Carbon monoxide poisoning is of concern during deep dives because the partial pressures of all gases in the breathing mixture (including impurities) increase greatly.

Urban areas are likely candidates for high levels of contaminants from automotive and industrial exhausts, including carbon monoxide and oxides of sulfur. One should never fill a scuba tank during air pollution or unhealthy air" alerts. Aside from the contaminants present in ambient air, operating gasoline or diesel engine compressors contributes additional carbon monoxide and oil impurities. Placing the compressor s engine exhaust downstream from the air intake eliminates this potential source of contamination. The antidote for carbon monoxide poisoning requires immediate breathing of hyperbaric oxygen. High pressures of inspired oxygen hasten dissociation of carbon monoxide from the hemoglobin molecule.

## Are Women at Risk?

About $35 \%$ of recreational scuba divers in the United States are women. They do not experience a greater risk than men of
equivalent physical fitness for decompression sickness, nitrogen narcosis, oxygen toxicity, air embolism, or diving accidents. Little research has assessed the risks of open-circuit scuba diving to the fetus during pregnancy. Prudent guidelines recommend that pregnant women refrain from scuba diving during pregnancy to eliminate risk of fetal injury from maternal breathing of compressed air at elevated pressures. ${ }^{33}$ However, firm data to support this recommendation remain lacking. ${ }^{31}$

## DIVES TO EXCEPTIONAL DEPTHS: MIXED-GAS DIVING

Commercial, military, scientific, rescue, and technical divers often descend to depths in excess of 160 fsw. Recall that at depths greater than 60 fsw , diving with compressed air and saturation diving (see p. 658) increase risk of oxygen toxicity. Diving lower than this depth requires breathing compressed mixed gases (nonair) with a lower $\mathrm{Po}_{2}$ (Fig. 26.10). Oxygen always exists in the breathing mixture in mixed-gas diving, but it represents only a small fraction of the mix in dives to extreme depths. Precise management of oxygen concentrations becomes a primary consideration in mixed-gas diving. Three mixtures of oxygen, nitrogen, and helium are used today for


Figure 26.10 Rationale for breathing gas mixtures other than compressed air when diving to great depths. Avoidance of nitrogen narcosis and oxygen poisoning are the overwhelming reasons for breathing nonair mixtures.
deep and saturation diving: (1) nitrox (nitrogen + oxygen), (2) heliox (helium + oxygen), and (3) trimix (helium + nitrogen + oxygen). Relatively shallow recreational dives employ nitrox, while heliox is used for deep diving, and trimix for dives to depths that may produce high-pressure nervous syndrome (see next section). ${ }^{3}$

## Helium Oxygen Mixtures

Helium, the second lightest known element, is the most common inert gas substituted for nitrogen in deep diving. Helium is colorless, odorless, tasteless, nonexplosive, and relatively nontoxic and does not induce narcosis at any inspired pressure. ${ }^{29}$

Helium in the breathing mixture in diving came into its own during the 1939 rescue of remaining crew members and salvage of the submarine Squalus (see p. 644). For these purposes, a compressor at the water s surface continually supplied the divers with a helium oxygen (heliox) mixture Because of helium s low density, breathing heliox mixtures reduces the typically increased breathing resistance imposed by nitrogen.

During rapid descent to depths in excess of 300 fsw up to 2280 fsw, divers can experience potentially incapacitating nausea, muscle tremors, and other central nervous effects breathing helium oxygen mixtures. This phenomenon was first noted in the 1960s and termed high-pressure nervous syndrome (HPNS), or initially as helium tremors. The condition probably results from the direct effects of extremes of hydrostatic pressure on excitable nerve cells. Slowing the rate of descent (compression) and adding a small amount of narcotic gas (e.g., $5 \% \mathrm{~N}_{2}$ ) to the heliox breathing mixture relieves the tremor associated with HPNS.

Two other negative effects of breathing helium include:

1. Changes in voice characteristics (high-pitched, cartoonlike quality), which interfere with voice communication among divers. Electronic voice unscramblers remedy this effect.
2. Considerable heat loss for divers living in a heliox environment, from helium s high thermal conductiv-

TABLE 26.4 Representative Oxygen Partial Pressure Limits for Surfacesupplied Heliox Diving

## Exposure Time (min)

Maximum Oxygen Partial Pressure (ata)

| 13 | 1.8 |
| :---: | :---: |
| 20 | 1.7 |
| 30 | 1.6 |
| 40 | 1.5 |
| 80 | 1.4 |
| Unlimited | $\mathbf{1 . 3}$ |

Adapted from United States Navy diving manual, vol 2. Mixed gas diving, rev 3. NAVSEA publ 0994 LP-001-9020. May 1991.
ity $(6 \times$ air $) .{ }^{23}$ The thermal challenge contributes to weight loss, common among saturation divers.

Increased risk for central nervous system oxygen toxicity when breathing surface-supplied heliox gas makes it crucial that the diver not exceed the oxygen exposure limits put forth in Table 26.4.

## National Oceanic and Atmospheric Administration (NOAA; http://www.dive.noaa. gov/): Recommendations to Avoid HPNS

- Do not dive heliox $\left(\mathrm{He}+\mathrm{O}_{2}\right)$ deeper than 400 fsw.
- Do not dive trimix $\left(\mathrm{He}+\mathrm{N}_{2}+\mathrm{O}_{2}\right)$ deeper than 600 fsw. Adding $10 \%$ nitrogen to $\mathrm{He}+\mathrm{O}_{2}$ mix buffers mix so it can be used to 600 fsw without experiencing HPNS.
- Use slow descent rates. Descending slower than one fsw per minute beyond 400 fsw on heliox and 600 fsw on trimix keeps HPNS at bay. Unfortunately, this slow rate of decent is only practical in commercial diving and is of no use in technical diving.


## Saturation Diving

Breathing a heliox mixture supports a safe dive to depths greater than 300 fsw , but the time the diver must remain inwater" for decompression becomes prohibitive. Thus, dives below 300 fsw generally take place with saturation diving in a deep-diving system using a helium oxygen nitrogen (trimix) breathing mixture that maintains oxygen pressure between 0.4 and 0.6 ata $\left(\mathrm{PO}_{2}, 300\right.$ to 450 mm Hg$)$. In saturation diving, each inert gas in a mixture begins to concentrate in body tissues as depth and duration progress. Within 24 to 30 hours, the gases equilibrate and saturate body tissues to equal the pressures of the inspired gases. Once the tissues saturate, the decompression procedure remains identical regardless of the dive s duration.

The deep-diving system consists of a chamber where the divers live under pressure for up to 4 weeks. The system also contains a deck decompression chamber and transfer capsule or diving bell for transport of personnel under pressure to and from the worksite. Once at the worksite, the divers exit, tethered to an umbilicus-supplied breathing apparatus. Saturation diving provides benefits in offshore oil-field work with dives up to 30 days at depths of 1500 fsw. Successful dives to depths of 2300 fsw in a dry chamber apply principles of saturation diving with a breathing mixture of hydrogen, helium, and oxygen. Decompression from a saturation dive takes 8 to 24 hours per $10-\mathrm{m}$ ascent.

A critical consideration in saturation diving with heliox mixtures is to maintain normoxic $\mathrm{PO}_{2}$. Breathing the wrong mixture or the correct mixture at the wrong pressure creates the potential for a tragic fatality. Oxygen percentages must

## FOCUS ON RESEARCH

## The Oxygen Cost of Swimming Underwater

Donald KW, Davidson WM. Oxygen uptake of booted and fin swimming divers. J Appl Physiol 1954;7:31.

> Scuba allows thousands of individuals to enjoy underwater diving. The duration of independence underwater depends on the depth of the dive and the physiologic/metabolic demands of physical activity before the tank empties of compressed air. Minute pulmonary ventilation increases with increasing muscular effort underwater, thus decreasing the duration of the stay.

Early research on underwater diving, particularly with closed-circuit scuba, attempted to establish the interactions among energy expenditure, pulmonary airflow, quantity of oxygen available in the tank, and the diver s rate of return to the surface, to avoid complications such as oxygen poisoning, anoxia, and nitrogen narcosis. Fundamental data required detailed measurements of oxygen consumption $\left(\mathrm{VO}_{2}\right)$ and carbon dioxide production $\left(\mathrm{VCO}_{2}\right)$ to determine the amount of oxygen supplied in the tank and the carbon dioxide absorbent required. The study by Donald and Davidson, completed in 1944 but not published until 1954, was among the first to quantify $\mathrm{VO}_{2}$ of divers and underwater swimmers during different forms of physical effort. This research demanded considerable technical expertise to permit accurate $\mathrm{VO}_{2}$ measurements in the underwater environment.

Subjects included 13 British military divers and 13 military commando" frogmen, each in top physical condition. Subjects underwent multiple measurements under diverse exercise conditions. The researchers used a modified closed-circuit breathing system. Divers breathed pure oxygen under all conditions, which included work in a tank (3.6-m [12-ft] depth) and open seawater. Divers wore either (1) a full rubber diving suit with leather or rubber boots (2.2 $2.7 \mathrm{~kg}[57 \mathrm{lb}]$ in the sole) that allowed them to assume the vertical position with ease or (2) the familiar frogman well-fitting rubber suit with rubber swim fins.

Measurements were taken during rest at the surface, sitting underwater (3.65-m [12-ft] depth), standing underwater, with minimum movement (moving along the bottom as slowly and gently as possible without stopping and avoiding any marked postural changes), and with maximum movement (moving as fast as possible to cover the greatest distance).

Additional $\mathrm{VO}_{2}$ measurements were made during underwater cycle ergometer leg exercise with paddles attached to the pedals to increase resistance. Pedal revolutions per minute (rpm) controlled exercise intensity. A metronome placed in the diver s line of vision maintained pedaling rate. Thirty
rpm represented light exercise maintained easily for 15 minutes, 40 rpm provided intense exercise for 15 minutes, and 45 rpm caused fatigue within 10 minutes. For heavy arm exercise, the diver stood underwater while alternately lifting a 21-pound weight by means of a pulley system. The frogmen swam 0.6 to $0.9 \mathrm{~m}(23 \mathrm{ft})$ below the surface at (1) a medium speed of 0.39 to $0.52 \mathrm{~m}(1.31 .7 \mathrm{ft}) \cdot \mathrm{s}^{-1}$ for $20 \mathrm{~min}-$ utes and (2) a fast speed of 0.52 to $0.70 \mathrm{~m}(1.72 .3 \mathrm{ft}) \cdot \mathrm{s}^{-1}$ for 10 minutes.

## Tank Series: Booted Divers

$\mathrm{VO}_{2}$ with subjects seated and standing still underwater remained low and remarkably near the divers calculated resting values. These men experienced near-neutral buoyancy underwater, so it is likely that lying and standing quietly required less postural effort than in air, hence the low underwater energy expenditure. While these resting data have little application to practical diving conditions, they do help to explain the prolonged periods that trained divers can remain underwater with limited oxygen supply if they remain inactive.
$\mathrm{VO}_{2}$ during the minimum-movement experiments reached the same magnitude as for walking about $3.22 \mathrm{~km} / \mathrm{h}$ $(2.0 \mathrm{mph})$ on the level in air; the underwater maximummovement $\mathrm{VO}_{2}$ equaled the out-of-water $\mathrm{VO}_{2}$ for walking at $6.4 \mathrm{~km} / \mathrm{h}(4 \mathrm{mph})$. Even though the energy expenditure values during underwater effort were relatively low, the divers complained of fatigue, possibly owing to the minimal involvement of the total leg musculature during work underwater.

## Underwater Swimming with Fins

Eight of the 13 swimmers had $\mathrm{VO}_{2} \mathrm{~s}$ of $2.3 \mathrm{~L} \cdot \min ^{-1}$ or above during a 20 -minute swim at the slower speed. At the faster speed, sustained for 10 minutes, 4 of 8 swimmers achieved $\mathrm{VO}_{2} \mathrm{~s}$ over $3.0 \mathrm{~L} \cdot \min ^{-1}$, with one swimmer exceeding $4.0 \mathrm{~L} \cdot \mathrm{~min}^{-1}$, just slightly below his maximum level in air. The $\mathrm{VO}_{2} \mathrm{~s}$ during underwater swimming are similar to those reported for athletes during different sustained sport activities out of water and considerably higher than previously calculated for underwater activities. The results indicated a need to reconsider the maximum size of carbon dioxide absorbent canisters used in most closedcircuit diving systems.

The figure shows the marked differences in $\mathrm{VO}_{2}$ under the different exercise conditions. These carefully designed experiments formed the foundation for further research on underwater energy expenditure. The data contributed to the growing understanding of diving physiology and construction of safer diving systems.

## FOCUS ON RESEARCH



Average and maximum values (shown as error bars) for $\mathrm{VO}_{2}$ for different activities during booted and finned diving. (From Donald KW, Davidson WM. Oxygen uptake of booted" and fin swimming" divers. J Appl Physiol 1954;7:31.)
remain within $\pm 0.10 \%$ of the desired value to avoid either hypoxia or oxygen toxicity. Figure 26.11 shows the typical recommended percentage of oxygen in heliox for various diving depths. For example, the oxygen concentration to obtain a desired $\mathrm{PO}_{2}$ of 0.35 ata $\left(\mathrm{Po}_{2}, 270 \mathrm{~mm} \mathrm{Hg}\right)$ at a depth of 1200 fsw requires a breathing mixture with approximately $0.7 \%$ oxygen.


## Technical Diving

The term technical diving defines untethered dives (scuba or closed-circuit rebreathing) beyond the traditional compressed air range for military operations, science, salvage, and recreational pursuits. Many recreational scuba divers now consider the typical depth limit of 130 fsw imposed by diving with compressed air too restrictive. They wish to expand diving

Figure 26.11 Range of oxygen concentrations for saturation diving. The green line represents the oxygen concentration that maintains oxygen at $0.35 \mathrm{~atm}\left(\mathrm{PO}_{2}=266 \mathrm{~mm} \mathrm{Hg}\right)$, a common choice for $\mathrm{PO}_{2}$. The yellow line shows the oxygen needed to provide the normoxic level of 0.21 atm . The red line represents $0.5 \mathrm{~atm}\left(\mathrm{PO}_{2}=380 \mathrm{~mm} \mathrm{Hg}\right)$, the upper limit of continuous exposure to avoid whole-body oxygen toxicity. The low oxygen concentrations needed at great depths become difficult to mix and analyze within acceptable tolerance limits; thus, they are usually mixed as the diving chamber becomes pressurized. (From Hamilton RW. Mixed-gas diving. In: Bove AA, Jefferson CD, eds. Diving medicine. 4th ed. Philadelphia: WB Saunders, 2004.)
depths for personal achievement, recreation, and exploration (e.g., cave diving). Technical diving requires special equipment, expertise, and vigilant management of gas mixtures. Technical divers routinely use various mixtures of trimix compressed gas to dive below 300 fsw . Blending a depth-specific gas mixture allows the diver to control the risk of hyperoxia and the narcotic potential of nitrogen.

Closed-circuit nitrogen oxygen and helium oxygen scuba originally developed for military operations now appear in the recreational technical-diving community. These highly sophisticated systems maintain a constant partial pressure of oxygen in the inhaled mixture regardless of depth. Figure 26.12 illustrates a closed-circuit mixed-gas system used by the U.S. Navy. An oxygen sensor (19) and microprocessor (21) in the breathing loop continually detect and regulate falling $\mathrm{PO}_{2}$. The sensors activate valves that add the precise quantity of $100 \%$ oxygen to regulate inspired $\mathrm{PO}_{2}$ at 0.75 ata ( 427 mm Hg ). One of two high-pressure gas bottles ( 9 and 14 ) supplies pure oxygen, and the other provides either air or a heliox mixture as the diluent gas. As with the typical closed-circuit system, a chemical bed absorbs carbon dioxide produced in metabolism.

Monitors within the facemask provide continual feedback about $\mathrm{PO}_{2}$ and diving depth. A fiberglass casing worn on the diver s back contains the microprocessor, gas bottles, breathing bag, and insulated carbon dioxide absorbent canister (cold decreases $\mathrm{CO}_{2}$ absorbent life).

## ENERGY COST OF UNDERWATER SWIMMING

As with surface swimming, drag forces impede the diver s forward movement and greatly increase the energy cost of swimming underwater. Figure 26.13 shows the curvilinear relationship between oxygen consumption and underwater swimming speed. For example, a swimmer with a $\dot{\mathrm{V}}_{2 \text { max }}$ of $35 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ could swim underwater at a speed of 1.2 knots ( 1.4 mph ) for only several minutes. This speed creates minimal stress for a diver with a $\dot{\mathrm{V}}{ }_{2 \text { max }}$ of $65 \mathrm{~mL} \cdot \mathrm{~kg}^{-1}$ $\cdot \min ^{-1}$. The location and density of the gear can alter the diver $s$ positioning in the water and increase the energy cost of swimming by as much as $30 \%$ at slow speeds. The type of


Figure 26.12 Closed-circuit mixed-gas system used by the U.S. Navy for diving to great depths. A microprocessor and oxygen sensors in the breathing loop continually detect falling $\mathrm{PO}_{2}$ and activate valves that add the precise amount of $100 \%$ oxygen to regulate the partial pressure of inspired oxygen. A single high-pressure gas bottle supplies pure oxygen, and a second provides either air or a heliox mixture as a diluent. A chemical bed continually absorbs the carbon dioxide produced in metabolism.


Figure 26.13 Generalized curvilinear relationship between oxygen consumption ( $\mathrm{mL} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~min}^{-1}$ ) and underwater swimming speed ( 1.0 knot $=1.15 \mathrm{mph}$ ).
fin used has an effect on the depth and frequency of the kick, thus influencing drag and swimming economy. ${ }^{27}$

## Summary

1. Breath-hold diving has been practiced for centuries. Deep-sea diving had its origins in the 14th century with the invention of diving bells supplied with surface air.
2. The underwater environment routinely exposes divers to high pressures (hyperbaria) and the possibility of rapidly changing pressures. Severe injury and even death ensue unless divers adjust to equalize pressures in the body s air-filled cavities.
3. Two factors limit snorkel size: (1) increased hydrostatic pressure on the chest cavity during descent and (2) increased pulmonary dead space from enlarging the snorkel s internal volume.
4. Duration of a breath-hold dive depends on time until arterial $\mathrm{PCO}_{2}$ reaches the breath-holding breakpoint.
5. Hyperventilation considerably lowers arterial $\mathrm{PCO}_{2}$ and increases breath-holding time; it also increases the likelihood of underwater blackout.
6. The point at which the diver s lung volume compresses to RLV generally determines maximum depth for breath-hold diving. Lung squeeze occurs below this critical depth when internal and external pressures cannot equalize.
7. Breath-hold diving by elite divers produces intense cardiovascular changes that resemble response patterns of diving mammals.
8. Scuba supplies breathing mixtures at great depths and pressures. Specific hazards result from improper equalization of pressures in the lungs, sinus, and middle-ear spaces with the external water pressure. Important dangers include air embolism, pneumothorax, mask and middle-ear squeeze, and aerosinusitis.
9. Gases breathed at high pressures move across the alveolar membrane to dissolve and equilibrate in the fluids of all tissues.
10. High tissue oxygen and nitrogen pressures exert profound negative effects on physiologic function. The maximum recommended diving depth for breathing compressed air is about $30 \mathrm{~m}(98.4 \mathrm{ft})$.
11. Prolonged breathing of a gas with a $\mathrm{PO}_{2}$ above 2 ata increases a diver s susceptibility to oxygen poisoning. Closed-circuit scuba systems that use pure oxygen severely restrict dive depth and duration.
12. Nitrogen bubbles form in tissues when excess nitrogen fails to exit through the lungs if ascent progresses too rapidly. Decompression sickness, or bends, describes this painful condition.
13. Diving to depths below 60 fsw requires inhalation of compressed mixed gases. Oxygen always exists in the breathing mixture in mixed-gas diving, but it represents only a small fraction of the mix in dives to extreme depths. Precisely managing oxygen concentrations becomes a primary consideration.
14. Breathing mixtures of helium and oxygen (heliox) allows dives to depths of 2000 fsw. Heliox diving eliminates nitrogen narcosis risk and minimizes risk of oxygen poisoning.
15. Rapid descent to depths from 300 fsw to 2800 fsw breathing heliox mixtures produces nausea, muscle tremors, and other central nervous system effects termed high-pressure nervous syndrome (HPNS).
16. Drag forces that impede a diver s forward movement increase the energy cost of swimming underwater.

References are available online at http://thepoint.lww.com/mkk7e.

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Mystic Aquarium Institute for Exploration www.ife.org
National Oceanic \& Atmospheric Administration Dive Page http://www.dive.noaa.gov/


## CHAPTER 27

## Microgravity: The Last Frontier

## CHAPTER OBJECTIVES

$>$ Define the term gravity and list factors that affect the magnitude of gravitational force
> Differentiate between zero-g and weightlessness
> Outline factors that contribute to a sense of free fall in a falling elevator
> Describe four strategies to simulate microgravity with inanimate objects and animals and humans
> Describe how the KC-135 airplane creates brief durations of microgravity during astronaut training
> List five physiologic/anatomic responses to microgravity exposure; differentiate between shortterm and long-term responses
> Give reasons for denitrogenation prior to extravehicular activity in space and procedures to achieve this effect
> Discuss the role of hind-limb unloading to study mammalian responses to microgravity
> Outline the goals of exercise countermeasures to ensure astronaut health and safety during missions and return to Earth
> Describe the rational for applying lower-body negative pressure and its role as a countermeasure during spaceflight
> Outline interactions among energy balance, nutrition, and protein dynamics during space missions
> Describe the time course for postflight recovery for physiologic systems from 2-week and 1-year space missions
> List 10 significant spin-off technologies from space biology research

## THE WEIGHTLESS ENVIRONMENT

The pioneering efforts of mainly German, Russian, and American scientists and engineers advanced aerospace medicine from the early test flights of rocket-propelled jet aircraft to the technologic innovations of today s International Space Station (ISS) that orbits 220 nautical miles (a nautical mile is 1852 m , or 1.852 km ; 1 nautical mile $=1.1508$ miles, or 6076 ft ) above Earth. The remarkable successes of man s escape from Earth s atmosphere and subsequent return originated in antiquity, when prophets and philosophers could only dream of contacting celestial bodies. From flying machine designs of da Vinci s Renaissance drawings five centuries ago at the dawn of modern science to successful hot-air balloon ascents during the mid-1700s, the obsession to explore the universe has not waned. By 2011, the reliability of powerful rocketry and new aircraft design and composite materials will make commercial, suborbital space adventure a reality. NASA also will face new challenges as it creates the Orion crew exploration vehicle, an advanced class of space vehicle for travel back to the moon in 2020 (www.nasa.gov/mission_pages/constellation/orion/). Future research efforts will determine how best to tame the longer-term physiologic stressors imposed by yearlong flights to Mars-and eventually beyond.

The early jet flights could not test human responses to changing gravitational forces because that era s test aircraft could not accommodate specialized laboratory equipment. Nevertheless, knowing how to cope with the unique environmental stressors (and health challenges) of high-altitude exposure still required new understanding unavailable from conventional medicine. The field of aerospace medicine (www.asma.org) emerged from a need to deal with unconven-
tional situations not encountered in normal gravity (g). Aerospace medical research progressed using the responses of mice, cats, dogs, monkeys, and eventually humans to spaceflight. Concurrently, research progressed by use of space cabin simulators on Earth. Scientists focused on human psychophysiologic responses to changing gravitational forces and prolonged isolation while performing complex motor and mental tasks. The experience from simulations and manned flights provided new understanding about spaceflights impact on human structure, function, and adaptation.

The United States is not the only country committed to reinvigorating its efforts to future space exploration. The concept of an Advanced Crew Transportation System, or ACTS, also known as Euro-Soyuz Crew Space Transportation System (CSTS), was developed by Russia during 2006 to replace the workhorse Soyuz spacecraft (www.astronautix .com/craftfam/soyuz.htm). Since then, the Russian Federal Space Agency (www.roscosmos.ru/index.asp?Lang=ENG) has put consderable resources into developing the next generation manned transport, a modified Soyuz vehicle capable of achieving lunar orbit. This effort was designed to coincide with the United States goal to return humans to the moon by 2020 with NASA s new Orion crew exploration vehicle, shown schematically in Figure 27.1 approaching the International Space Station in Earth orbit and tracking the sun to generate electricity as it circles the moon (www.nasa.gov/mission_pages/ constellation/main/index.html).

## Gravity

On the Earth s surface, gravity provides an invisible attraction that makes any mass exert downward force or have


Figure 27.1 NASA s Constellation Program is developing the new spacecraft to return humans to the moon and then onward to Mars and other destinations in the solar system. Initially, the new spacecraft will deliver crews and cargo to the International Space Station (right); it will be similar in shape to the Apollo spacecraft but significantly larger. The tried-and-true conical form is the safest and most reliable for reentering the Earth s atmosphere. Orion will rendezvous with a lunar landing module and an Earth departure stage in low-Earth orbit (left), and for Mars-bound vehicles, assembled in low-Earth orbit. Orion will serve as the Earth entry vehicle for lunar and Mars returns. Orion s design will take advantage of 21 st century technology in computers, electronics, life support, propulsion, and heat protection systems. (Photos courtesy of NASA and Lockheed Martin Corp.)


Figure 27.2 Top. Two different size masses ( $m_{1}$ and $m_{2}$ ), depicted as the green- and red-filled circles, and separated by a distance $r$ exert attractive gravitational forces ( $\mathrm{F}_{\mathrm{g}}$ ) on each other. The forces on each particle have equal magnitude even when their masses differ markedly. Bottom. Microgravity refers to the perceived weightlessness associated with free fall. The forces acting on an astronaut orbiting Earth in a spacecraft are not balanced—both astronaut and spacecraft accelerate toward the Earth s center. They do not fall to the Earth because its surface is curved and they are moving at a tangential velocity $\left(\mathrm{V}_{\mathrm{T}}\right)$ high enough to balance gravity s downward force on the spacecraft. No perceived force (i.e., weight) exists because nothing counteracts the force of gravity.
weight. Gravity behaves in the same fundamental way between the Earth and any object on it, between any of the planets that revolve about the sun in our solar system, or between a planet and its moons. The universality of the gravitational law, first proposed in 1687 by Sir Isaac Newton (1642 1727), can be stated as follows and is depicted in the top of Figure 27.2.

Every particle in matter in the universe attracts every other particle with a force directly proportional to the product of the masses of the particles and inversely proportional to the square of the distance separating them.

When a person sits in a chair on Earth, the force of gravity pulls the person into the seat because the chair provides an equal and opposite force (Newton s third law). Every mass $(m)$ on Earth requires support from a force $(F)$ equal to its weight $(w)$ such that $w$ (or $F)=m g$. Stated differently, the
constant acceleration force per second (s) of descent on a freely falling body at or near Earth s surface has a value of 1 g (acceleration due to gravity), with an equivalent magnitude of 9.80665 or $9.80 \mathrm{~m} \cdot \mathrm{~s}^{-2}, 980 \mathrm{~cm} \cdot \mathrm{~s}^{-2}$, or $32 \mathrm{ft} \cdot \mathrm{s}^{-2}$. On the moon s surface, the attractive force of the moon rather than Earth causes the acceleration of gravity, where $g=1.6 \mathrm{~m} \cdot \mathrm{~s}^{-2}$. Near the sun s surface, the $g$ value increases tremendously by a factor of nearly 169 to $270 \mathrm{~m} \cdot \mathrm{~s}^{-2}$.

## Microgravity and Weightlessness

To achieve an orbit around Earth or move away from it, the velocity of a rocket must exceed the downward pull of Earth s gravity. The gravitational pull on the rocket decreases as the rocket moves farther from Earth. When the rocket reaches a specified distance from Earth sufficient for orbit, a traveler experiences a weightless feeling because nearly all of the forces acting on the body remain in balance. To reach a point in space where the gravitational pull from Earth equals one-millionth the force at Earth s surface requires traveling 6.37 million kilometers, or 16.6 times, the distance from Earth to the moon, or 1400 times the highway distance between New York City and San Francisco. In a practical sense, a rock dropped from a window 5 m above the ground requires 1 s to touch ground. In an environment with only $1 \%$ of Earth s gravitational pull, the same drop takes 10 s . In a microgravity environment equal to one-millionth of the gravity on Earth, the same 5-m drop would take 1000 s , or approximately 17 minutes.

Spacecraft orbit Earth at a relatively close distance (typically 200 to 450 km [155 to 248 mi ]), so astronauts experience only an apparent sense of weightlessness. In essence, the force of gravity never truly reaches an absolute value of zero (called zero-g) because some gravitational force still exists. Consequently, the term microgravity, not weightlessness (or zero-g), correctly describes what astronauts feel during spaceflight in Earth s orbit when the rocket s altitude exceeds approximately $160 \mathrm{~km}(100 \mathrm{mi})$ at a velocity of approximately 17,500 mph.

The $121-\mathrm{ft}$ space shuttle orbiting laboratory can carry a payload of $29,479 \mathrm{~kg}$ into orbit, with each main engine producing a thrust of $170,068 \mathrm{~kg}$ at sea level while burning a mixture of liquid oxygen and hydrogen. After achieving orbital velocity, the astronaut and spacecraft continually accelerate toward a single point at the Earth s center. However, they do not fall to Earth because of the planet s curved surface and because both craft and crew move at a high enough tangential velocity $\left(\mathrm{V}_{\mathrm{T}}\right)$ to the Earth (see bottom of Fig. 27.2). The spacecraft s speed creates an outward centrifugal force that balances the downward gravitational force on the spacecraft. When spacecraft velocity decreases (reduced $\mathrm{V}_{\mathrm{T}}$ )—a planned maneuver during reentry-the craft plunges toward Earth under gravity s pull.

## Passenger in a Falling Elevator

When an elevator descends quickly, one feels a lessening of weight because of reduced force between the feet and
elevator floor. If the elevator cable suddenly snaps and the elevator plummets downward, the force against the feet equals zero until the elevator strikes bottom. Consider the example of a $60-\mathrm{kg}(132 \mathrm{lb})$ woman riding in an elevator. If she could lift her feet off the floor before hitting the ground, she would float within the elevator compartment. No force pushes her up because she and the elevator fall together at the same speed and acceleration. This applies equally to any other objects in the elevator. If a scale were present in the elevator, the woman s weight would not register because the scale too would be falling. During free-fall, everything in the elevator remains weightless because the person and elevator car (including a scale) accelerate downward at the same rate from gravity alone.

## Examples of Near Zero-G During Spaceflight

Spaceflight provides the ubiquitous condition of near zero-g. Liquids fail to remain in open cups or glasses, so drinks must be squeezed into the mouth from special containers. No up or down exists inside the space vehicle (Fig. 27.3); to keep from floating freely, astronauts must anchor or tether themselves to a fixed object within the cabin (e.g., a wall or other attached object).

In microgravity, blood and fluid volumes shift upward and move into the thoracocephalic region. This causes a puffy-face appearance as fluid relocates from extracellular to intracellular spaces. ${ }^{89}$ Correspondingly, a 2 - to $5-\mathrm{cm}$ decrease occurs in waist girth (a legitimate way in space to wear otherwise tight-fitting pants!). The initial net shift of fluid also


Figure 27.3 Demonstration of microgravity aboard Spacelab where no up or down exists.
produces eye redness, bird-type (skinny) legs, nasal congestion, headaches, and nausea. Concomitant reductions in blood volume affect cardiovascular function, manifested by decreased plasma and red blood cell volume, ${ }^{38}$ increased venous pooling, blunted baroreceptor reflex, and orthostatic intolerance, defined as compromised venous return to the heart during upright posture in a gravity environment.

On Earth, the constant downward pressure of 1 g compresses intervertebral disks. In microgravity, removal of gravitational force causes disks to expand, making stature increase up to 5 cm (Fig. 27.4, top). The bottom of Figure 27.4 illustrates that posture also changes during microgravity exposure. Compared with preflight, joints move toward the midpoint in their range of motion so that hips and knees flex slightly, causing the body to crouch. Arms tend to float in front of the body unless consciously forced downward. Note the postural sway with the head protruding forward with accompanying lordosis immediately upon return to Earth.

## Strategies to Simulate Microgravity

Different strategies have simulated spaceflight s microgravity environment. This allows researchers to manipulate various experimental conditions before deciding on the best procedure(s) for a particular mission. One strategy uses sophisticated test equipment that creates zero-g conditions for relatively brief times with nonhuman objects dropped from towers and into tubes or within sounding rockets as they fall to Earth after achieving a maximum altitude. Another tactic uses parabolic airplane flights with living and nonliving objects, and a third strategy simulates microgravity conditions with animals and humans using head-down bed rest, confinement, water immersion, or immobilization.

## Human Testing

Researchers have devised five basic strategies to simulate a microgravity environment and study its effects on humans (1) head-down bed rest, (2) wheelchair confinement of paraplegics, (3) water immersion, (4) immobilization and confinement, and (5) parabolic flights.

Head-Down Bed Rest. Head-down bed rest has yielded the most information about human physiologic dynamics in simulated microgravity (FIG. 27.5). These studies confirmed experimental findings in space about physiologic responses and adaptations including psychologic stress, hormonal changes, and immune function ${ }^{27,96}$; this makes the head-down bed-rest strategy a useful spaceflight analogue. Subjects remain confined to bed for an extended time (weeks, months, or a year) in a horizontal or headdown tilt position ( -3 to -12 ), often followed by physiologic measurements to positive acceleration at forces up to 3 g in a centrifuge.

Wheelchair Confinement of Paraplegics. Prolonged wheelchair confinement produces postural hypotension in


Figure 27.4 Top. Change in the center of gravity/mass $(C G \div M)$ and stature before (F), during an 84-day Skylab 4 mission, and 17 days postflight ( $R+17$ ). Bottom. General changes in posture under conditions of Earth $s$ gravity ( 1 g ) and microgravity. (From Thornton WE, et al. Anthropometric changes and fluid shifts. In: Johnson RS, Dietlein LF, eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: Government Printing Office, 1977.)
paraplegics who seldom experience full erect posture following their disability. ${ }^{42}$ As in longer spaceflight missions ( $>21$ days), years of sitting constrain fluctuations in hydrostatic gradients normally experienced by nonparaplegics during routine daily activities. Short-term exercise stress (e.g., graded, arm-crank exercise to maximum ${ }^{107}$ evaluates paraplegics responses for heart rate, systolic and diastolic blood pressure, forearm vascular resistance (FVR), and vasoactive hormones. In general, exercise eliminated orthostatic hypotension and increased FVR and baroreflex sensitivity independent of blood volume changes. The positive cardiovascular adjustments in paraplegics to less frequent but relatively intense exercise have relevance as a postflight countermeasure to the potentially debilitating effects of prolonged missions on
orthostatic stability and baroreflex functions following return to Earth s gravitational environment. The intriguing possibility of immediate benefit from short-term, intense postflight exercise would maximize overall mission efficiency by reducing time devoted to in-flight exercise and concomitant demands for additional food and water associated with daily exercise. ${ }^{49}$

Water Immersion. Subjects lie supine in a water tank for up to 24 hours (wet immersion technique) or lie on a thin sheet to prevent the skin from touching the water (dry immersion technique). In water, astronauts perform complex hand eye coordination tasks to mimic skills required in extravehicular activity (EVA) during orbital missions.


Figure 27.5 Bed-rest, head-down experimental strategy to simulate microgravity effects on postural hypotension and associated cardiovascular functions. (Photo courtesy of NASA, Lyndon B. Johnson Space Center, Houston, TX.)

## Immobilization and Confinement

1. Whole-body or segmental casts restrict limb and body movements in humans and animals. One approach immobilizes the nondominant arm in a sling, except during sleep and bathing, for 4 weeks. ${ }^{107}$ This procedure produces an effective analogue for simulating the effects of weightlessness on human skeletal muscle loading. Changes in muscle structure and function (e.g., torque production, cross-sectional area, histochemical muscle fiber analysis, and integrated electromyography or IEMG) produce results similar in magnitude and direction to data obtained from humans following exposure to real and simulated microgravity environments.
2. Confining animals to a small cage severely restricts their movement.
3. A harness provides partial body support by suspending an animal in a head-down position with gravitational loading removed from the hind limbs.

Parabolic Flights. Figure 27.6 (top) illustrates the strategy to evaluate physiologic responses to microgravity produced

Figure 27.6 Top. Parabolic (Keplerian trajectory) flight profile of NASAs KC-135 aircraft to achieve brief periods of weightlessness. KIAS, knots indicating air speed. (From Nicogossian AE, et al. Space physiology and medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994.) Bottom left. Evaluating the shock absorption qualities caused by vibrations while running on a motorized treadmill during KC-135 flights. Bottom right. Evaluating exercise equipment (aerobic and strength) during KC-135 flights. (Photos courtesy of NASA, Lyndon B. Johnson Space Center, Houston, TX.)


when NASA s KC-135 aircraft climbs rapidly at a 45 angle and then follows a path called a parabola (http://jsc-aircraftops.jsc.nasa.gov/Reduced_Gravity/KC_135_history.html/). The four- engine turbojet aircraft produces a near-zero-g effect $\left(1 \times 10^{-3} \mathrm{~g}\right)$ for about 30 seconds (center purple area in the figure) just as the aircraft achieves 9500 m of the $10,000-\mathrm{m}$ ascent (termed pull-up) before it slows. The plane then traces a parabola (pushover), descending rapidly at a 45 angle (termed pull-out) to 7300 m . The forces of acceleration and deceleration produce 2 to 2.5 times normal gravity during the pull-up and pull-out phases of the flight; the brief pushover at the apogee generates an environment with less than $1 \%$ of Earth s gravity. The nickname vomit comet aptly describes the gutwrenching sensations produced during KC-135 training flights.

During repeated brief parabolic roller coaster-like maneuvers, scientists evaluate how humans and equipment function during intermittent forces that range from 1.8 g to near-zero-g, similar to those experienced during liftoff and reentry of space vehicles. Depending on the mission, astronaut training can include up to 60 parabolic flights daily for a week, providing about 3 hours of cumulative weightlessness. The final flight of the KC-135 occurred on October 29, 2004; its replacement, a C-9 aircraft, is the military version of the DC-9 used by commercial airlines and military for medical evacuation, passenger transportation, and special missions.

The new field of bioastronautics focuses on biologic and medical effects of spaceflight on human systems. The National Space Biomedical Research Institute (NSBRI; www.nsbri.org) has developed long-range plans to implement research to prevent and reduce the known risks to astronaut health, safety, and mission performance. ${ }^{39,135}$ In 2008, the NSBRI and NASA selected 33 research proposals to help investigate questions of astronaut health and performance on future space exploration missions (www.nsbri.org).

## Mathematical Modeling and Computer Simulations

Researchers generally consider an entire physiologic system (e.g., cardiovascular, thermoregulatory, hormonal, respiratory, muscular) or subdivide it into its component parts. For example, elements of the cardiovascular system include the heart, lungs, blood vessels, and blood. Each constituent can further subdivide into parts and factors such as wall compliance, wall thickness, and blood flow within the heart s chambers or through its valves and specific vasculature. Researchers mathematically model each component on the basis of known values for a particular function (e.g., $\mathrm{HR}_{\text {max }}$ in young adults averages $200 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ ).

Armed with facts about the entire physiologic system, a computer-based model re-creates how the system would respond to weightlessness when changes affect single or multiple components. Researchers have applied mathematical models of the thermoregulatory and cardiovascular systems to establish design criteria for the astronaut s space suit. For example,
the model predicts the range of energy expenditures an astronaut might encounter with EVA (from 180 to $200 \mathrm{kCal} \cdot \mathrm{kg}^{-1}$ $\cdot \mathrm{h}^{-1}$ ) assessed during different space missions. ${ }^{106}$

## HISTORICAL OVERVIEW OF AEROSPACE PHYSIOLOGY AND MEDICINE

Today s astronauts must overcome numerous challenges as they prepare to live in space for prolonged periods. Perhaps during the middle of this century, thousands of individuals will routinely travel into space, some establishing permanent space colonies relatively near Earth orbit, while others will participate in exploration-class Mars missions.

As humans venture into unexplored regions of space, new scientific knowledge about adaptations to microgravity affects exploration efforts. Research in exercise physiology and interrelated disciplines has significantly expanded knowledge about microgravity s effects on human structure and function, and adaptations and countermeasure strategies to minimize undesirable outcomes. Throughout the history of aerospace exploration, achieving each new milestone fostered new challenges to improve human safety and health while at the same time matching aircraft performance with the ambitious demands of flying faster and higher. A single historical event in 1957-the Russian Sputnik 1 orbiting satellite (discussed shortly)—significantly impacted future research about physiologic function during high-altitude flights-accelerating man s quest to explore heavenly bodies beyond planet Earth.

## Early Years

The first national civil aeronautics laboratory, now known as National Aeronautics and Space Administration Langley Research Center, was established in 1917 in Hampton, Virginia. This research facility currently focuses on aeronautics, earth science, space technology and structures, and materials research (www.larc.nasa.gov/). In 1951, the Aeromedical Association created a Space Medicine Branch for systematic evaluation of human function in a weightless environment. Two new research laboratories, the U.S. Air Force School of Space Medicine and Naval Aerospace Medical Institute (www.hq.nasa.gov/office/pao/History/SP-60/cover.html) also devoted time and resources to study space medicine. These military research facilities partnered with universities and private sector laboratories to create a formidable team to study high-performance aircraft and unmanned guided missiles at high altitudes. Research eventually covered human adaptation to high-altitude exposure. This included development in the 1930s of pressurized suits to allow pilots to achieve higher altitudes than previously ( $50,000 \mathrm{ft}$ ), paving the way for the 19611963 Mercury series of suborbital flights and eventual lunar missions. ${ }^{98}$ From 1951 to 1957 , the two new laboratories and auxiliary support facilities produced significant information, mostly about hardware aspects of spaceflight but also biomedical evaluations during suborbital flights with lower animal forms (bacteria, mice) and primates.

## Suborbital Flights

In December 1946, experiments sponsored by the National Institutes of Health at Holloman s Aeromedical Field Laboratory (and later at Wright-Patterson Air Force Base and White Sands Air Force Base) studied cosmic radiation s effects on fungus spores (unsuccessful, as the cylinders carrying the microbes vanished on reentry) and how fruit flies survived without deleterious effects at an altitude of 171 km . The Albert Project (named for the monkey sealed in the nose cone of the V-2 rocket) attempted to record respiration during spaceflight, but the respiration apparatus failed just before launch and Albert perished. The mission was doomed anyway because the parachute recovery apparatus also failed on reentry.

A second launch (Albert II) occurred 1 year later on June 14,1949 , but the primate died on impact when the recovery chute again failed. Fortunately, respiratory and electrocardiographic instruments verified that the primate functioned well during the 83-mile ascent and return. Two additional V-2 rocket flights provided supportive evidence that a primate could successfully withstand reentry forces of 5.5 g and exposure to cosmic radiation. A fifth V-2 launch substituted a mouse for the monkey, and an onboard camera photographed the mouse at fixed intervals. The mouse died on impact (once again the recovery system failed), but the mouse displayed normal muscular function and coordination during the subgravity flight. Additional flights in 1951 that monitored cardiovascular and respiratory dynamics of primates showed no negative responses during these relatively brief missions.

With subsequent travel, rocketry systems improved and the onboard monkey and mice animalnauts survived intact during suborbital flights to altitudes of 36 miles. High-altitude balloon flights also proved successful. In September 1950, eight white mice withstood a $97,000-\mathrm{ft}$ ascent without negative physiologic consequences. The balloon experiments continued with fruit flies, mice, hamsters, cats, and dogs for up to 24 hours. Most of these experiments ended in failure, mainly from equipment malfunction. Nonetheless, the invaluable experience gained from rocket and balloon launchings, instrumentation and recovery techniques, and the growing body of scientific data related to cosmic radiation and subgravity physiologic responses would greatly benefit subsequent human endeavors. The years 1946 through 1952 marked the practical beginning of Air Force research in space biology, setting the stage for the next round of experimentation with more powerful rockets.

## High-Altitude Explorations

Between 1952 and 1957, research in high-altitude exploration matched the United States enthusiasm for its embryonic space biology programs. Study areas included human reaction to subgravity or near-zero-g conditions, human reentry into Earth s atmosphere, effects of abrupt and sustained
acceleration and deceleration on human response to rocket flight, and equipment design to better accommodate primate and human explorers as they pushed the envelope by ascending higher ( $120,000-\mathrm{ft}$ balloon ascent) and for longer durations (up to 74 h). In 1952, the National Advisory Committee for Aeronautics (NACA; established in 1915 to foster aviation) proposed new research to extend airplane velocity to Mach 10 (see below) at altitudes from 12 to 50 miles, and identify problems with spaceflights at speeds that required a $25,039-\mathrm{mph}$ $\left(40,200 \mathrm{~km} \cdot \mathrm{~h}^{1}\right.$, or $\left.1.12 \times 10^{4} \mathrm{~m} \cdot \mathrm{~s}{ }^{1} \mathrm{~m}\right)$ escape velocity from Earth s gravity.

Mach numbers were named to honor Austrian physicist Ernst Mach (1838 1916) who established basic principles of supersonics and ballistics. The Mach number represents the ratio of an object s velocity to the velocity of sound, which travels at $1089 \mathrm{ft} \cdot \mathrm{s}{ }^{1}$ or $331.9 \mathrm{~m} \cdot \mathrm{~s}^{1}$ at 0 C . For example, Mach 10 refers to 10 times the speed of sound. Interestingly, Professor Mach rejected Newton s concepts of absolute time and space before Einstein, who cited Mach s inertial theories in the early 1900s in developing his relativity theory.

By 1954, characteristics for a new hypersonic research aircraft had been defined, and 1 year later, North American Aviation won the competition to build the $\mathrm{X}-15$ airplane (http://history.nasa.gov/x15/cover.html). Construction began in September 1957, ushering in a new era that featured high-performance aircraft capable of hypersonic speeds ( 4250 mph ) at altitudes close to the fringes of the atmosphere ( 67 mi , or $353,760 \mathrm{ft}$ ). Concurrently, the United States had committed to launch an Earth-orbiting satellite as part of the International Geophysical Year (July 1, 1957, to December 31, 1958) to gather scientific information about our planet. At the same time, the early phases of developing a potential space vehicle and sophisticated satellite program were about to change in sudden and dramatic fashion.

## The Rocket Launch That Shocked the World

On October 4, 1957, the Russians shocked the world when their $83.6-\mathrm{kg}, 58-\mathrm{cm}$ diameter aluminum alloy Sputnik 1 (Fig. 27.7) became the first Earth-orbiting satellite. One month later on November 3, a larger 508-kg Sputnik 2 remained in orbit for almost 200 days with a dog on board. These space milestones-achieved 4 months before the Naval Research Laboratory launched its inaugural, tiny $1.6-\mathrm{kg}$ Vanguard 1 orbiting, unmanned satellite-jolted the United States scientific and government establishments into a sense of urgency to surpass Russia s apparent space technology supremacy. Two factors contributed to a space race to achieve dominance of this new frontier:

1. Fear of losing potential military superiority in space
2. Fear of losing the education race to an enlightened Russian youth who excelled in mathematics and science


Figure 27.7 Sputnik 1 satellite. This beach ball sized sphere took just 98 minutes to orbit the Earth on its ellipitical path—but its journey sent shockwaves around the globe. As a technical achievement according to NASA (http:// history.nasa.gov/sputnik/), Sputnik caught the world s attention and the American public off-guard. The public feared that the Soviets ability to launch satellites also translated into the capability to launch ballistic missiles that could carry nuclear weapons from Europe to the United States.

## MODERN ERA

In 1958, the newly formed NASA laid the groundwork for future discoveries that would affect almost every facet of our lives. These included discoveries about rocketry and propulsion systems, physiologic requirements and adaptations to manned spaceflight, and more than 30,000 practical technol-ogy-transfer payoffs (discussed on p. 714) from interdisciplinary experiments in physical chemistry, microbiology, genetics, medicine, and exercise physiology.

NASA had two main goals: (1) launching a man into space and returning him safely to Earth and (2) developing the capability of humans to endure space missions. ${ }^{102}$ Achieving this second goal had been a Herculean task because the current knowledge of microgravity s effects remained restricted to laboratory simulations. Scientists knew little about how humans would respond to the rigors of microgravity and what might happen during extended sojourns beyond Earth s gravitational field. Experts publicly expressed concern about possible deleterious effects of spaceflight on human function and overall health. In 1958, the National Academy of Sciences National Research Council Committee on Bioastronautics listed potential ill effects from human exposure to the space environment during launch and reentry (Table 27.1). Some concerns proved justified and are discussed in subsequent sections.

TABLE 27.1 Potential Deleterious Effects of Weightlessness for Launch, Travel, and Reentry

| Anorexia | Bone demineralization |
| :--- | :--- |
| Nausea | Renal calculi |
| Disorientation | Motion sickness |
| Sleeplessness | Pulmonary atelectasis |
| Fatigue | Tachycardia |
| Restlessness | Hypertension |
| Euphoria | Hypotension |
| Hallucinations | Cardiac arrhythmia |
| Decreased g tolerance | Postflight syncope |
| Gastrointestinal disturbance | Decreased work capacity |
| Urine retention | Reduced blood volume |
| Diuresis | Reduced plasma volume |
| Muscular incoordination | Dehydration |
| Muscle atrophy | Weight loss |
| Sleepiness | Infectious illnesses |

Modified from Dietlein LF. Skylab: a beginning. In: Johnston RS, Dietlein LF, eds. Biomedical results from Skylab (NASA SP-377). Washington, DC: U.S. Government Printing Office, 1977.

## United States Races into Space

NASAs top priority besides initiating human spaceflight centered on a plan to allow humans to work for extended periods during prolonged space missions. These two goals required advanced technologies in rocket design and effective approaches to prepare test pilots for missions never attempted previously. To put a human into Earth orbit required new ways of looking at the man machine interface. On the human side, engineers had to design a fail-safe life-support system, provide for food and water, integrate an efficient method to remove metabolic byproducts, and implement temperature control to ensure crew safety during liftoff, flight, and reentry. Research had to determine physiologic responses to extremes of acceleration and reduced gravity, including short- and long-term adjustments to prolonged weightlessness. Could a human function competently during liftoff, propelled upward at thousands of miles per hour and then perform flawlessly in maneuvering the space vehicle and returning it to Earth safely? Engineers needed to develop rocket engines with sufficient thrust to achieve escape velocity. The pilot s capsule required intricate communication and navigation controls. The capsule s weight and size had to dovetail with rocket design and launch requirements. In addition, a capsule recovery system required development for safe reentry. The human and engineering requirements facing NASA provided considerable challenges to say the least, but the race into space was on with no turning back.

## MEDICAL EVALUATION FOR ASTRONAUT SELECTION

Candidates for astronaut currently undergo extensive medical and psychologic evaluation ${ }^{64,116}$; the primary objective of U.S. Russian cooperation in space medicine is to maintain the health and fitness of space crews aboard joint missions to the

TABLE 27.2 Physiologic and Psychologic Testing of the First American Project Mercury Astronauts

## Physiologic Tests

1. Harvard step test: Subject steps up 20 inches to platform and down once every 2 s for 5 min to measure physical fitness.
2. Treadmill maximum workload: Subject walks at constant rate on moving platform elevated 1 each min; test continues until heart rate reaches $180 \mathrm{~b} \cdot \mathrm{~min}^{1}$; test of physical fitness
3. Cold pressor: Subject plunges feet into tub of ice water; pulse and blood pressure measured before and during test.
4. Complex behavior simulator: A panel with 12 signals, each requiring a different response, measures ability to react reliably in confusing situations.
5. Tilt table: Subject lies on steeply inclined table for 25 min to measure heart s ability to compensate for unusual body position for extended duration.
6. Partial pressure suit: Subject is taken to simulated altitude of $65,000 \mathrm{ft}$ for 1 h in MC-1 partial pressure suit; measure of cardiovascular efficiency and breathing at low ambient pressures.
7. Isolation: Subject enters a dark, soundproof room for 3 h to assess adaptation to unusual circumstances and coping without external stimuli.
8. Acceleration: Subject is placed in centrifuge with seat inclined at various angles; assesses near multiple gravity forces.
9. Heat: Subject spends 2 h in chamber at 130 F ; measures reactions of heart and body functions to this stress.
10. Equilibrium and vibration: Subject seated on chair that rotates simultaneously on two axes; subject required to maintain chair on even keel using control stick with and without vibration; subject tested with and without blindfold.
11. Noise: Subject exposed to different sound frequencies to determine susceptibility to high-frequency tones.

## Psychologic Tests

1. Extensive interviews (psychiatrists)
2. Rorschach (ink blot)
3. Thematic apperception (stories suggested by pictures)
4. Draw-a-person
5. Sentence completion
6. Self-inventory from 566 -item questionnaire
7. Officer effectiveness inventory
8. Personal-preference schedule from 225 pairs of self-descriptive statements
9. Preference evaluation from 52 statements
10. Determination of authoritarian attitudes
11. Peer ratings
12. Interpretation of the question Who am I?
13. Wechsler Adult Scale
14. Miller Analogies Test
15. Raven Progressive Matrices
16. Doppelt Mathematical Reasoning Scale
17. Engineering analogies
18. Mechanical comprehension
19. Air Force Officer Qualification Test
20. Aviation qualification test (United States Navy) space memory
21. Spatial orientation
22. Gottschaldt Hidden Figures
23. Guilford-Zimmerman Spatial Visualization

ISS. ${ }^{56,100}$ However, little factual information existed about what to expect during spaceflight or the personal characteristics necessary for mission success when NASA devised the first medical evaluation in 1959. Approximately 600 active military test pilots from the Navy, Air Force, Army, and Marine Corps served as the initial candidate pool. From this group, NASA invited 110 for further testing. Thirty-two pilot finalists qualified for the next phase of testing, which included the exhaustive 23-item test battery listed in Table 27.2.

## First Astronauts

The test battery identified a final group of candidates believed best qualified to achieve the following five goals:

1. Survive-Demonstrate ability to fly in space and return safely.
2. Perform-Demonstrate ability to perform effectively under the conditions of spaceflight.
3. Serve as a backup for automatic controls and instrumentation-Increase the reliability of flight systems.
4. Serve as a scientific observer-Go beyond what the instruments and satellites can observe and report.
5. Serve as an engineering observer and true testpilotImprove the flight system and its components.
In April 1959, NASA selected the final seven astronauts. This elite group, survivors of an extraordinarily elaborate search and selection process, would train to enter an unknown environment with a life-support system previously tested only during high-altitude balloon flights. Unknown at that time, NASA had identified, conducted, and completed similar tests with female test pilots with extensive flight experience. However, an executive decision was made that the new astronauts would only be males with commissions in the armed services and with prior fighter pilot training and experience. Although not commonly known, a program was in existence at the same time that had been training a final group of 13 highly experienced female aviators for future space missions. However, that program was unceremoniously scuttled because of bureacratic cronyism at the highest levels of the space agency. ${ }^{2,171}$

Shortly before the 13 finalists known as the First Lady Astronaut Trainees (FLATS) were scheduled to report for testing at Pensacola, FL, the Navy cancelled this effort. Without official NASA support to conduct the tests, the Navy would not allow the use of their facilities. NASA s official
position required that all astronauts be jet test pilots and have engineering degrees. Because no women could meet those requirements (although by every account they were as qualified for flight status as their male counterparts), no women could qualify to become an astronaut! Interestingly, Geraldine (Jerrie) Cobb was the first and only woman to undergo and successfully pass all three phases of Mercury astronaut testing (Fig. 27.8). ${ }^{28}$ Cobb passed the tests at the Lovelace Clinic in Albuquerque, NMthe same private clinic, doctors, and program that selected the astronauts who were to become the Mercury 7 crew (www. mercury13.com/). Cobb s autobiography and other books are highly recommended for insights into the previously maledominated world of test pilots and into these women s zeal to become the first NASA astronauts. ${ }^{11,67,103}$

Ironically, it was Colonel John Glenn (who did not have an engineering degree before he became one of the Mercury astronauts and therefore would have been eliminated from the program had NASA strictly enforced its regulations) who testified before a congressional committee, It is just a fact. The men go off and fight the wars and fly the airplanes and come back and help design and build and test them. The fact that women are not in this field is a fact of our social order. It may be undesirable. ${ }^{120}$

In October 1962, in it s annual report, the House Committee on Science and Astronautics issued these recommendations from the subcommittee on astronaut qualifications:

After hearing witnesses, both Government and nonGovernment, including Astronauts Glenn and Carpenter, the subcommittee concluded that NASA s program of selection was basically sound and properly directed, that the highest possible standards should continue to be maintained, and that some time in the future, consideration should be given to inaugurating a program of research to determine the advantages to be gained by utilizing women as astronauts. (Report of the Special Subcommittee on the Selection of Astronauts: Qualifications for Astronauts. Committee on Science and Astronautics. U.S. House of Representatives. 87th Congress. Second Session. Serial S. Washington, DC: U.S. Government Printing Office, 1962.)

It was not until 1978 that NASA selected six women as astronaut candidates (http://womenshistory.about.com/od/ aviationspace/a/timeline_space.htm). Ironically, this decision occurred 15 years after cosmonaut Valentina Tereshkova from the USSR became the first woman rocketed into space.

In addition to medical screening and testing, NASA conducts retrospective and longitudinal studies of astronauts matched against a large control group of Johnson Space Center employees. A behind-the-scenes view of astronaut training, written by the astronaut candidates in the form of journals, provides insights from the time they entered the program through spaceflight (www.nasa.gov/centers/johnson/ astronauts/journals_astronauts.html).

Until about age 40, astronauts score better on health and fitness variables than controls. The comparative data provide an important baseline for future studies of the possible effects of short- and long-term microgravity exposure on parameters


Figure 27.8 Top. Pilot Jerrie Cobb poses next to a Mercury spaceship capsule. Dr. Randy Lovelace, the NASA scientist who had conducted the official Mercury program physical exams, administered the tests at his private clinic without official NASA approval. Cobb passed all the training exercises and demanding physiological tests, ranking in the top 2 percent of all astronaut candidates. Bottom. Cobb tests the Gimbal Rig (formally called MASTIF, or Multiple Axis Space Test Inertia Facility) in the altitude wind tunnel at Lewis Research Center (now John H. Glenn Research Center) in April 1960. The Gimbal Rig trained astronauts to control the spin of a tumbling spacecraft.
concerned with long-term health and aging. NASA sponsors three types of studies:

1. Data analysis from single flights. Research involves ongoing data collection about space motion sickness symptoms experienced before, during, and after flights. Experiments aim to validate ground-based predictive tests of an individual s susceptibility to this malady and to define operationally acceptable countermeasures. ${ }^{104,121}$
2. Longitudinal studies spanning several missions. Such studies quantify the cumulative effects of repeated exposure to the space environment, particularly radiation effects on cancer risk and bone mineral loss. ${ }^{15,62}$
3. Longitudinal studies throughout careers. Long-term medical surveillance documents occupational injuries and maladies during or following space missions. ${ }^{115}$ The longest-duration study of physiologic responses after microgravity exposure involves studies of astronaut John Glenn, Jr. (1921) , the first American to orbit Earth, who piloted the 1962 Friendship 7 Earthorbital space mission. Thirty-six years later on October 29, 1998, at age 77, Glenn served as a Payload Specialist 2 on Shuttle Discovery STS-95 for an 8 -day mission. The experiments involved studies of bone and muscle loss, balance, and sleep disorders (www.spaceflight.nasa.gov/shuttle/archives/sts-95/ index.html).

## Occupational Health Program

In addition to NASA s exercise physiology laboratory, the Occupational Health Program (OHP) (www.ohp.nasa.gov/) consists of approximately 400 occupational medicine and environmental health professionals distributed across 10 primary NASA centers. This team provides comprehensive medical support to a diverse, highly technologic workforce of more than 60,000 civil servant and contractor employees involved in human exploration and development of space, aeronautics research, and Earth and space science activities. The traditional occupational health program elements include medical surveillance, industrial hygiene, health physics, emergency medical response, employee assistance programs, physical fitness programs, and overall health and wellness programs. Astronauts in training for a mission participate at the Johnson Space Center in developmental fitness regimens in modern facilities similar to most university and commercial gymnasia.

Radiation Effects. For astronauts living in low-Earth orbit for extended periods, including exploratory Mars missions and beyond, radiation exposure poses potentially serious health concerns. ${ }^{141,176}$ Current preflight requirements include projecting a mission radiation dosage, assessing the probability of solar flares during the mission, and quantifying the radiation exposure history of flight crew members. Each crew member carries a passive dosimeter (radiation-measuring
device), and highly sensitive dosimeters located throughout the spacecraft continually monitor radiation in case of solar flares or other radiation contingencies. ${ }^{113}$ Different kinds of radiation during liftoff and aboard the spacecraft on short-duration missions at nominal orbit generally pose an acceptable level of hazard to astronaut health (e.g., blood-forming organs, lens of eyes, skin). ${ }^{101,175}$

## PHYSIOLOGIC ADAPTATIONS TO MICROGRAVITY

Spaceflight has produced considerable biomedical information about human physiology in microgravity, beginning on May 5, 1961, with astronaut Alan Shepard s (1923 1998) solo flight aboard Freedom 7 (http://history.nasa.gov/40thmerc7/shepard. $\mathrm{htm})$. This capstone event launched suborbitally to an altitude of 116 miles, 303 statute miles downrange from the Cape Canaveral launch complex. His 15 -minute 28 -second flight attained a final velocity of 5134 miles per hour and pulled a maximum of 11 g s. From this point on, the race had begun for NASA and their astronaut heroes to explore uncharted paths outside of Earth s gravitational pull. In the ensuing 50 years, researchers have quantified physiologic adaptations to relatively brief space missions (1 14 d ) and flights lasting longer than 2 weeks, including postflight adaptations.

Figure 27.9 displays a generalized schema of the dynamics of physiologic functions with microgravity exposure. These include the effects of two major factors: reduced hydrostatic gradients and reduced loading and disuse of weight-bearing tissues. The graphic reveals how these two factors influence the following six systems: (1) cardiovascular and cardiopulmonary; (2) hematologic; (3) fluid, electrolyte, and hormonal; (4) muscle; (5) bone; and (6) neurosensory and vestibular. Each system has been color coded, with arrows indicating how one system might influence another. For example, trace the pathways between a decrease in hydrostatic gradients (top left) and reduced total blood volume (bottom center). How many different pathways interact to reduce total blood volume? Similarly, trace how altered sensory and balance information also affects blood volume and maximal exercise capacity. Two of the NASA research efforts focus on the impact of reduced bone density on risk of bone fractures and functional impact of skeletal muscle atrophy (reduced strength) on performing mission-related tasks. ${ }^{92,124}$

These physiologic responses to microgravity, in addition to reduced stroke volume related to orthostatic hypotension and possible syncope, have implications for developing and testing effective countermeasure strategies (see pp. 693 695).

In addition to the flow chart of physiologic events, we present separate tables with detailed information about the cardiovascular, pulmonary, body fluid, sensory, and musculoskeletal responses to microgravity. (http://thepoint.lww.com/mkk7e) The information comes from almost five decades of cumulative research from Mercury, Gemini, Apollo, ASTP, Vostok, Voskhod, Soyuz, Shuttle Spacelab, Skylab, Salyut, and Mir missions. Excellent summary resource materials exist about these responses. ${ }^{20,32,45,46,48,53,57,82,138,156,172}$



Figure 27.9 General schema of microgravity s effects on physiologic alterations from (1) reduced hydrostatic gradients and (2) reduced loading and disuse of weight-bearing tissues. (Modified from Lujan BF, White RJ. Human Physiology in Space; www.nsbri.org/humanphysspace/

## Cardiovascular Adaptations

The decrease in total fluid volume during the first few days in microgravity reduces the heart s total work effort. With continued microgravity exposure, overall heart size decreases mainly from reduced left ventricular volume, particularly left ventricular end-diastolic volume. Such adaptations
represent an appropriate response to microgravity without compromising normal cardiovascular function during a mission. ${ }^{55}$

TABLE 27.3 summarizes adaptations in 15 cardiovascular variables for space missions through 1992, while Figure 27.10 displays pre- to postflight changes in stroke volume during

TABLE 27.3 Changes in Cardiovascular Variables Associated with Microgravity

| Physiologic Measure | Short Space Flights (1 14 d) | Long Space Flights (>2 wk) |  |
| :---: | :---: | :---: | :---: |
|  |  | Preflight vs. In-Flight | Preflight vs. Postflight |
| Heart rate (resting) | Variable in flight; increased after flight; peaks during launch and reentry; RPB up to 1 w | Normal or slightly increased | Increased; RPB 3 w |
| Blood pressure (resting) | Normal; decreased after flight | Diastolic blood pressure reduced or unchanged | Decreased mean arterial pressure |
| Orthostatic tolerance | Decreased after flights longer than 5 h ; exaggerated cardiovascular responses to tilt test, stand test, and LBNP after flight; RPB 314 d | Exaggerated cardiovascular responses to in-flight LBNP (especially during first 2 w ); last in flight test comparable to recovery-day test | Exaggerated cardiovascular responses to LBNP; RPB up to 3 w |
| Total peripheral resistance | Decreased in flight; no increase at landing despite drop in stroke volume and increase in HR | Tendency toward decrease | Increased after landing |
| Cardiac size | Normal or slightly decreased C/T ratio after flight | C/T ratio decreased after flight |  |
| Stroke volume | Increased in flight by as much as $60 \%$ (SLS-1); compensated by decreased HR | Increased early in flight then decreased | 12\% decrease on average |
| Left end-diastolic volume | Same as stroke volume | Same as in short-duration missions | 16\% decrease on average |
| Cardiac output | Elevated $3040 \%$ in flight (SLS-1); reduced immediately after flight | Unchanged | Variable; RPB 34 weeks |
| Central venous pressure | Elevated above resting supine level before launch; transient increase followed by levels below preflight upon attaining orbit | Not measured | Not measured |
| Left cardiac muscle mass thickness | Unchanged | Unchanged | $11 \%$ decrease; return to normal after 3 w |
| Cardiac electrical activity (ECG/VCG) | Moderate rightward shift in QRS and T waves after flight | Increased P-R interval, QT interval, and QRS vector magnitude | Slight increase in QRS duration and magnitude; increase in P-R interval duration |
| Arrhythmia | Usually PABs and PVBs; isolated cases of nodal tachycardia, ectopic beats, and supraventricular bigeminy in flights | PVBs and occasional PABs; sinus or nodal arrhythmia at release of LBNP in flight | Occasional unifocal PABs and PVBs |
| Systolic time intervals | Not measured | Not measured; PEP/ET ratio RPB 2 w | Increase in resting and LBNP-stressed |
| Exercise capacity | No change or decreased $\leq 12 \%$ after flight; increased HR for same $\dot{\mathrm{V}}_{2}$; no change in efficiency; RPB $38 d$ | Submaximal exercise capacity unchanged | Decreased after flight; recovery time inversely related to amount of in-flight exercise rather than mission duration |
| Venous compliance in legs | Not measured | Increased: continues to increase for 10 d or more; slow decrease later in flight | Normal or slightly increased |

Data from Nicogossian AE, et al. Space physiology and medicine, 3rd ed. Philadelphia: Lea \& Febiger, 1994:216.
RPB, return to preflight baseline; LBNP, lower-body negative pressure; C/T, cardiothoracic; ECG, electrocardiogram; VCG, vectorcardiogram; PAB, premature atrial beat; PVB, premature ventricular beat; HR, heart rate; SLS-1, Spacelab Life Sciences 1.


Group 1 ( $\mathrm{n}=3$ ): Ex. $>3 \mathrm{x} /$ week, HR $>130,>20 \mathrm{~min} /$ session (regular exercise group) Group 2 ( $\mathrm{n}=5$ ): : $\mathrm{Ex} .>3 \mathrm{x} /$ week, $H R<130$, $>20 \mathrm{~min} /$ session (reduced intensity exercise group)
Group 3 ( $\mathrm{n}=8$ ): Ex. $<2 \mathrm{x} /$ week; HR and min/session variable (minimal exercise group)
EVA Only ( $n=4$ ): EVA subjects. Minimal other exercise peformed during flight (Hubble Mission)
Figure 27.10 Pre- to postflight changes in (A) stroke volume during upright exercise (Skylab 2 4). R, return to Earth, and (B) aerobic capacity related to intensity and frequency of 20-minute in-flight cycle ergometry. (Data for A from Michel EL, et al. Results of Skylab medical experiment M171-metabolic activity. In: Johnson RS, Dietlein LF, eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: Government Printing Office, 1977. Data for B from Sawin CF. Biomedical investigations conducted in support of the extended duration orbiter medical project. Aviat Space Environ Med 1999;70:169.)
upright exercise expressed as a percentage of preflight baseline. Also shown are changes in aerobic capacity (not listed in Table 27.3) as a function of intensity and frequency of 20 minute in-flight cycle ergometer exercise bouts during four different missions. Maximal oxygen consumption declined regardless of training regimen, except for group 1, which maintained heart rate above $130 \mathrm{~b} \cdot \mathrm{~min}{ }^{1}$ and exercised longer than 20 minutes more than three times weekly. In contrast to these studies, some in-flight ergometer and treadmill studies
have reported astronauts maintained their level of aerobic capacity during relatively brief missions.

Experiments have measured changes in cardiac function (left and right ventricular mass and left ventricular enddiastolic volume) assessed by magnetic resonance imaging to isolate whether microgravity per se or frank atrophy from physical inactivity produced changes in cardiac loading functions. In four astronauts on a 10-day mission and in controls on ground measured at 2,6 , and 12 weeks of bed rest and 6 weeks of routine daily activities, left ventricular mass declined by $12 \%$ ( $\pm 7.9 \%$ ). Thus, cardiac atrophy occurs both during relatively long 6 -week periods of horizontal bed rest (inactivity) and after short-term spaceflight (microgravity). The authors postulated that physiologic adaptation to reduced myocardial load and work in real or simulated microgravity produces the cardiac atrophy, demonstrating the plasticity of cardiac muscle under different loading conditions. ${ }^{110}$

## INTEGRATIVE QUESTION

Contrast the hemodynamic responses when a person moves from the upright to the upside-down position on Earth and in a microgravity environment.

## Pulmonary Adaptations

Tight linkage exists between the cardiovascular, pulmonary, and metabolic systems. The cells demand for oxygen during rest and exercise remains invariant regardless of environment. Any change in external work above a resting baseline triggers immediate ventilatory responses that increase breathing rate and tidal volume. Augmented alveolar ventilation maintains an adequate pressure differential for oxygen diffusion across lung tissues for delivery to the site of increased energy metabolism. ${ }^{117}$

TABLE 27.4 summarizes changes in pulmonary variables during two Spacelab missions. Figure 27.11 depicts changes in pulmonary diffusing capacity for carbon monoxide measured preflight on days 2 , 4 , and 9 during the mission and within 6 hours before or after landing and then at days $1,2,4$, and 6 postflight. Note that diffusing capacity increases in the sitting and standing positions during 3 days in microgravity and then returns to preflight baseline values.

## Denitrogenation and EVA

Before astronauts perform EVA maneuvers, they must wash out the nitrogen from their fluids and tissues to prevent decompression sickness (DCS, or bends) from differentials in gas pressures within the cabin and EVA garment. ${ }^{22,43,118}$ They do this by using a 10.2 lb per square inch atmosphere (psia) staged decompression of the shuttle

TABLE 27.4 Pulmonary System Changes Associated with Microgravity During Spacelab Life Sciences-1 (Flight STS-40, June 5, 1991) and German Spacelab Mission D-2 Aboard STS-55 (April 26, 1993)

| Physiologic Response to Microgravity $\text { (1 } 14 \text { D) }$ | Reference Letter | Number of Subjects | Changes in Microgravity (In-Flight vs. Preflight Standing Measurements) |
| :---: | :---: | :---: | :---: |
| Pulmonary blood flow |  |  |  |
| Total pulmonary blood flow (cardiac output) | A | 4 | 18\% increase |
| Cardiac stroke volume | A | 4 | 4\% increase |
| Diffusing capacity (carbon monoxide) | A | 4 | 28\% increase |
| Pulmonary capillary blood volume | A | 4 | 28\% increase |
| Diffusing capacity of alveolar membrane | A | 4 | 27\% increase |
| Pulmonary blood flow distribution | C | 7 | More uniform but some inequality remained |
| Pulmonary ventilation |  |  |  |
| Respiration frequency | E | 8 | 9\% increase |
| Tidal volume | E | 8 | 15\% decrease |
| Alveolar ventilation | E | 8 | Unchanged |
| Total ventilation | E | 8 | Small decrease |
| Ventilatory distribution | B | 7 | More uniform but some inequality remained |
| Maximal peak expiratory flow rate | E | 7 | Decreased by $\leq 12.5 \%$ early in flight, then returned to normal |
| Pulmonary gas exchange |  |  |  |
| $\mathrm{O}_{2}$ uptake | E | 8 | Unchanged |
| $\mathrm{CO}_{2}$ output | E | 8 | Unchanged |
| End-tidal $\mathrm{PO}_{2}$ | E | 8 | Unchanged |
| End-tidal $\mathrm{PCO}_{2}$ | E | 8 | Small increase when $\mathrm{CO}_{2}$ concentration in spacecraft increased |
| Lung volumes |  |  |  |
| Functional residual capacity | D | 4 | 15\% decrease |
| Residual lung volume | D | 4 | 18\% decrease |
| Closing volume | B | 7 | Unchanged as measured by argon bolus |

Modified from West JB, et al. Pulmonary function in space. JAMA 1997;277:1957.
Note: Pulmonary blood flow in normal subjects equals cardiac output. How well carbon monoxide diffuses into the blood is a standard clinical test of the integrity of the alveolar membrane and its surrounding capillary blood supply. The data indicate that more alveoli are expanded and ventilated in space than on Earth. Closing volume refers to the volume in the lung where the alveoli close in significant numbers.
A. Prisk OK, et al. Pulmonary diffusing capacity, capillary blood volume and cardiac output during sustained microgravity. J Appl Physiol 1993;75:15.
B. Guy HJB, et al. Inhomogeneity of pulmonary ventilation during sustained microgravity as determined by single-breath washouts. J Appl Physiol 1994;76:1719.
C. Prisk OK, et al. Inhomogeneity of pulmonary ventilation during sustained microgravity on Spacelab SLS-1. J Appl Physiol 1994;76:1730.
D. Elliott AR, et al. Lung volumes during sustained microgravity on Spacelab SLS-1. J Appl Physiol 1994;77:2005.
E. Prisk OK, et al. Pulmonary gas exchange and its determinants during sustained microgravity on Spacelab SLS-1. J Appl Physiol 1995;76:1290.
for at least 12 hours. This also includes 100 minutes of preoxygenation, breathing $100 \% \mathrm{O}_{2}$ at 14.7 psia prior to decompression and before decompression to the suit pressure of 4.3 psia (equivalent to $9144-\mathrm{m}$ altitude). Even a slight incapacitation from DCS during EVA could hinder safe return to the spacecraft and provoke a medical emergency. Scientists have proposed several ways to induce denitrogenation. First, reduce the total pressure inside the spacecraft from 760 to 630 torr (approximate barometric pressure of Denver, CO) to shorten overall time for denitrogenation prior to EVA. Second, have astronauts sleep in a special low-pressure compartment prior to EVA. Thus, the several hours devoted to
denitrogenation during sleep would not encroach upon valuable work time. A seemingly simple solution would increase the pressure within the space suit to keep $\mathrm{N}_{2}$ in solution to avoid bubble formation. Unfortunately, this would cause the suit to stiffen considerably, rendering limb maneuverability nearly impossible.

The rate of denitrogenation depends on at least two factors:

1. Tissue nitrogen capacity, which increases with body fat content $\left(\mathrm{N}_{2}\right.$ elimination takes longer in fatter people)


## $\square$ standing $\square$ Supine $\square 0-\mathrm{g}$

Figure 27.11 Pulmonary diffusing capacity for carbon monoxide preflight on flight days 2,4 , and 9 and 6 hours following landing and on days $1,2,4$, and 6 postflight. Data are referenced to the preflight standing value. (From Prisk GK, et al. Pulmonary diffusing capacity, capillary blood volume, and cardiac output during sustained microgravity. J Appl Physiol 1993;75:15.)
2. The tissues oxygenation, which ultimately depends on cardiac output, which decreases during flight in the supine position ${ }^{117}$

In prolonged missions, as lower limb muscles begin to atrophy in the weightless environment, the time for denitrogenation also may change.

Exercise-Enhanced Preoxygenation. Experiments with exercise-enhanced preoxygenation ( 10 min of upper- and lower-body exercise at $75 \%$ estimated $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ breathing $100 \%$ $\mathrm{O}_{2}$ ) eliminated DCS during $36 \mathrm{U}-2$ reconnaissance flights at altitudes of 29,000 to 30,000 feet in a pilot who previously experienced 25 episodes of DCS. ${ }^{63}$ Another experiment investigated the efficiency of either a 1 - or a 15-minute preoxygenation period, each beginning with 10 minutes of dual-cycle ergometry performed at $75 \%$ of $\dot{\mathrm{V}}{ }_{2 \text { peak }}$ for enhancing preoxygenation efficiency by increasing perfusion gradients and minute ventilation. ${ }^{170}$ Male subjects accomplished a 1-hour preoxygenation with exercise, a 15 -minute preoxygenation with exercise, or a 1-hour resting preoxygenation before exposure to 4.3 psia for 4 hours while performing light-to-moderate exercise. The incidence of DCS following the 1-hour preoxygenation with exercise was significantly lower ( $42 \% ; n=26$ ) than following the 1 -hour resting preoxygenation $(77 \% ; n=$ 26). The incidence and onset of DCS following the 15-minute
preoxygenation with exercise $(64 \% ; n=22)$ did not differ from the 1-hour resting control. Thus, 1 -hour of preoxygenation with exercise improves resistance to DCS, illustrating the potentially positive exercise effect on ameliorating DCS during critical mission EVA maneuvers.

## Body Fluid Adaptations

TABLE 27.5 summarizes preflight to postflight adaptations in 24 body fluid variables. Figure 27.12 (p. 684) reports data for three variables: (1) percentage change in plasma volume and red cell mass during Spacelab 1 and three Skylab missions, (2) percentage change in total hemoglobin during four Salyut (Russian) missions, and (3) blood volume related to orthostatically stressed heart rate response during Apollo, SMEAT (Skylab Medical Experiments Altitude Tests), and Skylab missions.

## Sensory System Adaptations

Table 27.6 summarizes spaceflight adaptations in the sensory system categories of audition, gustation and olfaction, somatosensory, and vision for relatively short ( $<14 \mathrm{~d}$ ) and longer ( $>14 \mathrm{~d}$ ) space missions. The bottom of the table lists general vestibular system changes. Figure 27.13A (p. 686) schematically shows multisensory interactions that readjust the sensory responses disturbed by microgravity. Sensorimotor integration plays a pivotal role in posture and movement control, ambulation, and manipulating objects at 1 g , which necessitate proper adjustment in body orientation. In essence, the sensorimotor control system consists of a highly complex, tightly integrated neural complex that modulates vestibular, visual, somatosensory, tactile, and proprioceptive input within a central command-processing center. Disturbance in one aspect of the system usually initiates an override, readjustment, or temporary substitution by other system components to maintain the system s functional integrity. ${ }^{51,86,111,165}$ Considerable research has assessed how microgravity affects spatial orientation, postural control, ${ }^{85}$ vestibuloocular reflexes, and vestibular processing. ${ }^{58}$ Studies have also focused on mechanisms related to space motion sickness and perceptual motor performance. ${ }^{105,106}$

Figure 27.13B (p. 686) displays the immediate effects of spaceflight on postural reflexes in crew members from eight missions that lasted 4 to 10 days. Immediate postflight measurements were made within 1 to 5 hours in 10 of the 13 subjects. The greatest postural instability occurred in tests that required vestibular information. These experiments demonstrated a two-stage readaptation process that followed microgravity exposure. The first stage occurred quickly, within a few hours after landing; in a second, slower stage, stability returned to near normal in approximately 4 days. On longer Russian Mir missions (140 and 175 d), recovery of postural parameters to preflight levels required approximately 6 weeks. Apparently, readaptation of postural control upon return from space coincides with mission duration, with a prominent role played by visual cues.

## TABLE 27.5 Body Fluid Changes Associated with Microgravity

|  | Short Space Flights (1 14 d) $)^{a}$ | Long Space Flights (>2 w) ${ }^{\text {b }}$ |
| :--- | :--- | :--- | :--- |

TABLE 27.5 continued

| Physiologic Measure | Short Space Flights (1 14 d) ${ }^{\text {a }}$ | Long Space Flights (>2 w) ${ }^{\text {b }}$ |  |
| :---: | :---: | :---: | :---: |
|  |  | Preflight vs. In-Flight | Preflight vs. Postflight |
| Insulin |  | Decreased during long missions | Decreased after flight |
| Serum/plasma metabolites and enzymes | Postflight increases in blood urea nitrogen, creatinine, and glucose; decreases in lactic acid dehydrogenase, creatinine phosphokinase, albumin, triacylglycerols, cholesterol, and uric acid |  | Postflight decrease in cholesterol, uric acid |
| Urine volume | Decreased after flight | Decreased early in flight | Decreased after flight |
| Urine electrolytes | Postflight increases in Ca , creatinine, $\mathrm{PO}_{4}$, and osmolality; decreases in $\mathrm{Na}, \mathrm{K}, \mathrm{Cl}, \mathrm{Mg}$ | Increased osmolality, $\mathrm{Na}, \mathrm{K}$, $\mathrm{Cl}, \mathrm{Mg}, \mathrm{Ca}, \mathrm{PO}_{4}$; decrease in uric acid excretion | Increased Ca excretion; initial postflight decreases in Na , $\mathrm{K}, \mathrm{Cl}, \mathrm{Mg}, \mathrm{PO}_{4}$, uric acid; Na and Cl excretion increased in second and third week after flight |
| Urinary hormones | In-flight decreases in 17-OHcorticosteroids, increase in aldosterone; postflight increases in cortisol, aldosterone, ADH, and pregnanediol; decreases in epinephrine, 17-OH-corticosteroids, androsterone, and etiocholanolone | In-flight increases in cortisol, aldosterone, and total 17-ketosteroids; decrease in ADH | Increased cortisol, aldosterone, norepinephrine; decreases in total 17-OH-corticosteroids, ADH |
| Urinary amino acids | Postflight increases in taurine and $\beta$-alanine; decreases in glycine, alanine, and tyrosine | Increased in flight | Increased after flight |

${ }^{a}$ Biomedical data from Mercury, Gemini, Apollo, ASTP, Vostok, Voskhod, Soyuz, Shuttle, Spacelab.
${ }^{b}$ Biomedical data from Skylab, Salyut, Mir missions.
Data from Nicogossian AE, et al. Space physiology and medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994:217.
SLS, Spacelab Life Sciences; RPB, return to preflight baseline; R, return to Earth.

## Musculoskeletal Adaptations

Table 27.7 (see page 687) examines musculoskeletal adaptations during exposure to microgravity. NASAs greatest biomedical concern involves the $1 \%$ per month loss in weight-bearing bone mass during space missions. ${ }^{114}$

## Increased Calcium Loss

Table 27.8 (see page 688) summarizes data from 18 male crew members aboard Russian Mir station missions lasting between 4 and 14.4 months. Bone mineral density (BMD) declined at all seven sites measured, with spine, neck of femur, trochanter, and pelvis decreasing more than $1 \%$ per month. On the shorter 4- to 14-day Gemini flights, BMD decreased 3 to $9 \%$ in the os calcis (heel bone). ${ }^{167}$ Loss of BMD at the os calcis and radius occurred during Apollo Skylab missions and showed no recovery, even 97 days postflight. ${ }^{155,166}$ During the Skylab 228 -day orbital mission, crew members experienced a daily negative $50-\mathrm{mg}$ calcium imbalance ${ }^{173}$; daily
calcium loss averaged 140 mg on the 84-day mission. Increased bone calcium loss, if coupled with a high fluid and salt intake, could alter plasma filtrate composition and pH to favor supersaturation of kidney stone forming salts. ${ }^{174}$

Figure 27.14 (see page 689) illustrates how reduced mechanical stress in microgravity affects calcium balance. The top panel shows how three skeletal loading factors-reduced gravity (microgravity), normal gravity, and above-normal gravity-adjust calcium distribution in the digestive (intestine), cardiovascular, renal (kidney), and skeletal (bone) systems. Under normal gravity conditions, the small intestine absorbs approximately 250 to 500 mg of calcium for every 1000 mg consumed, with the remainder excreted in feces $(\nabla \boldsymbol{\nabla})$. In a microgravity environment, reduced calcium intestinal absorption exacerbates calcium fecal loss ( $\boldsymbol{\nabla} \boldsymbol{\nabla}$ ). Abnormal calcium excretion from bone resorption disrupts calcium homeostasis, which in turn decreases total body calcium and bone mass. With increased gravitational loading, calcium absorption by bone increases to spare overall calcium loss ( $\boldsymbol{\nabla}$ ). In the bottom panel, the flow diagram shows

proposed parallel dynamics of the calcium endocrine response and skeletal structure and composition to altered gravitational loading with adequate diet and endocrine balance. ${ }^{68}$

Without suitable countermeasures, progressive calcium losses during future missions of several years duration will compromise astronaut well-being, increasing bone fracture risk upon return to Earth. Onboard, multimode exercise training and lower-limb exercise has not prevented BMD loss, despite United States and Soviet crew members commitment to intense workouts. Hopefully, future research using valid animal and bed-rest models will reveal the basic mechanism of bone remodeling during prolonged microgravity exposure. ${ }^{136,157,159,179,181}$ Biochemical markers of bone turnover during 120 days of bed rest (skeletal unloading) showed the combined effects of accelerated bone resorption and retarded bone formation accounted for bone loss. ${ }^{69}$ BMD measurements at the distal radius and tibia in 15 cosmonauts on the MIR space station on missions of 1,2 , and 6 months revealed the following: ${ }^{163}$

1. Cancellous and cortical bone of the radius decreased progressively at each of the time points.
2. For the weight-bearing tibial site, cancellous BMD appeared normal after 1 month and deteriorated thereafter. After 2 months, bone loss became noticeable in the tibial cortices.
3. At 6 months, cortical bone loss was less evident than cancellous bone loss; cumulative time in microgravity did not relate to BMD changes.
4. Tibial bone loss still persisted after return to Earth for durations similar to time in space (1 6 months).

Even with onboard, dedicated physical exercise intervention, bone loss persists and can remain pathologic for a prolonged period following a mission. Alterations in circulation to bone during microgravity exposure can alter the balance between bone resorption and bone formation. Thus, bone blood flow may play an important role in bone remodeling in microgravity. ${ }^{29}$

Part of the solution to the problem of bone loss in prolonged microgravity lies in selecting crew members with the greatest resistance to bone loss, including applying targeted prevention and/or treatment strategies. ${ }^{158}$ Individual differences

Figure 27.12 Pre- to postflight changes in (A) plasma volume and red blood cell mass (Spacelab 1; Skylab 2 4), (B) total hemoglobin (Salyut 3 4; 6), and (C) blood volume in relation to orthostatically stressed heart rate (Apollo, Skylab, and SMEAT [Skylab Medical Experiments Altitude Tests]). Error bars in A and B represent standard errors of measurement. (Data for $A$ and $B$ redrawn from Convertino VA. Physiological adaptations to weightlessness: effects on exercise and work performance. Exerc Sports Sci Rev 1990;18:119.)

TABLE 27.6 Sensory System Changes Associated with Microgravity

| Physiologic Measure | Short Space Flights (1 14 d ) | Long Space Flights ( $>2 \mathrm{w}$ ) |  |
| :---: | :---: | :---: | :---: |
|  |  | Preflight vs. In-Flight | Preflight vs. Postflight |
| Audition | No change in thresholds after flight | One report of lowered thresholds during a 1-year flight | No change in thresholds after flight |
| Gustation and olfaction | Subjective and varied human experience; no impairments noted | Same as shorter missions | Same as shorter missions |
| Somatosensory | Subjective and varied human experience; no impairments noted | Subjective experiences (e.g., tingling in feet) |  |
| Vision | Intraocular tension tends to increase during flight and decrease at landing; postflight decreases in visual field; retinal blood vessels constricted after flight; dark-adapted crews reported light flashes with eyes open or closed; decrease in visual motor task performance and contrast discrimination; no change in in-flight contrast discrimination or distant and near visual acuity | Light flashes reported by darkadapted subjects; frequency related to latitude (highest in South Atlantic, lowest over poles) | No significant changes except transient decreases in intraocular pressure |
| Vestibular system | $4070 \%$ of astronauts/cosmonauts exhibit in-flight neurovestibular effects including immediate reflex motor responses (postural illusions, sensations of tumbling or rotation, nystagmus, dizziness, vertigo) and space motion sickness (pallor, cold sweating, nausea, vomiting); motion sickness symptoms appear early in flight and subside or disappear in 27 days; postflight difficulties in postural equilibrium with eyes closed or other vestibular disturbances | In-flight vestibular disturbances are the same as for shorter missions; markedly decreased susceptibility to provocative motion stimuli (cross-coupled angular acceleration) after adaptation period of 27 days; cosmonauts reported occasional reappearance of illusions during long missions | Immunity to provocative motion continues for several days after flight; marked postflight disturbances in postural equilibrium with eyes closed; some cosmonauts exhibit additional vestibular disturbances after flight, including dizziness, nausea, and vomiting |

Data used by permission from Nicogossian AE, et al. Space physiology and medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994:219.
in the rate of bone loss during spaceflight relates to genetic factors. Identifying the genetic basis of osteoporosis may exclude susceptible individuals from prolonged missions. One hopes that effective combinations of pharmacologic, nutritional, and exercise countermeasures together with screening procedures can attenuate bone loss during space missions. Studying female crew members should offer a wealth of new information to compare with terrestrial research on genderrelated bone loss, including how reduced gravity affects hormone status. Carefully controlled, longitudinal studies in a microgravity environment (i.e., long-term studies on the ISS) become crucial to better understand skeletal biology. ${ }^{158}$ Altering the ratio of animal protein intake to potassium intake can affect bone metabolism in ambulatory and bed-rest
subjects. Changing this ratio may help attenuate bone loss on Earth and during spaceflight. ${ }^{180}$

## Skeletal Muscle Adaptations

Bone loss during prolonged microgravity exposure coincides with considerable decrements in muscle mass and strength. ${ }^{177}$ Deterioration in muscle structure and function (see Focus on Research, p. 690) could compromise crew health and safety, including performance of critical EVA tasks, landing maneuvers, and procedures for leaving orbit on return to Earth. The absence of gravity virtually eliminates the load-bearing effects on antigravity muscles, rendering them susceptible to impaired performance in emergencies.


Figure 27.13 A. Schematic representation of sensory motor system that controls eye movements and posture, and perception of orientation and motion. B. Changes in anterior posterior sway (composite equilibrium score) in 10 astronauts at various times after the space shuttle returned to Earth (wheels stop, 0 hour). The tests involved perturbation of a posture platform under different conditions of visual, vestibular, and proprioceptive input. Dashed horizontal line at 1.00 represents normal response. (Data reported in Daunton NG. Adaptation of the vestibular system to microgravity. In: Fregly MJ, Blatteis CM, eds. Handbook of physiology. Section 4, Environmental physiology, vol 2. American Physiological Society. New York: Oxford University Press, 1996:765. Data for A modified from Young LR, et al. M.I.T./Canadian vestibular experiments on the Spacelab 1 mission: 2. Visual vestibular tilt interaction in weightlessness. Exp Brain Res 1986;64:299. Data for B modified from Paloski WH, et al. Recovery of postural equilibrium control following spaceflight. Ann NY Acad Sci 1992;656:747.)

## TABLE 27.7 Musculoskeletal Changes Associated with Microgravity

| Physiologic Measure | Short Space Flights (1 14 d | ) Long Space Flights ( $>2 \mathrm{w}$ ) |  |
| :---: | :---: | :---: | :---: |
|  |  | Preflight vs. In-Flight | Preflight vs. Postflight |
| Stature | Slight increase during first week in flight ( $\sim 1.3 \mathrm{~cm}$ ); RPB 1 d | Increased during first 2 w in flight (maximum 36 cm ); stabilizes thereafter | Height returns to normal on $R+0$ |
| Body mass | Postflight weight losses average about $3.4 \%$; about $2 / 3$ of the loss from water loss, the remainder from loss of lean body mass and fat | In-flight weight losses average $34 \%$ during first 5 d ; thereafter, weight either declines or increases for the remainder of mission; early in-flight losses probably from fluid loss; later losses are metabolic | Rapid weight gain during first 5 d after flight, mainly replenishment from fluid; slower weight gain from $\mathrm{R}+$ 5 days to $\mathrm{R}+2$ or 3 w ; amount of postflight weight loss inversely related to in-flight caloric intake |
| Protein synthesis | Elevated $40 \%$ on flight day 8 (SLS-1), suggesting a stress response |  |  |
| Body composition |  | Fat is probably replacing muscle tissue; muscle mass is partially preserved depending on exercise regimen |  |
| Total body volume | Decreased after flight | Center of mass shifts headward | Decreased after flight |
| Limb volume | In-flight leg volume decreases exponentially during the first flight day; thereafter, rate of decrease declines and plateaus within 35 d; postflight decrements in leg volume up to $3 \%$; rapid increase immediately after flight, followed by slower RPB | Same as short missions early in flight; leg volume continues to decrease slightly throughout mission; arm volume decreases slightly | Rapid increase in leg volume immediately after flight followed by slow RPB |
| Muscle strength | Decreased during and after flight; RPB 12 w |  | Postflight decrease in leg muscle strength, particularly extensors; increased use of in-flight exercise reduces postflight losses in strength regardless of mission duration; arm strength normal or slightly decreased after flight |
| EMG analysis | Postflight EMGs from gastrocnemius suggest increased susceptibility to fatigue and reduced muscular efficiency; EMGs from arm muscles show no change |  | Postflight EMGs from gastrocnemius show shift to higher frequencies, suggesting deterioration of muscle tissue; EMGs indicate increased susceptibility to fatigue; RPB in about 4 d |
| Reflexes (Achilles tendon) | Reflex duration decreased after flight |  | Reflex duration decreased after flight by $30 \%$ or more; reflex magnitude increased; compensatory increase in reflex duration about 2 w after flight; RPB about 1 month |
| Nitrogen and phosphorus balance |  | Negative balances early in flight shift to less negative or slightly positive balances later | Rapid return to markedly positive balances after flight |

TABLE 27.7 continued

| Physiologic Measure | Short Space Flights (1 14 c | Long Space Flights ( $>2 \mathrm{w}$ ) |  |
| :---: | :---: | :---: | :---: |
|  |  | Preflight vs. In-Flight | Preflight vs. Postflight |
| Bone density | Os calcis density decreased after flight; radius and ulna show variable changes depending on measurement method |  | Os calcis density decreased after flight; amount of loss correlated with mission duration; little or no loss from non weight-bearing bones; RPB is gradual; time course undetermined |
| Calcium balance | Progressive negative calcium balance in flight | Ca excretion in urine increases during first month in flight, then plateaus; fecal Ca excretion declines until day 10 , then increases continually throughout flight; Ca balance becomes increasingly negative throughout flight | Urine Ca content drops below preflight baselines by day 10 ; fecal Ca content declines but does not reach preflight baseline by day 20 ; markedly negative Ca balance after flight, becomes less negative by day 10 ; Ca balance remains slightly negative on day 20 ; RPB at least several weeks |

Data used by permission from Nicogossian AE, et al. Space physiology and medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994:220.
RPB, return to preflight baseline; SLS, Spacelab Life Sciences; R, return to Earth; EMG, electromyography.

| TABLE 27.8 | Bone Loss on Mir Space Station Expressed as Percentage of Bone Mineral Density Lost Per Month |  |  |
| :---: | :---: | :---: | :---: |
| Variable | Crew Members ( n ) | Mean Loss (\%) | SD ${ }^{\text {a }}$ |
| Spine | 18 | $1.07{ }^{\text {b }}$ | 0.63 |
| Neck of Femur | 18 | $1.16{ }^{\text {b }}$ | 0.85 |
| Trochanter | 18 | $1.58{ }^{\text {b }}$ | 0.98 |
| Total body | 17 | $0.35{ }^{\text {b }}$ | 0.25 |
| Pelvis | 17 | $1.35{ }^{\text {b }}$ | 0.54 |
| Arm | 17 | $0.04{ }^{\text {b }}$ | 0.88 |
| Leg | 16 | $0.34{ }^{\text {b }}$ | 0.33 |
| From LeBlanc A, et al. Bone mineral and lean tissue loss after long duration space flight. Am Soc Bone Miner Res 1996;11:S323. <br> ${ }^{a}$ Standard deviation. ${ }^{b} p<0.01 .$ |  |  |  |

## Concentric and Eccentric Strength

The important role of concentric and eccentric muscle actions in space missions has focused experiments on pre- and postflight assessment of submaximal and maximal muscle functions. ${ }^{4,17,23,26,30,33,40,41,60}$ The preponderance of research in exercise countermeasures supports the use of resistanceexercise training on various modes of exercise equipment to hypertrophy space-bound muscle to improve its force-generating capacity and produce positive ultrastructural changes and complimentary neural components. ${ }^{1,3,8,9,44,66,152}$ Standard concentric and eccentric methods, including isokinetic loading devices and newer onboard equipment, ${ }^{5}$ 7,131,134,151 produce such improvements. For example, concentric strength of Skylab
crews tested isokinetically before and 5 days after the 28-day flight showed decrements of approximately $25 \%$ in leg extensor strength. ${ }^{154}$ Greater losses would probably have occurred had testing been conducted immediately upon landing. Subsequently, longer Skylab missions (59, 84, and 59 d) provided preflight fitness and conditioning that emphasized strengthening exercises for the lower extremities. This emphasis on preflight fitness produced smaller strength decrements during flight than during Skylab 2. On longer (110 237 d) and short (7 d) Russian missions, isokinetic concentric strength declined up to $28 \% .^{61}$ The 7 -day Salyut 6 mission decreased torque-velocity relationships in the gastrocnemius/soleus, anterior tibialis, and ankle extensor musculature. On longer 110to 237-day missions, cosmonauts average triceps strength loss


Figure 27.14 Influence of gravitational loading on calcium balance. Top. How the digestive system (intestine), cardiovascular system (kidney), and skeletal system (bone) adjust calcium distribution in response to (1) reduced (microgravity), (2) normal ( 1 g ), and (3) increased ( 2 g ) gravitational skeletal loading. The degree of shading within the circles in the right panel represents the adaptation in whole-body bone mineral (darker shading, greater calcium accretion) to the different loading conditions. Bottom. Flow diagram proposing parallel calcium/endocrine and skeletal adaptive responses to changing gravitational loading, assuming adequate diet and endocrine balance. (Adapted from Morey-Holton ER, et al. The skeleton and its adaptation to gravity. In: Fregly MJ, Blatteis CM, eds. Handbook of Physiology. Section 4, Environmental Physiology, vol 2. American Physiological Society. New York: Oxford University Press, 1996.)

## FOCUS ON RESEARCH

## Microgravitys Effects on Muscle Fibers

Edgerton VR, et al. Human fiber size and enzymatic properties after 5 and 11 days of space flight. J Appl Physiol 1995;78:1733.
$>$ From the beginning of manned spaceflight, it has been assumed that prolonged exposure to near zero-g would negatively affect neuromuscular function. Early experiments by the Soviet Union showed that spaceflight impaired a number of neuromotor components. Some neural adaptations persisted for days and weeks after spaceflight. A principal issue not addressed by the Soviets was the degree to which neuromotor changes related to muscular components. This study by Edgerton and colleagues was the first to objectify spaceflight s effects on human muscle fibers. The researchers measured size and capillarization of single muscle fibers and activities of myofibrillar adenosine triphosphatase (ATPase), succinate dehydrogenase (SDH), and $\alpha$-glycerophosphate dehydrogenase (GPD) of astronauts who flew either one 11-day or one of two 5day missions.

Five male (age 40 y ; range 3346 y ) and three female (age 38 y , range 3640 y ) astronauts served as subjects.



Figure 1 Muscle fiber-type percentage before and immediately after 11 days of spaceflight.

Five subjects participated in a 261 -hour flight; two subjects flew for 120 hours; and one subject flew for 128 hours. Preflight ( 316 weeks before the mission) and postflight (2 3 h after landing), a 6-mm needle was used to obtain muscle biopsies from the midportion of the vastus lateralis muscle. For postflight measures, all subjects minimized their walking and standing between landing and the biopsy. Tissue was quick-frozen in liquid nitrogen for subsequent analyses according to standard procedures.

Figures 1 and 2 present results for muscle fiber type and cross-sectional area (CSA), respectively, for type I and type II muscle fibers. The percentage of fibers classified as type I averaged 6 to $8 \%$ less after the mission. This reduction seemed to be compensated for by an increase in the percentage of type IIA fibers, with no change in type IIB fibers. A similar pre- to postflight difference was noted for the three subjects who flew for 5 days, but this difference was not statistically significant.

After the 11-day flight, CSA averaged 16 to $36 \%$ smaller than preflight values. Relative atrophy among fiber types was greatest for type IIB and least for type I fibers,


Figure 2 Cross-sectional area of type I and type II muscle fibers before and immediately after 11 days of spaceflight.

## FOCUS ON RESEARCH

## Continued

yet mean fiber size decreased for all fibers. Crew members of 5-day missions also exhibited evidence of muscle atrophy.

The table presents results for fiber enzyme activities, enzyme ratios, total enzyme activities per fiber, and number of capillaries per fiber for all subjects on 5- and 11-day missions. A $32 \%$ decrease in total SDH activity in type II fibers was the only significant difference in enzyme activity during spaceflight. SDH activity per unit mass of the fibers did not change for either type I or type II fibers, but SDH activity per fiber decreased from muscle atrophy. No loss of total activity occurred for ATPase or GPD because the increase in activity per unit mass countered any atrophy effect.

The absolute number of capillaries supplying each type of muscle fiber decreased significantly from spaceflight. Mean fiber size also decreased (Fig. 2), so capillary number per unit muscle CSA remained unchanged.

Because of the close association between the CSA of single fibers, motor units, and whole muscle and the
muscle s force-generating capacity, the present results suggest a loss in strength of the vastus lateralis within 11 days of spaceflight. The loss in CSA within 11 (and perhaps even 5) days of microgravity exposure agrees with previous data on rats and supports the usefulness of animal models to study human responses to space travel. Astronauts showed considerable variation in preflight and in-flight physical activity levels. More than likely, some of the between-subject variation in muscle atrophy related to physical activities during flight. For example, two of the three subjects who exercised four or more times during the flight showed little or no atrophy, while an astronaut with a high level of preflight physical fitness exhibited the greatest atrophy.

The work of Edgerton and colleagues demonstrated that skeletal muscle adapts rapidly to microgravity exposure, with a significant loss in CSA, selected enzyme activity, and fiber capillarization. These highly variable responses may partly relate to physical fitness level before launch and the extent of in-flight exercise.

Effects of 5 to 11 Days of Spaceflight on Muscle Fiber Capillarization and Selected Enzyme Levels

| Variable | Type I Fibers |  |  | Type II Fibers |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Preflight | Postflight | \% Diff | Preflight | Postflight | \% Diff |
| ATPase activity | 383.0 | 376.0 | -2 | 471.0 | 413.0 | $-9^{a}$ |
| SDH activity | 232.0 | 203.0 | -13 | 184.0 | 158.0 | -14 |
| ATP/SDH | 1.8 | 2.1 | 17* | 2.9 | 4.0 | $38^{a}$ |
| GPD activity | 5.9 | 10.6 | 80 | 25.0 | 23.0 | -8 |
| Total ATPase | 212.0 | 177.0 | -17 | 258.0 | 211.0 | -18 |
| Total SDH | 133.0 | 97.0 | -27 | 105.0 | 71.0 | $-32^{a}$ |
| Capillaries per fiber | 4.7 | 3.8 | -19* | 4.8 | 3.6 | $26^{a}$ |

${ }^{a}$ Significantly different at the 0.05 level.
ranged between 20 and $50 \%$. Considerable losses in peak torque occurred for isokinetic ankle flexion and extension at all measured angular velocities of movement (Fig. 27.15). Studies of cosmonauts investigated the use of functional electrostimulation (FES) to minimize atrophy, morphologic changes, and neuromuscular coordination patterns of skeletal muscles during prolonged space missions. ${ }^{97}$ FES trains lower-extremity muscle groups using 1 -second tetanic muscle actions followed by 2 seconds of relaxation continuously at 20 to $30 \%$ of maximum tetanic muscle force up to 6 hours daily.

Extended-Duration Orbiter Medical Project. Table 27.9 displays changes between 17 astronauts preflight and landing (postflight) concentric and eccentric abdominal strength,
eccentric strength of the quadriceps/soleus, and concentric quadriceps strength assessed at $30 \cdot \mathrm{~s}^{-1}$. Note that for each muscle group tested, a greater strength loss occurred in concentric than eccentric modes, with the greatest losses in the back $(-23 \%)$ and quadriceps ( $-12 \%$ ) muscles within 5 hours postflight. The three inset figures display the percentage strength changes in upper- and lower-leg and trunk flexor muscles. The unique aspect of these data compares space exercisers with nonexercisers. ${ }^{130}$ The exercisers trained by running on the treadmill (see p. 696) at intensities from 60 to $85 \%$ of preflight $\dot{\mathrm{V}} \mathrm{O}_{2 \text { peak }}$ estimated from heart rate. Interestingly, testing conducted 7 days postflight revealed that onboard treadmill exercise did not ameliorate strength loss in all muscle groups. Preservation of muscle integrity even after


## 「 Preflight - Postflight

Figure 27.15 Force velocity relationship of ankle flexors (anterior tibialis) and extensor calf muscles measured by isokinetic dynamometry at four angular velocities in six cosmonauts before and after 110 to 237 days in microgravity on Salyut 7. (Data summarized from Convertino VA. Effects of microgravity on exercise performance. In: Garrett WE, Kirkendall DT, eds. Exercise and Sport Science. Philadelphia: Lippincott Williams \& Wilkins, 2000.)
only 9 to 11 days of spaceflight may target those muscles ex-ercised-in accord with the principle of specificity of exercise training.

## Muscle Ultrastructural Changes

Permanent neuromuscular dysfunction has not yet been demonstrated during prolonged space missions. ${ }^{24}$ Nevertheless, in-flight and postflight changes during missions of nearly 1 year reveal altered muscular coordination patterns, some delayed-onset muscle soreness (DOMS), and generalized muscular fatigue and weakness. Many unanswered questions remain about human muscle physiology and biochemical adaptations related to microgravity exposure in humans. Animal models using head-down, tail-suspended, non weight-bearing rodents rely on reduced gravity s effects on skeletal muscle contractile morphology and physiology. Placing rodents in a harness that elevates the hindquarters or tail eliminates the normal loading of weight-bearing hindlimb muscles (FIg. 27.16). The model mimics the fluid shifts of microgravity; it produces reduced sensory input to the motor centers and less mechanical stimulation of connective, muscular, and osseous tissues. Specifically, both spaceflight and non weight-bearing confinement atrophies rat skeletal muscles, mainly the slow twitch (type 1) leg-extensor fibers. ${ }^{72,73,123,126,177}$ Also, non weight bearing in microgravity reduces contractile activity assessed by EMG of male rat hind-limb soleus muscle by $75 \%$.


Figure 27.16 Hind-limb suspension. This uploading technique limits the activity or movement of the animal by immobilizing or restraining its hind limbs or tail to simulate the non weight-bearing effects of microgravity.

## Maximal Explosive Leg Power Before and After Space Missions

Figure 27.17 shows different duration spaceflight effects on maximal explosive power (MEP) and maximal cycling power (MCP) assessed preflight and 26 days postflight for astronauts exposed to microgravity for up to 180 days. The inset illustration at bottom left shows the ergometer dynamometer to assess MEP. Subjects made six maximal pushes with both feet against the force platform for approximately 250 ms at a knee angle of 110 with a 2-minute rest between pushes. MCP involved five to seven all-out pedal revolutions for 5 to 6 seconds on a bicycle ergometer following either 5 to 7 minutes of mild aerobic exercise or free-wheel pedaling. The top figure shows the percentage of premission scores for MEP and MCP for four astronauts at four periods after mission completion. Astronaut 1, who spent 31 days in orbit, recovered nearly all MEP by 11 days postflight. For the other three astronauts, whose missions lasted 169 to 180 days, MEP recovery approached only $77 \%$ of the preflight value. For the two astronauts tested 26 days postflight, MEP for astronaut 3 was $80 \%$ of his premission score, while astronaut 4 achieved only $57 \%$. In contrast, each astronaut s MCP, a measure of more sustained power output, recovered more rapidly throughout the postflight measurement period, with final scores within $10 \%$ of premission values.

The bottom figure (right) compares all values for MCP plotted relative to the corresponding MEP scores expressed as a percentage of premission values. On average, MCP deterioration exceeded MEP loss. The researchers attributed the differential deterioration in the two forms of maximal exercise to muscular and neurologic factors involved in each form of effort. In essence, the absence of gravity appears to rearrange postural muscle tone and locomotor coordination substantially. This adversely affects the motor control system; in one astronaut, it negatively affected the normal pattern of motor unit recruitment. Changes in neural drive during long-term

TABLE 27.9 Top Left. Changes in Skeletal Muscle Strength Performance on Landing Versus Preflight. Bottom Left. Percentage Changes in Upper-Leg, Lower-Leg (Top Right), and Trunk Strength (Bottom Right) Following Spaceflight in Space Exercisers vs. Nonexercisers

|  | Test Mode |  |
| :--- | :---: | ---: |
| Muscle Group | Concentric | Eccentric |
| Back | $-23( \pm 4)^{*}$ | $-14( \pm 4)^{*}$ |
| Abdomen | $-10( \pm 2)^{*}$ | $-8( \pm 2)^{*}$ |
| Quadriceps | $-12( \pm 2)^{*}$ | $-7( \pm 3)$ |
| Hamstrings | $-6( \pm 3)$ | $-1( \pm 0)$ |
| Tibialis anterior | $-8( \pm 4)$ | $-1( \pm 2)$ |
| Gastroc/soleus | $1( \pm 3)$ | $2( \pm 4)$ |
| Deltoids | $1( \pm 5)$ | $-2( \pm 2)$ |
| Pecs/lats | $0( \pm 5)$ | $-6( \pm 2)$ |
| Biceps | $6( \pm 6)$ | $1( \pm 2)$ |
| Triceps | $0( \pm 2)$ | $8( \pm 6)$ |

*Significantly lower than preflight value.



Data from Extended Duration Orbiter Medical Project. 1989 1995. Final report NASA/SP-1999-534. NASA. Lyndon B. Johnson Space Center. Houston, TX, 1999.
missions of 90 to 180 days could impact the contractile and elastic characteristics of lower limb musculature. ${ }^{76}$

## COUNTERMEASURE STRATEGIES

Countermeasures systematically attempt to neutralize (or minimize) spaceflights potentially harmful deconditioning effects on crew physiologic function, performance, and overall health during mission-critical maneuvers, particularly reentry and landing. ${ }^{14,87}$ In the absence of gravity, no linear, downward head-to-foot acceleration forces (referred to as +Gz ) act on the body. This makes normal biologic functions more susceptible to short- and longer-term maladaptations such as space motion sickness (SMS). This syndrome usually manifests within the first 72 hours of a mission and often is characterized by clumsiness, difficulty concentrating, disorientation, persisting sensation aftereffects, nausea, pallor, drowsiness, vomiting, vertigo
while walking and standing, difficulty walking a straight line, blurred vision, and dry heaves. Some symptoms resemble those of terrestrial motion sickness. SMS symptoms often dissipate on their own or with medication during the first few days of spaceflight. On reentry after short-duration missions, SMS can manifest as a general reentry syndrome (GRS) that imposes potentially deleterious effects on astronaut performance. GRS symptoms include vertigo, nausea, instability, and fatigue induced by reimposition of increased +Gz during reentry and landing. In contrast to the relatively acute emergence of SMS, weeks and months of prolonged absence of normal gravitational loading adversely affect bone and muscular structure and function. Concurrently, fluid shifts within the vascular system produce considerable loss of electrolytes and bone minerals. Cumulative negative effects during sustained missions could trigger more severe medical complications that include increased risk for developing renal stones, orthostatic intolerance,


Figure 27.17 A. Effects of up to 180 days in microgravity on changes in maximal explosive power (MEP) and maximal cycling power (MCP). B. The ergometer dynamometer assessed MEP of the lower limbs by varying either force or velocity. HJ, hydraulic jack; WT, wire tachometer; CS, carriage seat; FP, force platform; Cy, isokinetic cycle ergometer; Hi, hinge. MEP was assessed within less than 0.3 s , and MCP was determined during all-out pedaling on a cycle ergometer for 5 to 6 s . C. Plot of MCP versus MEP scores expressed as a percentage of premission values. (Data modified from Antonutto G, et al. Effects of microgravity on maximal power of lower limbs during very short efforts in humans. J Appl Physiol 1999;86:85.)
neurosensory and motor dysfunctions, and musculoskeletal injuries (including bone fracture) in the weeks and months following return to Earth.

Without appropriate countermeasures, microgravitys deleterious effects mimic the adverse changes with prolonged bed rest. For example, 30 days of bed rest dramatically impairs skeletal muscle function; knee extensor strength declines nearly $23 \%$, while knee flexor strength and leg volume decrease 10 to $12 \%$. Reductions in limb volume result from
decreased muscular cross-sectional area from muscle fiber protein loss. The 28-day Skylab 2 mission decreased muscular function and leg volume to an extent comparable with bed rest. The protein loss has been attributed in part to a normal adaptive response to decreased workload on weight-bearing muscles. ${ }^{147}$ Decrements in cardiovascular function generally parallel losses in muscle strength and size, ${ }^{150,153}$ including problems related to low back pain. ${ }^{128}$ Projected travel time for an exploration-class mission to Mars requires approximately 6 months of isolation

TABLE 27.10 Adverse Effects of Spaceflight and Proposed Countermeasures

| Area | Major Findings | Clinical/Operational <br> Consequences | Countermeasures under <br> Evaluation |
| :--- | :--- | :--- | :--- |
| Cardiovascular | Fluid loss <br> Electrolyte changes <br> Electrical activity disturbances <br> Neuroreflex readjustments | Orthostatic intolerance | Fluid/electrolyte replenishment <br> Exercise |
|  | Electrolyte changes <br> Electrical activity disturbances <br> Neuroreflex readjustments <br> Motion sickness <br> Gait disturbances <br> Motor performance degradation <br> Bone mass loss <br> Muscle mass loss | Decreased productivity | Renal stone formation |

From Nicogossian AE, et al. Countermeasures to space deconditioning. In: Nicogossian AE, et al., eds. Space physiology and medicine. 3rd ed.
Philadelphia: Lea \& Febiger, 1994:447.
Note: Third column lists factors (renal stone formation, muscle/joint injuries, bone fractures) undocumented in NASA reports.
in microgravity, more than a year of planetary habitation at 0.38 g , followed by a 6 -month return trip to Earth (in microgravity). Thus, onboard countermeasures play a critical role in minimizing pathology or impaired motor task performance to preserve crew health and safety. ${ }^{129,132,140}$ More than likely, gender-related factors affect these health and performance goals. ${ }^{52}$ In-flight resistance and endurance exercises show the greatest overall potential as exercise countermeasures to combat microgravity s sustained deleterious effects. Table 27.10 lists examples of adverse effects and clinical consequences of prolonged microgravity exposure in four functional body areas and possible countermeasure strategies. Countermeasure strategies (fluid loading, G-suit inflation, pharmacologic agents, artificial gravity, short-term physical exercise to elicit maximal effort) help to minimize microgravity-induced orthostatic intolerance. ${ }^{36}$ A compelling argument posits that combining multiple countermeasures could afford astronauts optimal protection against potential adverse effects of long-duration space missions.

## In-Flight Exercise

Four exercise modes have played predominant roles during in-flight workouts aboard space missions:

1. Treadmill walking and running
2. Cycle ergometry, including maximal exercise performed 24 hours before landing ${ }^{99}$
3. Leg rowing
4. Upper- and lower-body multijoint dynamic resistance exercise
The latest resistance-exercise training equipment aboard the ISS, the interim Resistance Exercise Device (iRED), allows astronauts to exercise dynamically with increasing
resistance throughout a full range of motion (ROM) for three basic exercise movements that stress the hip, back, and spine. Peak force, average force, and ROM are recorded for each repetition. ${ }^{131}$ FIGURE 27.18 shows four examples of different exercise modes during KC-135 flights and space missions.

## Lunar Mars Life Support Test Experiment

NASA conducts research to examine the efficacy of exercise testing and prescription protocols for onboard countermeasures on future spaceflights. The experiments provide insights into potentially useful training methodologies for application to space missions, particularly targeted resistance exercise for lower-extremity muscles-those most likely to suffer impairment. The trial studied men and women before, during, and after a 60 -day confined-chamber experiment at 1 g in the Life Support Systems Integration Unit, a component scheduled for a future ISS mission. A combined exercise countermeasure protocol quantified the following:

1. Training effects from exercise countermeasures
2. Tolerance to combined aerobic and resistance training countermeasures
3. Methods to quantify the performance of exercise countermeasures for valid monitoring of exercise compliance
Measurements included:
4. $\dot{V} O_{\text {2peak. }}$. Subjects pedaled an electronically braked cycle ergometer in the upright position at 75 rpm at increasing workloads of 50,100 , and 150 W for men and 50,75 , and 100 W for women. Exercise then continued in 25-W increments to volitional termination.


Figure 27.18 Examples of exercise training and measurement for different exercise modes during microgravity conditions. A and B. Tethered treadmill exercise during a space shuttle mission. Note the strap arrangement around the upper body and straps anchored to the hips to keep the astronaut tethered to the treadmill. C. Exercise training during different space shuttle missions showing back and arm, cycling, and rowing exercise modes. D. Astronaut using the short bar for the Interim Resistive Exercise Device (IRED) to perform upper-body strengthening exercise in the Unity node of the ISS. (Photos courtesy of NASA, Lyndon B. Johnson Space Center, Houston, TX.)
Alkner BA, et al. Effects of strength training using a gravity-independent exercise system, performed during 110 days of simulated space station confinement. Eur J Appl Physiol 2003;90:44.
Convertino VA. Planning strategies for development of effective exercise and nutrition countermeasures for long-duration spaceflight. Nutrition 2002;18:880.
Cowell SA, et al. The exercise and environmental physiology of extravehicular activity. Aviat Space Environ Med 2002;73:54. Lee SM, et al. Foot-ground reaction force during resistive exercise in parabolic flight. Aviat Space Environ Med 2004 75:405. McCrory JL, et al. Locomotion in simulated zero gravity: ground reaction forces. Aviat Space Environ Med 2004 75:203.
2. Submaximal and maximal sustained aerobic exercise. Subjects cycled for three 5-minute periods at 75 rpm at exercise intensities of $25,50,75$, and $100 \%$ Vㅇㅇ $_{2 \text { peak }}$.
3. Resistance exercise. Subjects performed maximaleffort bench press, seated shoulder press, latissimus dorsi pull, squat, and heel raise on a multifunction exercise station preprogrammed for fast- and slowspeed movement velocities.

In the chamber, subjects exercised 6 days a week, alternating between preprogrammed 32-minute cycle ergometer aerobic workouts at 40 to $80 \%$ of $\mathrm{V}^{2 \text { peak }}$ and the five resistance exercises in the pretest assessment. They performed three
sets of 6- to $12-\mathrm{RM}$ of each exercise, beginning with a warmup at $50 \% 1-\mathrm{RM}$. Movement speed varied from $10 \cdot \mathrm{~s}^{-1}$ at the slow speed to $20 \cdot \mathrm{~s}^{-1}$ at the fastest speed. Submaximal ergometer tests were administered on days 15,30 , and 58 in lieu of the aerobic workout. Subject compliance averaged $91 \%$ with the exercise program.

Figure 27.19 shows peak torque developed at low, medium, and high movement speeds with resistance exercises during training weeks 2,5 , and 8 . Within-subject evaluation revealed that all subjects improved in strength measures (peak torque, average peak torque, total work) at each speed over the 8 -week period. The pre- to postchamber exercise oxygen consumptions shown in the top left panel of Figure 27.20 reveal that average $\dot{\mathrm{V}} \mathrm{O}_{2 \text { peak }}$ increased $7 \%$ during chamber


Week $2 \square$ Week $5 \square$ Week 8
Figure 27.19 Peak torque developed at low, medium, and high movement during bench press, seated press, lat pull, squat, and heel raise during weeks 2, 5, and 8. (Adapted from Lee SL, et al. Exercise Countermeasures Demonstration Project during the LunarMars Life Support Test Project. Phase IIA. NASA. NASA/TP-98-206537. Lyndon B. Johnson Space Center, Houston, TX. 1998.)
confinement, ranging between 1 and 20\%; the initially highfit subjects improved the least. Peak posttraining workload also increased (13\%), as did exercise duration (7\%). Submaximal exercise heart rate (bottom left panel) declined $6 \%$ during the last test session ( submax 3 ) compared with pretraining values. Ratings of perceived exertion and systolic blood pressure during the three training sessions did not change. In contrast, diastolic blood pressure declined by $19 \%$ after 30 days ( submax 2 ) and $13 \%$ at 58 days ( submax 3 ).

## Countermeasures on

## Long-Duration Missions

The prolonged Russian Mir missions made extensive use of exercise countermeasures based on considerable prior experience with extended space missions. Like their American counterparts, cosmonauts did not exercise during the flight s first 48 to 72 hours to provide sufficient recovery from SMS that affects nearly $70 \%$ of astronauts and cosmonauts on their first flight. On current space shuttle missions, an intramuscular injection of Phenergan relieves SMS, replacing Dexedrine and other drug combinations that evoke strong negative central nervous system responses.

Toward the end of the flight s first week and over the next 24 days, cosmonauts exercised twice daily, progressing
to 1 hour of continuous ergometer cycling at an initial workload of $900 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{-1}$. Exercise intensity progressively increased to maintain heart rate between 80 and $90 \%$ of agepredicted maximum. They added 5 to 15 minutes of daily strengthening exercise (hamstrings, trunk extensors) using bungee-cord devices. On missions exceeding 1 month, cosmonauts exercise twice daily for 1 hour on a passive (subjectdriven) treadmill with a restraint system similar to that used by space shuttle astronauts (see Fig. 27.21 for schematic of U.S. Space Shuttle passive treadmill in which a rapid-onset centrifugal brake provides seven braking levels to control drag forces on the running track). To simulate gravitational forces, straps from their side-called subject load devicessecure the cosmonaut to the treadmill. Treadmill exercise, using a harness and bungee tether system, generates the effects of 0.5 to 0.7 g , while exercise on Salyut and Mir treadmills generated a gravitational pull of 0.62 g . The nonmotorized treadmill requires running at a positive percentage grade to overcome frictional resistance. At present, the treadmill provides the only mode of onboard exercise. Astronauts wear a monitor secured to the ear (ear oximeter) to record heart rate continuously by an infrared sensor that detects pulsating blood flow in the earlobe. A mechanical sensor wire on the side of the treadmill displays distance run from the number of treadmill revolutions completed.


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SBP Pre }\square\mathrm{ SBP Post }\square\mathrm{ DBP Pre }\square\mathrm{ DBP Post
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Figure 27.20 The 60-day Lunar-Mars countermeasures experiment. Top, Comparison of pre- and post-ㅊㅇ ${ }_{2 \text { peak }}$, peak workload, and test duration on the bicycle ergometer. Bottom, Heart rate, rating of perceived exertion (RPE), and blood pressure during three submaximal test sessions. SBP, systolic blood pressure; DBP, diastolic blood pressure. (Adapted from Lee SL, et al. Exercise Countermeasures Demonstration Project during the Lunar-Mars Life Support Test Project. Phase IIA. NASA. NASA/TP-98-206537. Lyndon B. Johnson Space Center, Houston, TX. 1998.)

Figure 27.22 compares heart rate response during continuous (top) and intermittent (bottom) treadmill exercise during two shuttle missions. Astronauts did not attain assigned target heart rates (representing 60,70 , or $80 \% \mathrm{VO}_{2 \max }$ ) when exercising continuously for 30 minutes during an 11-day mission. More than likely, altered running mechanics while wearing the bungee apparatus reduced target heart rates.

## INTEGRATIVE QUESTION

What type of exercise training program would you advise an astronaut to undertake 6 months prior to a Mars mission and during the mission?

## New Approach: Human-Powered Centrifuges Simulate Gravitational Loading

NASA currently supports new countermeasures that use unique exercise devices to combat the deleterious effects of spaceflight deconditioning. ${ }^{14}$

## Self-Powered Human Centrifuge

Force and acceleration represent two distinct entities ( $F=$ $m \times a$ ), so simply applying force to an object (e.g., bungee cord or lower-body negative-pressure device) in microgravity does not mean that it regulates a beneficial loading of the skeleton similar to exercise on Earth. An animal or human placed in a rotating centrifuge experiences the force benefits produced by a sustained-acceleration gravity field. In this regard, a self-powered human centrifuge displayed schematically in Figure 27.23 offers promise for counteracting adverse physiologic effects of extended-duration space missions. ${ }^{10,74}$ Pedaling the Space Cycle propels the centrifuge in a curvilinear motion about a fixed central shaft rigidly fixed within the spacecraft. A centrifuge effect produces artificial gravity as the rider rotates about the shaft while pedaling. Irregularly shaped cams fixed to the foot crankshaft allow an adjustable spring-loaded device to trace a path around the cam and provide resistance to pedaling. Altering cam configuration generates foot force profiles to simulate walking, jogging, and cycling. Combining artificial


Figure 27.21 Schematic details of subject-driven U.S. Space Shuttle treadmill.
gravity with impact-loading exercise offers the potential for an effective countermeasures strategy against orthostatic intolerance, macro- and microscopic skeletal muscle deterioration, and loss of bone mass.

The Space Cycle designed for the ISS simulates gravitational acceleration $(+G z)$ experienced while standing on Earth and provides axial loading on the rider s long bones. The added stress in microgravity should provide similar 1 g stresses on the musculoskeletal system. Thus, missions lasting a year or more should benefit from artificially induced gravity produced by human powered, in-flight centrifugation. A recent experiment comparing Gz (upright cycle ergometry) and 2 Gz conditions (Space Cycle) at the same work rate on hemodynamic measures (heart rate, systolic and diastolic blood pressure, oxygen uptake) revealed few differences between the two experimental conditions. The authors concluded that the subject s hemodynamic responses were well tolerated under the Space Cycle s low hypergravity conditions. ${ }^{21}$

In addition to the Space Cycle, NASA s Ames Research Center has developed its own self-powered human centrifuge to evaluate the countermeasure potential of this exercise mode with and without the effect of +Gz acceleration
(Fig. 27.24). ${ }^{59}$ The Ames centrifuge consists of a short-arm, dual-couch device powered by a chain-linked cycle foot drive. Approximately two pedal revolutions produce a 360 rotation of the centrifuge to generate a maximum of 5 g . Research with this device required subjects to perform exercise under two conditions: (1) pedaling the centrifuge for 2 minutes at 25,50 , and $75 \%$ of maximum cycling rpm, defined as all-out until volitional fatigue and (2) exercising at the same three intensities without centrifuge acceleration. Changes in heart rate under the two conditions assessed the effects of only exercise and exercise coupled with +Gz acceleration. Subjects remained blindfolded during exercise to prevent nausea or vertigo. They achieved $3.9 \mathrm{Gz}(43.7 \mathrm{rpm})$ for maximal-acceleration exercise, 0.2 Gz at $25 \%$ (11.0 rpm), 1.0 Gz at $50 \%(21.8 \mathrm{rpm})$, and $2.2 \mathrm{Gz}(32.8 \mathrm{rpm})$ at $75 \%$ maximum Gz. The bottom of Figure 27.24 compares the effects of the two conditions (exercise acceleration and passive acceleration) on heart rate response at different percentages of maximal acceleration. The numbers at the end of each trial (shown at the right) represent heart rate at the end of exercise minus heart rate at the start. Pedaling the Ames centrifuge produced its intended effect-it augmented heart rate response to exercise at $75 \%$ maximum Gz. Additional research must quantify the most effective exercise and artificial gravity exposure (optimal magnitude, frequency, and duration) during space missions for full adaptation of head, arm, and leg movement equilibrium. ${ }^{75}$

## Space Pharmacology

SMS remains the most persistent short-term problem during spaceflight. Approximately $50 \%$ of cosmonauts, $60 \%$ of Apollo astronauts, and $71 \%$ of first-time shuttle astronauts encountered mild-to-severe SMS. Table 27.11 lists the incidence and severity of SMS during 36 space shuttle flights through 1991. Note the decline in prevalence from 77 episodes to 34 episodes for crew members on their second shuttle flight. On the 1993 Space Shuttle Life Sciences mission (SLS-2), only one astronaut experienced nausea, but without sickness during the mission s first few days. ${ }^{142}$

SMS is not confined to orbital flight; nearly $10 \%$ of astronauts experience it during reentry or immediately upon landing, including training during parabolic flights. ${ }^{130}$ Ninety-two percent of cosmonauts report SMS upon return from missions that last several months or longer. ${ }^{71}$ To date, no single pharmacologic treatment prevents or cures SMS. On shuttle missions, the disorder shows no preference for commanders, pilots, or mission specialists, gender or age, career versus noncareer astronauts, or first-time versus repeat flyers. Incomplete understanding of the cause(s) of SMS hampers its treatment, but pharmacologic treatment usually relieves most symptoms within the first 3 days in the space environment. Additional countermeasure strategies to minimize SMS effects include mechanical and electrical stimulation and biofeedback techniques. Despite these efforts, medication provides the most effective pharmacologic therapy against SMS.


Figure 27.22 Top. Heart rate during continuous treadmill exercise at 60,70, and 80\% of $\mathrm{VO}_{2 \text { max }}$ on an 11 -day shuttle mission. The light-green shaded area shows the exercise heart rate range during workout days 3 to 11 . Green circles represent heart rate during a familiarization run on flight day 2 . The intense workouts helped to minimize orthostatic dysfunction upon landing. Bottom. Heart rate during five intervals of a treadmill exercise routine using the shuttle treadmill. (Adapted from Lee SL, et al. Exercise Countermeasures Demonstration Project during the Lunar Mars Life Support Test Project. Phase IIA. NASA. NASA/TP-98-206537. Lyndon B. Johnson Space Center, Houston, TX. 1998.)

TABLE 27.11 Incidence and Severity of Space Motion Sickness During 36 Space Shuttle Flights

|  | Number of Crew Members |  |  |
| :--- | :---: | :---: | ---: |
| Motion Sickness <br> Rating | First Shuttle <br> Flight | Later Shuttle <br> Flight | Totals |
| None | $32(29 \%)$ | $28(45 \%)$ | $60(35 \%)$ |
| Mild | $36(33 \%)$ | $24(39 \%)$ | $60(35 \%)$ |
| Moderate | $29(27 \%)$ | $10(16 \%)$ | $39(23 \%)$ |
| Severe | $12(11 \%)$ | $0(0 \%)$ | $12(7 \%)$ |
| Total | $\mathbf{1 0 9}(\mathbf{6 4 \%})$ | $\mathbf{6 2 ( 3 6 \% )}$ | $\mathbf{1 7 1}(\mathbf{1 0 0 \%})$ |
|  |  |  |  |
| From Nicogossian AE, et al. Countermeasures to space deconditioning. In: Nicogossian AE, et al., eds. Space |  |  |  |
| physiology and medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994:230. |  |  |  |



Figure 27.23 Pedaling the self-powered human centrifuge (Space Cycle) creates artificial gravity by producing head-tofoot acceleration (+Gz). Added instrumentation can monitor extremity strength, power output, body mass, and other parameters for ongoing functional and medical research. Restricting head movements by wearing a harness attached to the frame, combined with virtual reality headgear to maintain a horizontal visual experience, could minimize sensory input conflict during cycling, dramatically reducing space motion sickness. (From Kreitenberg A, et al. The Space Cycle ${ }^{\text {TM }}$ self powered human centrifuge: a proposed countermeasure for prolonged human space flight. Aviat Space Environ Med 1998;69:66.)

## Medications

The following classes of drugs help to minimize SMS effects:

1. Anticholinergics (parasympatholytics) blunt parasympathetic nervous system effects. Scopolamine in a dose of 0.6 to 1.0 mg proves most effective to eradicate approximately $90 \%$ of symptoms. Researchers believe that scopolamine blocks neural communication between the nerves of the vestibule and the brain s vomiting center (located in the reticular formation of the medulla) to retard the action of acetylcholine. Scopolamine also may work directly on the vomiting center.
2. Antihistamines (action antagonistic to histamine) offer some protection but are not as effective as scopolamine.
3. Sympathomimetics mimic sympathetic nervous system effects. Amphetamine with scopolamine confers beneficial effects.
4. Sympatholytics inhibit sympathetic nervous system effects.

Scope-dex, a combination of scopolamine (parasympatholytic) and amphetamine (sympathomimetic) exhibits the best overall success in minimizing SMS. Meclazine, a promising medication in land-based trials to maintain optimal cognitive functioning (histamine receptor blocker medication), also may blunt SMS s deleterious effects. ${ }^{108}$

## Lower-Body Negative Pressure

Figure 27.25 shows the in-flight lower-body negative pressure (LBNP) apparatus aboard Skylab (A, B) and Shuttle (C) missions. This device serves two functions:

1. Assesses orthostatic deconditioning during spaceflight and postlanding
2. As a countermeasure against adverse orthostatic changes with short- and long-term missions
The LBNP device applies negative pressure to the lower limbs. ${ }^{47}$ This forces fluid in the vascular system to migrate downward from the upper torso to the lower body-an effect that counters the in-flight response to microgravity. During three 6-month Mir missions, cosmonauts wore thigh cuffs (rather than rely on an LBNP device) at 1,3 to 4, and 5 to 5.5 months and assessed cardiovascular parameters with echocardiography. Data were contrasted with control sessions 30 days preflight and 3 and 7 days postflight. ${ }^{65}$ In all cosmonauts, a reduced vasoconstrictive response and a less efficient blood flow redistribution toward the brain coincided with orthostatic intolerance during postflight stand tests. ${ }^{133}$ The vascular response to LBNP tests remained depressed during the flights. Thus, the thigh cuffs compensated partially for the cardiovascular changes induced by microgravity, but not for microgravity deconditioning. Upregulation of nitric oxide (NO, a potent vasodilator and natriuretic) may explain orthostatic intolerance in microgravity. ${ }^{161}$ If this mechanism proves correct, administration of an inducible nitric oxide synthase inhibitor (iNOS) may attenuate orthostatic intolerance when astronauts return to Earth following a mission; it also may benefit patients following extended bed rest.

## Assessing Orthostatic Deconditioning Effects

Disruptions in cardiovascular dynamics-heart rate, blood pressure, and leg volume changes during space missionscould compromise crew performance and mission success. ${ }^{19,35}$ For example, orthostatic testing conducted after Gemini (14 days) and during Skylab (80 days) missions documented the degree of orthostatic deconditioning effects. The Gemini vehicles (including Mercury and Apollo) barely had enough room


100\% $\square 75 \% \max \square 50 \%$ max $\square 25 \%$ max
Figure 27.24 Top. The Ames centrifuge. Bottom. Comparison of the effects of two conditions (exercise acceleration and passive acceleration) on heart rate response at different percentages of maximal acceleration. Numbers at the end of lines represent final HR increase above rest. (Modified from Greenleaf JE, et al. Cycle-powered short radius [ 1.9 m ] centrifuge: effect of exercise versus passive acceleration on heart rate in humans. NASA technical memorandum 110433. 1997. NASA. Ames Research Center. Moffett Field, CA.)


Figure 27.25 Schematic diagram of the lower-body negative pressure (LBNP) apparatus (used aboard Skylab) illustrating the upper- and lower-body restraint assembly, including the leg volume measuring system (LVMS) leg band. The waist seal shroud maintains controlled and regulated negative pressure from 0 to 50 mm Hg below ambient pressure. During ground tests, a vacuum provides negative pressure; during flight, negative pressure occurs from the space vacuum. (From Nicogossian AE, et al., eds. Space Physiology and Medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994.)
for the astronauts, so the mission could not accommodate an onboard LBNP chamber. Thus, testing on Gemini took place only before and after flights. Also, Gemini flights used a tilt table rather than LBNP (Fig. 27.26, top panel). A 15-minute, 70 vertical LBNP tilt test produced dramatic changes in heart rate, systolic and diastolic blood pressure, and leg volume during the prolonged Skylab mission compared with the same variables assessed 3 weeks prior to liftoff. Heart rate increased $100 \%$ from $70 \mathrm{~b} \cdot \mathrm{~min}^{-1}$ at rest at the start of the LBNP tilt test to 140 b . $\min ^{-1}$ at the end of the procedure. Systolic blood pressure declined more ( $30 \%$ ) than diastolic blood pressure $(<10 \%$ ) during the tilt, whereas leg volume increased 10 -fold during the test.

The bottom of Figure 27.26 shows the pattern of resting heart rate in a $-50-\mathrm{mm} \mathrm{Hg}$ LBNP test in one crew member during the 80-day Skylab 4 mission and 2 months postflight. Although not as dramatic as the shorter duration Gemini experiments, the resting heart rate increase in response to LBNP during Skylab confirmed the relative instability (and variability) of heart rate, particularly during the first month of spaceflight compared with the end of the mission. Heart rate with LBNP during preflight never exceeded $75 \mathrm{~b} \cdot \min ^{-1}$, but it always exceeded this value throughout the mission. On Skylab missions 2 and 3, resting heart rate averaged $109 \mathrm{~b} \cdot \mathrm{~min}^{-1}$, a $55 \%$ increase over preflight values.

## LBNP Combined Countermeasures

A countermeasure combination of LBNP and increased fluid ingestion during spaceflight improves performance on
an upright standing posture test postflight. ${ }^{162}$ For example, two groups of 26 male astronauts consumed either no fluid or a loading volume of 32 oz of water or juice plus eight salt tablets (to facilitate fluid retention) 1 hour before leaving Earth orbit during shuttle missions 1 through $8 .{ }^{25}$ Figure 27.27 shows the fluid-loading countermeasure effects on postflight heart rate responses in the supine and standing positions. All crew members showed similar preflight heart rates. Crew members who used the liquid countermeasures did not experience syncope after landing mainly because about $40 \%$ of the ingested fluid increased plasma volume for nearly 4 hours. Astronauts who loaded fluid before reentry also had lower heart rates and maintained a more stable mean blood pressure. Overall, the hyperhydration countermeasures were more effective during short 3- to 7-day missions than during longer 10-day ones.

The protective benefits of combined countermeasures ${ }^{169}$ reduce the incidence of orthostatic intolerance assessed by postural tests postflight to only $5 \%$. ${ }^{127}$ In contrast, fluid loading alone prior to reentry loses its effectiveness after 7 days in microgravity ${ }^{34}$ or during a 7 -day, 6 head-down bed rest ${ }^{31}$ because the vascular space cannot maintain enough fluid to restore plasma volume to a level that exerts benefits. Another countermeasure tactic reduces air temperature inside the space cabin the night before landing. Keeping the cabin as cold as tolerable helps to dissipate heat in the cabin (and ultimately in the space garments) during reentry and postlanding, when cabin air temperature can reach 26.7 to 32 C ( 8090 F ). The astronaut s liquid cooling garment uses a

$\square$ Preflight mean $\square$ Postflight
thermoelectric cooler to keep the precirculated water cool before it circulates through the full-torso garment. Reducing sweating response during reentry and landing minimizes fluid loss.

## Nutrition

An optimal diet for spaceflight should theoretically provide energy (calorie) intake equal to the energy required for the mission. ${ }^{12,13,77} 79,109$ Dietary management also may counter the diverse, adverse effects of physiologic adaptation to microgravity. ${ }^{49,156}$ This goal, seemingly straightforward, has not been reached successfully on most missions. Almost every space journey produces weight loss compared with similarduration ground-based activities on Earth.82,122,142,164 Disruption in energy balance results from combined effects of the two important factors-demands of the physical requirements of spaceflight and decreased food intake during microgravity exposure. Both factors negatively affect the space traveler s energy balance. The effects of a negative energy balance became manifested not only in weight loss but in impaired fluid, electrolyte, and mineral balance. ${ }^{81,84}$ Each of these factors influences cardiovascular, musculoskeletal, immunologic, and endocrinologic functions. Cosmonauts in the Russian space program also have reported weight loss during extended missions.


## $\square$ Stressed ( -50 mm Hg ) $\square$ Resting control

Figure 27.26 LBNP evaluation of cardiovascular dynamics during space missions: Top. Gemini 14-day pre- to postflight changes in heart rate, blood pressure, and leg volume. Bottom. Resting heart rate in a $-50-\mathrm{mm}$ Hg LBNP test in one crew member during an 80-day Skylab mission. (From Charles JB, et al. Cardiopulmonary function. In: Nicogossian AE, et al., eds. Space Physiology and Medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994.)


Figure 27.27 Effect of forced liquid-loading countermeasures on heart rate response to moving from supine to standing before (preflight) and after (postflight) spaceflight. Postflight refers to period of space mission 1 h before leaving Earth orbit. (Modified from Bungo MW, et al. Cardiovascular deconditioning during spaceflight and the use of saline as a countermeasure to orthostatic intolerance. Aviat Space Environ Med 1985;5:985.)

## Effects on Body Weight

The graphs in Figure 27.28 summarize the large individual variation in body weight changes for the commander, scientist pilot, and pilot crew members during three Skylab missions lasting 24, 56, and 84 days. On each mission, all crew members lost weight and did not regain it except for the commander (Skylab 4), whose weight returned to prelaunch values by mission s end. The most dramatic weight loss of 3 to $4 \%$ generally occurred over the first 10 days of each mission, mainly from fluid loss. Weight loss reversed within 5 days after the crew returned to Earth. This same weight loss pattern during spaceflight and weight regain postflight occurred during the 1996 Life Sciences and Microgravity (LSM) mission. ${ }^{143}$

## INTEGRATIVE QUESTION

How would you measure an astronauts body weight in microgravity? (Hint: Refer to these citations for insights. $)^{54,127}$

Altered Protein Dynamics. Atrophy of skeletal muscles that support posture and locomotion represents a characteristic maladaptation to microgravity during short- and long-duration exposures. ${ }^{50}$ Decreases in lean body mass, muscle volume, and muscle strength, and changes in muscle fiber microarchitecture ${ }^{178}$ accompany space-induced muscle atrophy. Such changes suggest poor adaptation in whole-body protein (nitrogen) balance. ${ }^{93,142,144}$ Isotopic methods that assess tissue protein turnover show that astronauts increase protein breakdown rate by approximately $30 \%$ on mission days 2 to 8 , thereby producing negative nitrogen balance. In addition, increases occur in urinary cortisol, fibrinogen, and interleukin-2 (IL-2). These changes suggest that spaceflight triggers a stress response similar to response patterns from physical injury. ${ }^{142}$ In both of these stressful situations, tissue protein serves as a substrate for energy metabolism that fosters a negative nitrogen balance (protein catabolism). This supports the recommendation of a daily protein intake of 1.5 g per kg of body mass during space travel. ${ }^{83}$ In addition, long space missions (4 to 9 months on the Russian Mir Space Station) and shorter duration space shuttle flights (up to 15 d ) are associated with decreased oxidative damage owing to reduced oxygen radical production (in the electron transport chain) from reduced energy intake. Increased oxidative damage occurs postflight from combined increases in metabolic rate and possible loss of in-flight host antioxidant defenses. ${ }^{146}$ The potential beneficial effects of postflight antioxidant supplementation remain unknown.

Figure 27.29 plots daily energy intake and urine-based nitrogen balance assessment during three Skylab missions and two SLS missions. Note the in-flight negative nitrogen balance on Skylab compared with a preflight baseline despite nearnormal energy intake. On the two shuttle missions, daily calorie intake and nitrogen balance were affected negatively compared with preflight values. Based on Russian data aboard the Salyut-7 space mission, the estimated energy cost of twice-daily inflight exercise sessions was approximately 20 kCal per kg of body mass. Adding this energy requirement to an already inadequate daily energy intake would provoke further protein loss to absorb the energy deficit. ${ }^{70}$ Research must determine effective combinations of exercise and nutritional supplementation to stabilize energy and protein balance during space missions, including development of renal stones that can seriously impact the health of the crew member and mission. ${ }^{112}$

## IQ <br> INTEGRATIVE QUESTION <br> Explain whether consuming additional protein during a space mission would help to restore fatfree body mass.

## Energy Expenditure and Balance Dynamics on the Space Shuttle

The 1996 LMS shuttle mission measured energy expenditure and energy balance in four crew members for 12 days before liftoff, during the 17-day flight, and 15 days


Figure 27.28 Changes in body weight of crew personnel during three Skylab missions. Top, Skylab 2, 24 days. Middle, Skylab 3, 56 days. Bottom three, Skylab 4, 84 days. Orange circles denote body weight at transitions at various phases in mission sequence. Note that each astronaut s body weight decreases dramatically during microgravity exposure. (From Thornton WE, Ord J. Physiological mass measurements in Skylab. In: Johnson RS, Dietlein LF, eds. Biomedical results from Skylab. NASA SP377. Washington, DC: Government Printing Office, 1977.)


Figure 27.29 Daily energy intake (left axis) and daily urinebased nitrogen balance (right axis) during spaceflight on three Skylab missions and two Life Sciences Space Shuttle missions (SLS-1 and SLS-2). Values are means $\pm$ SE. Solid bars represent preflight values and striped bars represent measures taken in flight. (Modified from Stein TP, et al. Diet and nitrogen metabolism during spaceflight on the shuttle. J Appl Physiol 1996;81:82.)
postflight. ${ }^{143}$ In addition, a complementary bed-rest study with a 6 head-down tilt to simulate microgravity evaluated energy expenditure and energy balance in eight subjects. The bed-rest study had three phases: (1) 15-day pre bed-rest ambulatory period, (2) 17 days of bed rest (except when subjects exercised to match the in-flight exercise routines), and (3) a 15-day recovery period. Subjects in both experiments performed submaximal and maximal bicycle ergometer exercise tests on days 13 and 8 before launch and on days 4 and 8 postflight. During spaceflight days 2,8 , and 13 , crew members performed an additional ergometer test to assess cardiorespiratory responses to exercise at $85 \% \dot{\mathrm{~V}}_{2 \max }$.

Measurements included doubly labeled water (DLW, ${ }^{2} \mathrm{H}_{2}{ }^{18} \mathrm{O}$ ) and body composition by dual-energy X-ray absorptiometry (DXA) before and after spaceflight/bed rest to quantify positive energy balance (fat stored) or negative energy balance (fat catabolized). Subjects quantified each food item consumed and not consumed with a bar code reader and verbal description (using a cassette recorder) to estimate the contents remaining in the individual food package. During pre- and postflight periods, subjects consumed prepared meals of known nutrient content. The Spacelab contained a system to collect, measure, and save a $20-\mathrm{mL}$ daily urine sample to estimate nitrogen balance from nitrogen and creatinine excretion.


[^49]Figure 27.30 Top. Daily energy intake before, during, and after spaceflight on shuttle LMS. The histogram inset expresses the data as average $\mathrm{kCal} \cdot \mathrm{d}^{-1}$ during each mission phase. Bottom. Daily energy intake during the first 2 weeks of spaceflight for Skylab missions 2 (28 d), 3 ( 56 d), and 4 ( 84 d); two shuttle missions (SLS-1 and SLS-2 combined); and shuttle LMS. (Data modified from Stein TP, et al. Energy expenditure and balance during spaceflight on the space shuttle. Am J Physiol 1999;45:R1739.)

The top of Figure 27.30 displays three energy intake periods expressed as $\mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~d}^{-1}$ during preflight, flight, and postflight. Note that within each period, a relative stabilization (adaptation) takes place for energy intake. This probably occurs from resetting of setpoint mechanisms that regulate
energy balance. The histogram inset expresses average energy intake in kCal daily to highlight the dramatic $45 \%$ lower in-flight energy intake ( $1708 \mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~d}^{-1}$ ) compared with the remarkably similar values preflight $\left(3025 \mathrm{kCal} \cdot \mathrm{kg}^{-1}\right.$. $\mathrm{d}^{-1}$ ) and postflight ( $3151 \mathrm{kCal} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~d}^{-1}$ ) intakes.

The bottom graphic compares the energy intake during the first 2 weeks of spaceflight for Skylab missions 2, 3, and 4 and the two shuttle LMS missions. Astronauts on the shuttle LMS (bottom red curve) remained in substantial negative energy balance throughout the flight. Astronauts on the previous three Skylab missions participated in a metabolic balance study, so daily energy intakes remained fairly stable during the different-duration missions. In contrast, astronauts on shuttle LMS consumed food ad libitum. At the same time, they performed vigorous daily exercise that contributed to their relatively high average total daily energy expenditure of $40.8 \mathrm{kCal} \cdot \mathrm{kg}^{1} \cdot \mathrm{~d}^{1}$ (3238 kCal). No differences occurred among the three methods of estimating energy balance. This result supported the validity of the methodology and the main two research conclusions:

1. Severe negative energy balance and corresponding loss of body mass, body fat, and protein could compromise a mission and adversely affect an astronaut $s$ health in a manner resembling prolonged malnutrition.
2. High levels of physical activity during spaceflight may disrupt mechanisms that maintain energy balance.

Persistent, severe $1400-\mathrm{kCal}$ negative daily energy balance on future extended-duration flights would ultimately mobilize an astronaut $s$ entire fat energy reserves (approximately $160,000 \mathrm{kCal}$ ) within 120 days and produce terminal starvation. Researchers obviously must determine how best to ensure that astronauts consume adequate daily nutrition to counterbalance the following ${ }^{148}$ :

1. Energy requirements of spaceflight
2. Demands of exercise countermeasures and normal work tasks
3. Decreased efficiency in removing the metabolic byproducts of exercise (e.g., $\mathrm{CO}_{2}$, heat)

Cosmonauts on the Mir mission partially resolved their inflight energy deficits by curtailing physical activity. Theoretically, they could remain in orbit for 660 days before severe undernutrition compromised physiology, performance, and health.

## International Space Station (ISS)

One of the difficulties facing space medicine scientists is how to plan for optimal nutrient requirements during longduration space exploration missions. ${ }^{80}$ The International Space Station provides a unique vehicle to assess nutritional changes during long-duration spaceflights of 128 to 195 days. A unique series of experiments aboard the ISS has examined body composition, bone metabolism, hematology, general blood chemistry, and blood levels of selected vitamins and
minerals in 11 astronauts before and after such long-duration missions. Crew members consumed a mean of $80 \%$ of their recommended energy intake, and on landing day their body weight was significantly lower than before flight. Hematocrit, serum iron, ferritin saturation, and transferrin were decreased and serum ferritin significantly increased after flight. The finding that other acute-phase proteins were unchanged after flight suggests that the changes in iron metabolism were not solely responsible for an inflammatory response. Urinary 8 -hydroxy-2'-deoxyguanosine concentration was greater and red blood cell superoxide dismutase was depressed after flight, indicating increased oxidative damage. The astronauts consumed vitamin D supplements during flight, yet serum 25hydroxycholecalciferol decreased after flight. Bone resorption was increased after flight, but bone formation did not consistently rise 1 day after landing. Bone loss, compromised vitamin D status, and oxidative damage are among critical nutritional concerns that require resolution for long-duration space travelers. ${ }^{139}$

## Nutritionally Related Effects of Spaceflight on Physiologic Functions

Since the first space missions, researchers have tracked adaptations in physiologic function during microgravity exposure. A prevailing theory about such changes concerns the interactions among nutritional variables and endocrine functions and their combined effects on cardiopulmonary, hormonal, skeletal, and body fluid functions, and body mass and composition. ${ }^{37,92,94,137,149}$ Figure 27.31 shows the triad of nutritionally related effects of spaceflight on physiologic systems. The interrelated triad components-fluid shifts, physical unloading of weight-bearing structures, and metabolic changes-in many ways link to shifts in endocrine function. The inset table shows endocrine changes during stress, simulated microgravity (bed rest), and spaceflight. Note that the responses to bed rest do not generally mirror endocrine changes in spaceflight, but instead mimic the stress-mediated responses. An attractive hypothesis posits that the endocrine effects of spaceflight relate more to nutritional changes characterized by stress-related models, not a model that includes bed rest. ${ }^{85}$ The similarity between the catabolic effects of the increased demands on energy metabolism (and negative energy balance) and catabolic effects of spaceflight stress help to explain space-induced decreases in body mass, lean body mass, and bone density. This includes shifts in extracellular and intracellular water compartments.

Body Composition Changes. Figure 27.32 shows percentage changes in body composition variables of 10 astronauts assessed by densitometry and bioelectrical impedance analysis before and 2 days following 7 - to 16 -day missions. No changes occurred in body fat or extracellular water, with the $2.3 \%$ decline in body mass attributable to a loss in fatfree body mass (FFM). Note that all three components of FFM (water, protein, and mineral) declined from 3 to $4 \%$ in the postflight measures. The $3 \%$ loss of intracellular


Figure 27.31 Triad of nutritionally related effects of spaceflight on physiologic systems. The inset shows endocrine changes during stress, simulated microgravity (bed-rest studies), and spaceflight. $\uparrow$, increase; $\uparrow \uparrow$, large increase; $\downarrow$, decrease; $\leftrightarrow$, no change. (Modified from Lane HW, Gretebeck RJ. Nutrition, endocrinology, and body composition during space flight. Nutr Res 1998;18:1923.)
water-attributable to decreased protein and mineral levels within other tissues including muscle-explains the decrease in total-body water. ${ }^{145} \mathrm{An}$ integrative approach assesses regional body composition (calf muscle volume) ${ }^{168}$ and MRI-derived characteristics of muscle (transverse relaxation of calf muscles) following multiple shuttle/Mir missions lasting 16 to 28 weeks. ${ }^{91}$ The newer technique of bioelectrical impedance spectroscopy (BIS) has assessed nutritional status during spaceflight, but its limitations in precision and insensitivity to short-term intracellular water changes require further validation. ${ }^{16}$

## INTEGRATIVE QUESTION

Explain what role diet and exercise should play in prolonged-duration space missions.

## OVERVIEW OF PHYSIOLOGIC RESPONSES TO SPACEFLIGHT

Numerous research reports discuss short- and long-term consequences of spaceflight on human physiology. ${ }^{18,31,88,119}$ From the first single-pilot flights of Project Mercury in the
early 1960s to the extended Soviet Soyuz missions of the 1990s and latest manned Chinese space missions, scientists have pondered how best to minimize the deleterious effects of microgravity during flight and upon return to Earth. Figure 27.33 diagrams the two main physical stressors from space travel:

1. Decreased hydrostatic pressure gradients within the cardiovascular system (displayed on the left)
2. Decreased weight loading on muscles (displayed on the right)

Both factors ultimately increase physiologic strain (orange box at the bottom) and negatively affect an astronaut s physical performance (red box at the bottom).

Note that the three effects (decreased $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ and muscular strength and increased fatigability), combined with an increased thermal load, add substantially to the total physiologic strain. Exercise countermeasures (specifically site-specific lower-body eccentric and concentric resistance exercise) coupled with relatively intense cardiovascular workouts on a cycle ergometer and treadmill can mitigate deleterious effects from prolonged microgravity sojourns. This is particularly germane when astronauts return to a 1 g Earth environment.


Figure 27.32 Percentage changes ( $\Delta$ ) in body composition variables of 10 astronauts assessed by densitometry and multifrequency bioelectrical impedance analysis before and 2 days after 7 - to 16 -day missions. $B M$, body mass; FFM, fat-free body mass; TBW, total body water; ICW, intracellular water; TBM, total body mineral; TBP, total body protein. (Data from Greenisen MC, et al. Functional performance evaluation. In: Extended Duration Orbiter Medical Project. NASA Johnson Space Center final report. 19891995. [NASA/SP-1999-534] NASA. Lyndon B. Johnson Space Center. Houston, TX. 1999.)

## Short- and Long-Term Responses

Two categories, short- and long-term, describe the time course of physiologic response and adaptation in the transitions from Earth s 1 g environment to microgravity in lowEarth orbit and then return to 1 g following a mission. Short-term responses occur within 24 hours or the first few days of a mission. The second category describes longer-term changes following a mission. Figure 27.34 presents a generalized flow diagram of the immediate or short-term ( $<24 \mathrm{~h}$ ) and delayed or long-term ( $>24 \mathrm{~h}$ ) responses. Both immediate and delayed responses eventually contribute to orthostatic hypotension (bottom purple box), the most common malady following spaceflight.

In space, body fluids no longer move downward from gravity s pull, so fluids redistribute toward the chest and upper body (note facial puffiness from cranial edema). Lower-body fluid loss gives the legs a birdlike appearance. Excess fluid buildup in the torso triggers fluid elimination by the kidneys. Mean arterial pressure increases in the cranial region from a preflight normal of 70 mm Hg to 100 mm Hg in space (Fig. 27.34, top), while mean pressure at the feet declines $50 \%$ from its normal 200 mm Hg ; heart volume also decreases slightly. The immediate change in body fluid distribution activates a plethora of additional responses and lower sympathetic nervous system activity. Restricted stimulation environments such as spaceflight and other stress-inducing situations from prolonged confinement and isolation share many of the same responses and adaptations. ${ }^{95}$

## Time Course of In-Flight Adaptations

Figure 27.35 depicts the time course for shifts in four main categories of physiologic function during 1 year of sustained microgravity. The green horizontal line represents baseline function on Earth (denoted as 0\% change). Within the first 3 weeks, up to a $10 \%$ change in cardiovascular function reflects a deconditioning response; within 14 days, a $10 \%$ change occurs in body fluid redistribution; and within 3 months, bone mass declines by $5 \%$. Bone mass declines further, to $15 \%$, between months 5 and 6 , when it stabilizes for several months before decreasing farther to $17 \%$ after 1 year. Like bone mass, muscle structure and function deteriorate at a slower rate than do cardiac deconditioning and fluid redistribution, but the magnitude of the decrement reaches higher values.

## Time Course of Postflight Readaptations

Figure 27.36 shows how 3 months of recovery (readaptation) affects neurovestibular and cardiovascular functions, fluid and electrolyte balance, red blood cell mass, and lean body mass. For reference, the lower horizontal line, indicated by the arrow at bottom left ( 1 g set point), represents baseline measures expected under normal 1 g conditions. The colored lines for each variable indicate average trends, but considerable inter- and intraindividual differences exist.

Analysis of the recovery curves reveals two characteristics:

1. The response rate is nonlinear, with some processes appearing bimodal with relatively high rate constants.
2. Recovery time varies depending on the variable evaluated.

For example, the rapid change in fluid distribution during the first few weeks of microgravity exposure shown previously in Figure 27.34 recovers to baseline within the first week of return to 1 g (yellow curve). In contrast, the light green curve for lean body mass and purple curve for cardiovascular deconditioning require approximately 6 weeks to approach baseline.

## VISION FOR THE FUTURE OF SPACE EXPLORATION

On January 4, 2004, the United States committed to a longterm human and robotic program to explore the solar system, starting with a return to the moon to ultimately enable future exploration of Mars and other destinations. The plan for human and robotic space exploration is based on the following goals:

1. America will complete its work on the ISS by 2010, fulfilling the United States commitment to the 15 partner countries involved in the space program. The United States will launch a refocused research effort onboard the ISS to better understand and overcome the effects of human spaceflight on astronaut health, increasing the safety of future space missions. To accomplish this goal, NASA will return the Space


Figure 27.33 Model of the relationship between physical stress of the space environment and adaptation of cardiovascular and muscular systems, with resulting increased physiologic strain and decreased physical performance. SNS, sympathetic nervous system; CVP, central venous pressure; $\beta$, beta-adrenergic; $N E$, norepinephrine; $H R$, heart rate; $S V$, stroke volume; $a-v O_{2}$ diff, arteriovenous oxygen difference; $\uparrow$, increase; $\downarrow$, decrease; $\downarrow \downarrow$, large decrease; $\leftrightarrow$, no change. (From Convertino VA. Effects of microgravity on exercise performance. In: Garrett WE, Kirkendall DT, eds. Exercise and Sport Science. Philadelphia: Lippincott Williams \& Wilkins, 2000.)

Shuttle to flight consistent with safety concerns and the recommendations of the Columbia Accident Investigation Board. The shuttle s chief purpose is to help finish assembly of the ISS before it will be retired by the end of this decade, following 30 years of service.
2. The United States will develop a new manned exploration vehicle to explore beyond our orbit to other
worlds-the first of its kind since the Apollo Command Module. The new spacecraft, the Crew Exploration Vehicle (CEV; www.nasa.gov/missions/ solarsystem/cev_faq.html), is currently in testing and should fly its first manned mission by 2014. The CEV will transport astronauts and scientists to the ISS after the shuttle retires.


Figure 27.34 Proposed immediate ( $<24 \mathrm{~h}$ ) and delayed ( $>24 \mathrm{~h}$ ) responses to microgravity compared with those under preflight (1g) and postflight ( 1 g ) conditions. AVP, arginine vasopressin; ANP, atrial natriuretic peptide; GFR, glomerular filtration rate; RCM, red cell mass; SNS, sympathetic nervous system; $\uparrow$, increase; $\downarrow$, decrease, ?, possible. (Photos courtesy of NASA, Lyndon B. Johnson Space Center, Houston, TX.
Figures denoting changes in mean arterial pressure modified from Hargens AR, et al. Control of circulatory function in altered gravitational fields. Physiologist 1992;35:S80. Additional graphic information modified from Maillet A, et al. Cardiovascular and hormonal changes induced by isolation and confinement. Med Sci Sports Exerc 1996;28:S53.)


Figure 27.35 Time course of four main shifts in physiologic function during 1 year in microgravity. The horizontal green line represents baseline function on Earth at 1 g (denoted as zero percent change). The cardiac index of deconditioning (red line) reflects severity of orthostatic intolerance to gravitational stress. (Modified from: Nicogossian A, et al. Overall physiologic response to space flight. In: Nicogossian AE, et al., eds. Space Physiology and Medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994.)


Figure 27.36 Time course of physiologic shifts during readaptation to 1 g , in which flight duration only minimally affects the readaptations. (Modified from Nicogossian AE, et al., eds. Space Physiology and Medicine. 3rd ed. Philadelphia: Lea \& Febiger, 1994.)
3. America will return humans to the moon as early as 2015 and no later than 2020 (twice-yearly lunar missions from lunar orbit to the moon s surface), including it as a stage that will ferry astronauts to Mars. A series of robotic missions to the moon, similar to the Spirit Rover that currently transmits remarkable images back to Earth from Mars (marsrovers.nasa.gov/ home/index.html), will explore the lunar surface to research and prepare for future human exploration. Using the CEV, humans will conduct extended lunar missions as early as 2015, with the goal of living and working for increasingly extended periods. The extended human presence on the moon will enable astronauts to develop new technologies and harness the moon s abundant resources to allow manned exploration of more challenging environments. NASA will increase the use of robotic exploration to maximize new knowledge about the solar system and pave the way for more ambitious manned missions using probes, landers, and similar unmanned vehicles. Astronauts will conduct cutting-edge research in astrobiology, geology, astronomy, physics, and space biology. One of the main reasons for returning to the moon is to master the technologies required for future extended-duration Mars explorations.

## PRACTICAL BENEFITS FROM SPACE BIOLOGY RESEARCH

Of a $\$ 3.0$ trillion budget, less than $0.8 \%$ is spent on the entire United States space program. That amounts to less than 1 penny for every dollar the government spends on its diverse programs. The average American spends more of their budget on a monthly cable bill or eating out at fast food restaurants. For every dollar the United States spends on research and development in the space program, seven dollars come back as corporate and personal income taxes from increased jobs and economic growth. Hundreds of companies that apply NASA technology in non space-related areas create hundreds of thousands of jobs that ultimately affect citizens worldwide. Technologies developed over the past 40 years to meet the challenges of space exploration have produced more than 30,000 secondary commercial applications in seven categories. We provide salient examples below (www.thespaceplace .com/nasa/spinoffs.html):

## 1. Computer Technology

Ground processing scheduling system. Computerbased scheduling system uses artificial intelligence to provide real-time planning and optimization of manufacturing operations, integrated supply chains, and customer orders.

Structural analysis. Originally created for spacecraft design, this NASA program appears in a broad array of non-aerospace applications including the
automobile industry, manufacture of machine tools, and hardware designs.
Semiconductor cubing. The Memory Short Stack offers faster computer processing speeds, higher levels of integration, lower power requirements than conventional chip sets, and dramatic reduction in the size and weight of memory-intensive systems such as medical imaging devices.
Virtual reality. Users with assistance from advanced technology devices can figuratively project themselves into a computer-generated environment that matches the user s head motion to create a telepresence experience.
Air Quality Monitor. An air quality monitor system was created using a NASA-developed, advanced analytical technique software package capable of separating various gases in bulk smokestack exhaust streams and determining the amount of individual gases present within the stream for compliance with smokestack emission standards.
Other spin-offs include advanced keyboards, customer service software, database management system, laser surveying, aircraft controls, lightweight compact disk, expert system software, microcomputers, and design graphics.

## 2. Consumer/Home/Recreation

Enriched baby food. A microalgae-based, vegetablelike oil called Formulaid contains two essential fatty acids found in human milk, believed important for mental and visual development.
Water purification system. NASA-developed municipal-sized water treatment system for developing nations, called the Regenerable Biocide Delivery Unit, uses iodine rather than chlorine to kill bacteria.
Scratch-resistant lenses. A modified version of a dual ion beam bonding process involves coating lenses with a film of diamond-like carbon that provides scratch resistance, decreases surface friction, and reduces water spots.
Ribbed swimsuit. Riblets applied to competition swimsuits produced 10 to $15 \%$ faster speeds than any other swimsuit due to small, barely visible grooves that reduce friction and hydrodynamic drag by modifying the turbulent flow of water next to the skin.
Athletic shoes. Moon Boot material encapsulated in running shoe midsoles improves shock absorption and provides superior stability and motion control.
Other spin-offs include Dustbuster, shock-absorbing helmets, home security systems, smoke detectors, flat panel televisions, high-density batteries, trash compactors, food packaging and freeze-dried technology, cool sportswear, sports bras, hair-styling appliances, fogless ski goggles, self-adjusting
sunglasses, composite golf clubs, hang gliders, art preservation, and quartz crystal timing equipment.
3. Environmental and Resource Management Microspheres. The first commercial products manufactured in orbit were tiny microspheres whose precise dimensions allowed their use as reference standards for accurate calibration of instruments in research and industrial laboratories. The microspheres are used in environmental control, medical research, and manufacturing.
Solar energy. Photovoltaic power systems for spacecraft applications expand terrestrial applications as a viable alternative energy source.
Forest management. A scanning system monitors and maps forestation by detecting radiation reflected and emitted from trees.
Fire-resistant material. Materials include chemically treated fabric for sheets, uniforms for hazardous material handlers, crew s clothing, furniture, interior walls of submersibles, and auto racer and refueler suits.
Other spin-offs include whale identification method, environmental analysis, noise abatement, pollution measuring devices, pollution control devices, smokestack monitor, radioactive leak detector, earthquake prediction system, sewage treatment, energy-saving air conditioning, and air purification.

## 4. Health and Medicine

Digital imaging breast biopsy system. The LORAD Stereo Guide Breast Biopsy system incorporates advanced Charge Coupled Devices (CCDs) to image breast tissue clearly and efficiently. This less traumatic nonsurgical system greatly reduces the pain, scarring, radiation exposure, time, and money associated with surgical biopsies.
Breast cancer detection. A solar cell sensor is positioned directly beneath X-ray film and determines when film receives sufficient radiation and has been exposed to optimum density. Reduction of mammography X-ray exposure reduces radiation hazard and doubles the number of patient examinations per machine.

Laser angioplasty. Laser angioplasty with a cool type of laser, called an excimer laser (excimer stands for excited dimer, a short-lived diatomic molecule that bonds two identical molecules only when in an electronic excited state), does not damage blood vessel walls. It offers precise nonsurgical cleanings of clogged arteries with precision and fewer complications than balloon angioplasty.
Ultrasound skin damage assessment. Advanced instrument using NASA ultrasound technology enables immediate assessment of burn damage depth and improved patient treatment.

Human tissue stimulator. Employing NASA satellite technology, the device is implanted in the body to help the patient control chronic pain and involuntary motion disorders through electrical stimulation of targeted nerve centers or particular areas of the brain.
Automated urinalysis. System that automatically extracts and transfers sediment from a urine sample to an analyzer microscope that replaces the manual centrifuge method.
Other spin-offs include arteriosclerosis detection, ultrasound scanners, automatic insulin pump, portable X-ray device, invisible braces, dental arch wire, palate surgery technology, clean room apparel, implantable heart aid, MRI, bone analyzer, and cataract surgery tools.
5. Industrial Productivity/Manufacturing Welding sensor system. Laser-based automated welder for industrial use incorporates a laser sensor system to track the seam where two pieces of metal are to be joined, measures gaps and minute misfits, and automatically corrects the welding torch distance and height.
Microlasers. Transmits communication signals that can drill, cut, and melt materials.
Interactive computer training. Known as Interactive Multimedia Training (IMT), trains new employees to upgrade worker skills with a computer system that uses text, video, animation, voice, sounds, and music.
Other spin-offs include gasoline vapor recovery, self-locking fasteners, machine tool software, laser wire stripper, lubricant coating process, wireless communications, engine coatings, and engine design.
6. Public Safety

Radiation hazard detector. NASA technology has made commercially available new, inexpensive, conveniently carried device for protection of people exposed to potentially dangerous levels of microwave radiation. Weighing only 4 ounces and about the size of a pack of cards, it can be carried in a shirt pocket or clipped to a belt. The unit sounds an audible alarm when microwave radiation reaches a preset level.
Emergency response robot. Remotely operated robot reduces human injury levels by performing hazardous tasks that would otherwise be handled by humans.
Personal alarm system. Pen-sized ultrasonic transmitter used by prison guards, teachers, the elderly, and disabled to call for help is based on space telemetry technology. The pen transmits a silent signal to a receiver that displays the exact location of the emergency.
Firefighters air tanks. Lighter weight firefighter s air tanks weigh only 20 pounds for a 30-minute air supply, 13 pounds less than conventional firefighting tanks. The tanks are pressurized at 4500 psi (twice current tanks). A warning device tells the firefighter when air runs out.

Personal storm warning system. Lightning detector gives 30-minute warning to golfers, boaters, homeowners, business owners, and private pilots.
Other spin-offs include storm warning services (Doppler radar), firefighters radios, lead poison detection, fire detector, flame detector, corrosion protection coating, protective clothing, and robotic hands.

## 7. Transportation

Studless winter tires. Viking Lander parachute shroud material is adapted and used to manufacture radial tires, increasing the tire material s chainlike molecular structure to five times the strength of steel, which should increase tread life by 10,000 miles.
Better brakes. New, high-temperature composite space materials provide better brake linings. Applications include trucks, industrial equipment, and passenger cars.
Advanced lubricants. An environment-friendly lubricant provides lubricants for railroad track maintenance, electric power company corrosion prevention, and hydraulic fluid with an oxidation life of 10,000 hours.
Energy storage system. The Flywheel Energy Storage system provides a chemical-free, mechanical battery that harnesses the energy of a rapidly spinning wheel and stores it as electricity with 50 times the capacity of a lead acid battery; very useful for electric vehicles.
Other spin-offs include safer bridges, emission testing, airline wheelchairs, electric cars, auto design, methane-powered vehicles, windshear prediction, and aircraft design analysis.

NASA maintains an active database of all its programs and technologies with commercial potential and benefits (www.sti.nasa.gov/tto/spinoff2001/cbs_div.html). TABLE 27.12 lists examples of spin-off technologies from the Apollo Space Program, and Table 27.13 lists spin-off contributions from the Space Shuttle Program.

Final Words. As we close this chapter, NASA s Phoenix Mars Mission, launched in August 2007, has been studying the history of water and habitability potential in the Martian arctic s ice-rich soil for the equivalent of 242 Earth days (as of October 13, 2009). On July 31, 2008, laboratory tests aboard the Phoenix Lander confirmed what researchers had speculated about for a long time-the existence of water in a soil sample (www.nasa.gov/mission_pages/phoenix/main/ index.html). The Landers 8-foot-long robotic arm delivered the sample to an instrument that identifies vapors produced by the heating of samples. Future tests conducted by the Phoenix Lander will provide evidence about the hostile Martian environment that might once have supported some form of primitive life as we know it. In addition, the mission will attempt to answer these three important questions:

1. Can the Martian arctic support life?
2. What is the history of water at the landing site?
3. How is the Martian climate affected by polar dynamics?

The Phoenix Lander is not the only Explorer mission that will continue to provide a vast storehouse of new knowledge about worlds beyond our own. The intricate Wide-Field Infrared Survey Explorer (WISE) program scheduled for launch in November 2009, will measure the diameters of more than 100,000 asteroids, the debris trails

## TABLE 27.12 Examples of Spin-off Technologies from the Apollo Space Program

## Spin-Off Device

Digital signal-processing techniques, originally developed to computer-enhance pictures of the moon for the Apollo Program, are an indispensable part of computer-aided tomography (CAT) scan and magnetic resonance imaging (MRI) technologies in hospitals worldwide.
As a medical CAT scanner searches the human body for tumors or other abnormalities, the industrial version or advanced computed tomography inspection system finds imperfections in aerospace castings, rocket motors, and nozzles.
Cool suits, which kept Apollo astronauts comfortable during moon walks, are worn by race car drivers, nuclear reactor technicians, shipyard workers, persons with multiple sclerosis, and children with a congenital disorder known as hypohidrotic ectodermal dysplasia.
Kidney dialysis machines were developed from a NASA-developed chemical process that removed toxic waste from used dialysis fluid.
A cardiovascular conditioner developed for astronauts in space led to the development of a physical therapy and athletic development machine used by football teams, sports clinics, and medical rehabilitation centers.
Cordless power tools and appliances.
Athletic shoe design and manufacture incorporated technology from NASA spacesuits into a shoe s external shell. A stress-free blow molding process is used in the shoe s manufacture.
Insulation barriers made of aluminum foil laid over a core of propylene or Mylar, which protected astronauts and their spacecraft s delicate instruments from radiation, protects cars and trucks and dampens engine and exhaust noise.

## TABLE 27.13 Examples of Spin-off Technologies from the Space Shuttle Program

$\left.\begin{array}{ll}\text { Spin-off Device } & \text { Description } \\ \text { Artificial heart } & \begin{array}{c}\text { Technology used in space shuttle fuel pumps led to the development of a miniaturized ventricular assist } \\ \text { pump. }\end{array} \\ \text { Automotive insulation } & \begin{array}{c}\text { NASCAR racing cars use materials from the space shuttle thermal protection system to protect drivers } \\ \text { from extreme engine heat. }\end{array} \\ \text { Balance evaluation systems } \\ \text { Medical centers use balance systems to measure the equilibrium of space shuttle astronauts upon return } \\ \text { from space; the balance systems diagnose and treat patients that suffer head injury, stroke, chronic } \\ \text { dizziness, and central nervous system disorders. } \\ \text { A rotating cell culture apparatus simulates some aspects of the space environment or microgravity on the } \\ \text { ground. Tissue samples grown in the bioreactor help to design therapeutic drugs and antibodies. }\end{array}\right\}$
of comets, and the most luminous galaxies (Fig. 27.37). The sophistication of this type of future mission will provide important data about the solar system, the Milky Way, and the Universe.

We are hopeful that the United States, along with its dedicated international space partners, will continue to commit substantial resources to space exploration so the next generation of space explorers (maybe one of you reading this text) will de-


Figure 27.37 Artist s conception of the WISE unmanned satellite in Earth orbit. Only 9.4 ft tall, 6.6 ft wide, and 5.7 ft deep, it will carry an infrared-sensitive telescope to image the entire sky (the infrared spectrum includes light beyond the red part of the rainbow invisible to our eyes). Scheduled for launch in November 2009, the electricity to power WISE will come from solar panels oriented toward the Sun. After 6 months, WISE will have transmitted nearly 1.5 million pictures to create an atlas that covers the entire celestial sphere (http://wise.ssl.berkeley.edu/mission_faq.html\#launch). (Image courtesy of NASA, Lyndon B. Johnson Space Center, Houston, TX). Technical details in: Mainzer, AK, Eisenhardt P, et al. Preliminary design of the Wide-Field Infrared Survey Explorer (WISE). UV/optical/IR space telescopes: innovative technologies and concepts II. In: MacEwen, HA, ed. Proceedings of the SPIE 2005;5899:262 273)
velop better ways to understand the impact of the last frontier on humankind. This should indeed be an exciting time for NASAs new streamlined efforts, and for the rest of us.

## Summary

1. On Earth s surface, gravity provides an invisible attraction force that makes any mass exert downward force or have weight. Sir Isaac Newton (1642 1727) discovered the universality of the gravitational law.
2. The escape velocity of an object or celestial body depends on the mass and radius of that body. Escape velocity from Earth equals $25,039 \mathrm{mi} \cdot \mathrm{h}^{-1}$.
3. The force of gravity never reaches an absolute zero value (called zero-g) because a gravitational force still exists. The term microgravity, not weightlessness (or zero-g), best describes what an astronaut perceives during spaceflight.
4. When an elevator descends quickly, one perceives a lessening of weight because of reduced force between the feet and elevator floor.
5. Two different strategies have simulated spaceflights microgravity environment: (1) test equipment to create microgravity conditions for brief periods using sounding rockets and objects dropped from towers or into tubes or (2) simulated microgravity conditions using humans in head-down bed rest, wheelchairbound individuals, water immersion, immobilization and confinement, and parabolic flights plus in vitro centrifugation, mathematical modeling, and computer simulations.
6. On October 4, 1957, the Russian s Sputnik-1 became the first Earth-orbiting satellite. One month later, Sputnik-2 remained in orbit for almost 200 days with a dog on board.
7. NASA had two main early goals: (1) launch a man into space and return him safely to Earth and (2) develop human capability to endure space missions.
8. The most significant technologic achievement of the 20th century took place when Apollo 11 astronauts Aldrin and Armstrong landed on the moon s surface.
9. During the first few days in microgravity, fluid shifts from the lower body to the upper body. Total fluid volume also decreases to reduce the heart s work effort.
10. The greatest postural instability in microgravity occurs in tests that require vestibular information.
11. NASA s greatest biomedical concern during space missions involves the $1 \%$ per month loss in weightbearing bone mass.
12. Permanent neuromuscular dysfunction has not occurred during prolonged space missions.
13. In-flight and postflight changes during missions of nearly 1 year reveal altered muscular coordination patterns, delayed-onset muscle soreness, and generalized muscular fatigue and weakness.
14. Countermeasure strategies attempt to minimize spaceflight s potentially harmful deconditioning effects on crew physiologic function, performance, and overall health during mission-critical maneuvers with reentry and landing.
15. Without gravity, normal biologic functions become more susceptible to short- and longer-term maladaptations such as space motion sickness (SMS).
16. The energy balance equation has not been satisfied successfully on most space missions because of the increased energy demands of spaceflight and decreased food intake.
17. Maladaptations to microgravity include decreases in lean body mass, muscle volume, and muscle strength, altered muscle fiber microarchitecture, and atrophy of skeletal muscles that support posture and locomotion.
18. Technologies developed by NASA over the past 40 years have produced more than 30,000 secondary commercial spinoff applications, many providing life-altering breakthroughs in computer technology, consumer/home/recreation, transportation, environmental and resource management, industrial productivity/manufacturing, health and medicine, and public safety.
19. References are available online at http://thepoint.lww.com/mkk7e.

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## SECTION



## Body Composition, Energy Balance, and Weight Control

## OVERVIEW

Six major reasons justify an accurate appraisal of body composition in a comprehensive program of total physical fitness:

1. It provides a starting point on which to base current and future decisions about weight loss and weight gain.
2. It provides realistic goals about how to best achieve an ideal balance between the bodys fat and nonfat compartments.
3. It relates to general health status and plays an important role in the health and fitness goals of all individuals.
4. It monitors changes in the fat and lean components during exercise regimens of different durations and intensities.
5. It allows allied health practitioners (sports nutritionist, dietician, personal trainer, coach, athletic trainer, physical therapist, physician, exercise leader) to interact with the individuals they deal with to provide quality information related to nutrition, weight control, and exercise.
6. It provides the athlete, coach, and scientist with objective information relating body composition assessment to sports performance.

Many diverse methods, both complex and simple, assess human body composition. Of the simpler methods, the popular height-weight tables have become a frequently used standard in the medical community and elsewhere to assess overweight and obesity status. ${ }^{33,89,154}$ Unfortunately, this approach is of limited value as overweight and excess body fat do not necessarily coincide. Many large-sized athletes, for example, typically exceed the average weight for height by gender but otherwise possess relatively low levels of body fat. Most of these individuals obviously do not require weight loss, which might adversely affect their sports performance. In contrast, a prudent weight loss program would surely benefit the extreme number of overweight men and women not only in the United States but worldwide. This group spends nearly $\$ 50$ billion each year to purchase diet books, products, and services at more than 1500 weight-control clinics in the hope of permanently reducing excess fat. Medicaid and Medicare finance almost half of the more than $\$ 100$ billion spent annually on obesity-related medical costs in the United States. Worldwide, more than 300 million people fall within the definition of overweight, and this may be a conservative estimate.

From antiquity to the present, regular physical activity and dietary restraint have played an important role to combat the overweight and obese conditions. In Galens treatise De Sanitate Tuenda [On Hygiene], penned five centuries after Hippocrates communicated about overweight and obesity in his many writings (refer to p. xxiii in the Introduction), he describes the treatment for an obese patient using a combination of exercise and food restriction as follows ${ }^{130}$ :

> Now, I have made any sufficiently stout patient moderately thin in a short time by compelling him to do rapid running, then wiping off his perspiration with very soft or very rough muslin, and then massaging him maximally with diaphoretic inunctions, which the younger doctors customarily call restoratives, and after such massage leading him to the bath, after which I did not give him nourishment immediately, but bade him rest for a while or do something to which he was accustomed, then led him to the second bath and then gave him abundant food of little nourishment, so as to fill him up but distribute little of it to the entire body.

This section discusses body composition, its components and assessment, and the differences in body size and composition between sedentary and physically active men and women. We also consider topics relevant to obesity and discuss the use of diet and exercise for weight management, as Hippocrates, Galen, and others considered over 3000 years ago!

## Interview with Dr. Claude Bouchard



Education: BPed (Laval University, Quebec City, Canada); MSc (University of Oregon, Eugene, OR); PhD (population genetics, University of Texas, Austin); postgraduate training (Deutsche Sporthochschule, Institute for Research on Circulation and Sport Medicine, Cologne; Growth Research Center, Universit de Montreal)

Current Affiliation: Professor and Executive Director, George A. Bray Chair in Nutrition, Louisiana State University System, Pennington Biomedical Research Center, Baton Rouge, LA

Honors and Awards: See Appendix E, available online at http://thepoint.lww.com/mkk7e.

Research Focus: Genetics of adaptation to exercise and nutritional interventions, and genetics of obesity and its comorbidities

Memorable Publication: Bouchard C, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE Family Study, J Appl Physiol 2000;88:551.

## STATEMENT OF CONTRIBUTIONS: ACSM Honor Award

In recognition of his impressive research accomplishments in exercise science, genetics, child growth and maturation, diet and exercise clinical trials, and public health.

Dr. Bouchard has made important contributions to many areas of human performance research, and has been a leader in synthesizing current knowledge to produce consensus statements in exercise science. Among other things, he has conducted innovative research on the
effects of experimental manipulation of diet and exercise in monozygotic twins.

He has collected more data on energy balance from carefully controlled studies in this unique population than anyone in the world. This research has led to a better understanding of the variability of responses to dietary manipulation and exercise training and to the genetics of these complex processes.

Dr. Bouchards career is characterized by high scientific standards, immense productivity, breadth of interests, creative study designs, and a willingness to collaborate with others. He serves as an ideal role model for us all.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

> As a student in what was known as College Classic (the equivalent of high school, but it takes 9 years and emphasizes the humanities), I became fascinated with human movement and performance. At that time, it was a very diffuse interestthat is, I was curious about the biomechanics, the exertion and the physiology, or the medical aspect, and the aesthetic of human movement. I had several career options but came rapidly to the conclusion that I would move on to the local university, Universit Laval, to learn about exercise and sports with the goal of approaching them
from a scientific point of view. As you can see, even before I became a student in physical education, I was fascinated by science and human movement.

During my undergraduate studies, I was very frustrated by the poor science to which I was exposed, so I decided to go on to graduate studies. For 2 years during the summer, I traveled with friends on the East Coast of the United States and in the Midwest for the purpose of visiting universities and meeting faculty to select one for a masters degree program. I visited at least 15 such institutions and finally ended up at the University of Oregon, an institution that had been highly recommended to me. There, I was exposed to the teachings of Sigerseth, Clarke, Brumbach, Poley, and others.

After earning my masters degree in Oregon, I felt that I was not quite ready to benefit from a PhD program. Following the advice of a few of my friends, I decided to go to the Sporthochschule in Cologne to work with Professor Wildor Hollmann. He was the Director of the Institute f r Kreislaufforschung und Sportmedizin, or the Institute for Research on Circulation and Sport Medicine. I knew that I could not obtain a degree there but wanted to get more handson research experience. By then, my interests included not only performance but also the health implications of exercise. I stayed there for 18 months and learned much.

Then I was offered a position at my alma mater, Laval University in Quebec. I decided to accept the position with the expectation to leave after 3 years or so to obtain my PhD . If I had done so immediately, I would have entered an endocrinology PhD program, as I had made contact to be admitted in the lab of Professor Hans Selye at the Universit de Montreal. But I became so involved in the development of the programs and the facilities at Laval University that it was 8 years before I left for my doctoral studies. By then, I had decided that genetics and biological individuality would be the focus of my research for the last decades of my career.

I opted to work with Professor Robert Malina, a colleague who had training in both physical education and biological anthropology, at the University of Texas. I spent 3 productive years there, which I completed with 10 months of postgraduate work at the Universit de Montreal in the Human Growth and Development Center.

Obviously, mine has not been a linear career path. But I always felt that I was sharpening the focus of my research interest all along. Every phase in my career has been a useful one in the sense that it took me closer to what I am doing todayinvestigating the genetic and molecular basis of the response to exercise and of obesity and its comorbidities. It would have been impossible to select this line of research 35 years ago, since the field did not exist. The study of individual differences could not be even contemplated at the molecular level then.

## Who were the most influential people in your career, and why?

> Three scientists have played key roles at different times of my career. The first was Professor Fernand Landry. He was a faculty member at the University of Ottawa, but he was from the same city where I was born and went to the same colleges and community organizations that I later attended. He stimulated my interest in the biological sciences in general and the marvels of the human bodys adaptation to exercise and training. He had a lasting impact on my career choices.

The second was Professor Wildor Hollmann. I got to know him very well during my stay in Cologne at his Institute. He stimulated my interest in the general topic of physical activity and health, particularly cardiovascular health. He was a very kind and patient mentor.

The last one was Professor Robert Malina. We became good friends during my doctoral studies at the University of Texas. Bob is a scholar with a strong interest in human diversity. We shared this research focus and many of the small pleasures of life.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> The most enjoyable aspect is that you always think out of the commonly accepted paradigm and look toward the future. You verify one fact only to refocus on the new questions generated by the previous experience. You also constantly meet people who are of the same mind, colleagues who are always trying to be innovative and creative in the presence of the same set of facts as you. The life of a scientist is never dull if you have the chance to interact with the best in your field.

The least enjoyable aspect is the fact that you have to hunt for research funds all the time, particularly if you run a large laboratory operation. At one point, there were 55 people working on my research projects, and I was spending at least a third of my time writing grant applications or renewals to maintain all of these positions.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

$>$ If I have contributed anything, it is evidence for the magnitude of the individual differences in fitness and performance in the sedentary state and in the response to regular exercise. My group has also demonstrated over a period of 20 years that these individual differences were not random. They are characterized by familial clustering and are accounted for by a substantial genetic effect. We have identified some of the areas responsible for the heterogeneity in fitness and performance levels, and in trainability.

I have also spent considerable research resources investigating the genetic and molecular basis of obesity and the metabolic disturbances seen in some obese individuals, but not in others. To this end, we have used a combination of twin and family studies as well as intervention protocols to begin the dissection of the complex genotypes that predispose individuals to become overweight and then obese.

I am also proud of my contributions to the efforts undertaken over the past 15 years to arrive at evidence-based consensus concerning the role of physical activity in health and disease.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

> You will eventually need to become highly specialized in your own research pursuit, but try to acquire a broad-based understanding of the parent discipline. If you elect to become an exercise molecular biologist, you will find it useful to become an excellent biologist first. Maintaining a reasonable understanding of the changes occurring in biology in general will be a strong asset throughout your career. First, you will derive more satisfaction from your own research because you will be able to see the general implications of your work. Second, you are likely to find that a career in exercise science is more interesting if you understand what is going on in the broader field of science to which you are related.

## What interests have you pursued outside of your professional career?

> At age 20, I learned to ski and enjoyed it tremendously for many years. I shifted progressively from downhill to crosscountry skiing, which I still like to do. At present, my preferred activities are hiking, fly fishing for trout and salmon, working out at the gym, reading, classical music, and wine tasting. I also enjoy traveling, but these days most of my travel is for business purposes.

## Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 20 years?

> In the next 20 years, the field of exercise science will incorporate the advances in molecular biology and genetics, something that it has failed to do in the past 10 years. The techniques of genomics and proteomics will become common technologies in our field. The benefits should be enormous, as exercise science can offer a wealth of opportunities to verify the functional consequences of DNA sequence variations in people who are not symptomatic for any disease. Such advances in the field of exercise science should make it possible for the exercise science discipline to become a significant player in preventive medicine and public health, as it will be able to develop the probes to identify those who are likely to benefit most from a physically active lifestyle. It will also change the way exercise science contributes to sports performance, as it will have the tools to identify the talented individuals at an early age.

## You have the opportunity to give a last lecture. Describe its primary focus.

> It would be on the extent and the causes of biological individuality and its implications for human health in a Darwinian evolutionary perspective.



## CHAPTER 28

## Body Composition Assessment

## CHAPTER OBJECTIVES

> Summarize the early research on inadequacies of height weight tables
> Distinguish among overweight, overfat, and obesity
> Outline current systems to classify overweight and obese conditions
> Delineate characteristics of the reference man and reference woman, including values for storage fat, essential fat and sex-specific essential fat
> Discuss the prevalence of menstrual irregularities within the general population and specific athletic groups, and factors associated with their occurrence
> Describe Archimedes principle applied to human body volume measurement
$>$ Discuss limitations in assumptions for computing percentage body fat from whole-body density
> Summarize the rationale, strengths, and weaknesses of air-displacement plethysmography for assessing body composition

- Give the anatomic locations for six frequently measured skinfolds and girths
- Describe how skinfolds and girths provide meaningful information about body fat and its distribution
> Discuss the rationale for bioelectrical impedance analysis and factors that affect body composition estimates with this technique
- Summarize the rationale, strengths, and weaknesses of bioelectrical impedance analysis, nearinfrared interactance, ultrasound, computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry to assess body composition
> Give representative average values with variation limits for percentage body fat of typical young and older adult men and women

The life insurance actuary-based height weight tables (weight measured with clothes and height measured with 2 -inch heels) provide a popular means to assess the extent of overweightness on the basis of gender and body frame size (see In a Practical Sense, p. 727). These tables, however, provide unreliable information about an individuals relative body composition (muscle, bone, fat). Rather, they provide statistical landmarks based on the average ranges of body mass related to stature associated with the lowest mortality rate for persons ages 25 to 59 years. They do not consider specific causes of death or quality of health (morbidity) before death.

A person may weigh considerably more than the average weight-for-height standard yet still rate underfat for body composition; extra weight for this person exists as muscle mass. According to the tables, the desirable body weight (assuming a large frame size) for a professional American football player $188-\mathrm{cm}$ tall and weighing 116 kg ranges between 78 and 88 kg . Similarly, body weight without regard for frame size for young adult men $188-\mathrm{cm}$ tall averages 85 kg . Using either criterion, conventional standards would classify this player as overweight, implying that he should lose at least 28 kg just to achieve the upper limit of the desirable body weight range. He must lose an additional 3 kg to match his average American male counterpart. If the player followed these guidelines, he most likely would no longer play football and could jeopardize overall health. Body fat for the football player (even though he weighed 31 kg more than the average)
was only $12.7 \%$ of body mass, compared with about $15.0 \%$ body fat for untrained young men of normal weight.

## Limitations of Height Weight Tables

## Uses unvalidated estimates of body frame size <br> Developed from data derived primarily from white populations

Specific focus on mortality data that may not reflect obesity-related comorbidities
Provides no assessment of body composition
Navy physician Dr. Albert Behnke (1898-1993) first observed body composition variations between elite athletes and untrained individuals in studies of football players in the early 1940s (see Focus on Research, p. 729). Careful evaluation of each players body composition revealed that extreme muscular development primarily contributed to excess weight. These observations clearly pointed out that the term overweight refers only to a body mass in excess of some standard, usually the average for a given stature. Being above an average, ideal, or desirable body mass based on heightweight tables should not necessarily dictate whether someone begins a reducing regimen. A better alternative determines body composition by one of the laboratory or field techniques reviewed in this chapter. Table 28.1 lists terms and definitions common to the area of body composition evaluation.

TABLE 28.1 Terms Frequently Used in Describing and Measuring Body Composition
Term Definition

Abdominal fat
Adipose tissue mass (ATM)
Anthropometry
Body density (Db)
Body mass index (BMI)
Densitometry
Essential lipids
Fat mass (FM)
Fat-free body mass (FFM)
Intraabdominal fat
Lean body mass (LBM)
Minimal body mass
Nonessential lipids
Reference man and reference woman

Relative body fat (\%BF)
Specific gravity
Stature
Subcutaneous fat
Visceral adipose tissue (VAT)

## Definition

Subcutaneous and visceral fat in the abdominal region
Fat (about $83 \%$ ) plus its supporting structures (about $2 \%$ protein and $15 \%$ water); consists predominantly of white adipocytes (cells with a single fat droplet, mainly as triacylglycerol)
Standardized techniques (e.g., calipers, tapes) to quantify (or predict) body size, proportion, and shape (anthropo, human; metry, measure)
Body mass (BM) expressed per unit body volume (body mass body volume)
Ratio of BM to stature squared (body mass $\div$ stature $^{2}$ )
Archimedes principle of water displacement to estimate whole-body density; other terms include hydrostatic weighting, hydrodensitometry, underwater weighing
Compound lipids (phospholipids) needed for cell membrane formationabout $10 \%$ of total body fat All extractable lipids from adipose and other body tissues
All residual lipid-free chemicals and tissues, including water, muscle, bone, connective tissue, and internal organs
Visceral fat in the abdominal cavity
FFM plus essential body fat
BM plus essential fat (includes sex-specific essential fat); 48.5 kg for the reference woman; computed from bone diameters, stature, and constants
Triacylglycerols found mainly in adipose tissueabout $90 \%$ of total body fat
Behnkes reference standards for men and women that partition body mass into lean body mass, muscle, and bone, with fat subdivided into storage and essential fat; standards for body dimensions developed from military and anthropometric surveys
FM expressed as a percentage of total body mass
Body mass in air divided by loss of weight in water (body mass $\div$ [body mass - body weight in water])
Height expressed in metric units; e.g., 72 in $=182.88 \mathrm{~cm}=1.829 \mathrm{~m}$
Adipose tissue beneath the skin
Adipose tissue within and surrounding thoracic (e.g., heart, liver, lungs) and abdominal (e.g., liver, kidneys, intestines) cavities

## IN A PRACTICAL SENSE

## Determining Body Frame Size from Stature and Two Bone Diameters

Body frame size (BFS) becomes a useful measure for evaluating normalcy of body weight with standardized charts that categorize weight by frame size (bony structure). A combination of stature and bony widths (bone diameter measurements) adequately defines BFS, because BFS relates to the fat-free body mass (bone and muscle) and not body fat.

## MEASUREMENTS

1. Stature (height [ Ht ]) measured in cm
2. Biacromial diameter ( cm ) measured as the distance between the most lateral projections of the acromial processes (see figure)
3. Bitrochanteric diameter ( cm ) measured as the distance between the most lateral projection of the greater trochanters (see figure)

## CALCULATIONS

Regression analyses determine BFS values for women and men from Ht and sum of the biacromial and bitrochanteric bone diameters ( $\Sigma \mathrm{Bia}+\mathrm{Bitroc}$ ) with the following equations:

$$
\begin{aligned}
& \text { Female: } B F S \times H t+10.357+(\Sigma B i a+B i t r o c) \\
& \qquad \text { Male: } B F S \times H t+8.239+(\Sigma B i a+B i t r o c)
\end{aligned}
$$

## STEPS

1. Measure stature and biacromial and bitrochanteric diameters; use the average of two measurements.
2. Sum the average biacromial and bitrochanteric diameter measurements ( $\Sigma \mathrm{Bia}+\mathrm{Bitroc}$ ).
3. Compute BFS by substituting in the appropriate gender-specific formulas (example illustrated in Table 1).
4. Determine frame-size category by referring to Table 2.

## EXAMPLE

Table 1 shows calculations of BFS for a male and female of different heights and bony diameters. The males height corresponds to a value below the 10th percentile for height-by-age for men in the U.S. population. This height, combined with large breadth measurements, results in a medium frame-sized ranking (Table 2). In contrast, the females height of 173.4 cm ranks above the 90th percentile for

the U.S. population. However, her small breadth measurements also result in a medium frame-sized ranking (Table 2).

## TABLE 2 BFS Categories

|  | Frame-Size Category |  |  |
| :--- | :---: | :---: | :---: |
| Sex | Small | Medium | Large |
| Male | $<1459.3$ | $1459.4-1591.9$ | $<1592.0$ |
| Female | $>1661.9$ | $1662.0-1850.7$ | $>1850.08$ |

From Katch VL, Freedson PS. Body size and shape: derivation of the HAT frame-size model. Am J Clin Nutr 1982;36:669.

| Example of BFS Calculations for a Male and Female of Different Heights and Bony Measurements |  |  |
| :---: | :---: | :---: |
| Variable | Subject A (Male) | Subject B (Female) |
| Ht | 167.3 cm | 173.4 cm |
| Biacromial diameter | 48.0 cm | 29.8 cm |
| Bitrochanteric diameter | 35.0 cm | 22.2 cm |
| ¿Bia + Bitroc | 83.0 cm | 52.0 cm |
| BFS value | 1461.4 cm | 1847.9 cm |
|  | $[$ BFS $=\mathrm{Ht} \times 8.239+$ EBia + Bitroc $]$ | $[\mathrm{BFS}=\mathrm{Ht} \times 10.357+$ EBia + Bitroc $]$ |
|  | $[\mathrm{BSF}=167.3 \times 8.239+83.0]$ | $[\mathrm{BSF}=173.4 \times 10.357+52.0]$ |
| Frame-size category (from Table 2). | $[\mathrm{BSF}=1461.4]$ <br> Medium | $[\mathrm{BSF}=1847.9]$ Medium |

[^50]
## OVERWEIGHT, OVERFATNESS, AND OBESITY: NO UNANIMITY FOR TERMINOLOGY

Confusion surrounds the precise meaning of the terms overweight, overfat, and obesity as applied to body weight and body composition. Each term often takes on a different meaning depending on the situation and context of use. The medical literature infers the term overweight to an overfat condition despite the absence of accompanying body fat measures while obesity refers to individuals at the extreme of the overweight (overfat) continuum. The body mass index (see next section) is the measure most often used for this distinction.

Research and contemporary discussion among diverse disciplines reinforces the need to distinguish between overweight, overfat, and obesity to ensure consistency in use and interpretation. In proper context, the overweight condition refers to a body weight that exceeds some average for stature, and perhaps age, usually by some standard deviation unit or percentage. The overweight condition frequently accompanies an increase in body fat, but not always (e.g., male power athletes), and may or may not coincide with the comorbidities glucose intolerance, insulin resistance, dyslipidemia, and hypertension (e.g., physically fit overfat men and women).

When body fat measures are available (hydrostatic weighing, skinfolds, girths, bioelectrical analysis [BIA], dual energy X-ray absorptiometry [DXA], it becomes possible to more accurately place body fat level on a continuum from low to high, independent of body weight. Overfatness then would refer to a condition where body fat exceeds an age- and/or gender-appropriate average by a predetermined amount. In most situations, overfatness represents the correct term when assessing individual and group body fat levels.

The term obesity refers to the overfat condition that accompanies a constellation of comorbidities that include one or all of the following components of the obese syndrome: glucose intolerance, insulin resistance, dyslipidemia, type 2 diabetes, hypertension, elevated plasma leptin concentrations, increased visceral adipose tissue, and increased risk of coronary heart disease and cancer. In all likelihood, excess body fat, not excess body weight per se, explains the relationship between above average body weight and disease risk. Such findings emphasize the importance of distinguishing the composition of excess body weight to determine an overweight persons disease risk.

Many men and women may be overweight or overfat yet not exhibit components of the obese syndrome. For these individuals, we urge caution in using the term obesity (instead of overfatness) in all cases of excessive body weight. We acknowledge that these terms are often used interchangeably (as we at times do in this text) to designate the same condition.

## THE BODY MASS INDEX: A POPULAR CLINICAL STANDARD

Clinicians and researchers frequently use the body mass index (BMI), derived from body mass and stature, to assess normalcy for body weight. This measure exhibits a somewhat higher yet still moderate association with body fat and disease risk than estimates based simply on stature and body mass.

## BMI Computation

BMI computes as follows:

$$
\mathrm{BMI}=\text { Body mass }(\mathrm{kg}) \div \text { stature }\left(\mathrm{m}^{2}\right)
$$

## Example

Malestature: $175.3 \mathrm{~cm}, 1.753 \mathrm{~m}$ (69 in.); body mass: $97.1 \mathrm{~kg}(214.1 \mathrm{lb})$

$$
\begin{aligned}
\mathrm{BMI} & =97.1 \div(1.753)^{2} \\
& =31.6 \mathrm{~kg} \cdot \mathrm{~m}^{-2}, \text { or simply } 31.6
\end{aligned}
$$

The importance of this easily obtained index lies in its curvilinear relationship with the all-cause mortality ratio. As BMI increases throughout the range of moderate and severe overweight, so also does risk increase for cardiovascular complications (including hypertension and stroke), certain cancers, diabetes, Alzheimers disease, gallstones, sleep apnea, osteoarthritis, and renal disease. ${ }^{22,113,121,140}$

A large prospective study of more than 1 million United States adults during 14 years of follow-up reveals the relationships between BMI and mortality risk. Figure 28.1A shows that smoking status and presence or absence of disease at time of enrollment in the study substantially modified the association between BMI and risk of premature death from all causes. Men and women who never smoked and remained disease free at the studys start (light blue lines) experienced the greatest health risk from excess weight. Excessive leanness related to increased death risk among current and former smokers with a history of disease. In healthy people, the nadir of the curve for BMI and mortality occurred between a BMI of 23.5 and 24.9 for men (e.g., $5^{\prime} 10^{\prime \prime}$ at 174 lb ) and 22.0 and 23.4 for women (e.g., $5^{\prime} 5^{\prime \prime}$ at 150 lb ), with a gradient of increasing risk associated with moderate overweight. Among white men and women with the highest BMI, relative death risk equaled 2.58 (men) and 2.00 (women) compared with counterparts with a BMI of 23.5 to 24.9 (relative risk of 1.00 ).

Figure 28.1B shows the clear association in men and women between excess weight and a greater death risk from heart disease or cancer. A positive relationship emerged between BMI and cancer risk, with no elevation in risk among the leanest men and women. A J-shaped curve described BMI and cardiovascular disease risk, while a U-shaped curve predicted risk of death for all other causes. The authors attribute the increased death risk among the leanest men and women depicted in the J- and U-shaped curves to the presence of disease at the time of measurement.

## FOCUS ON RESEARCH

## Overweight But Not Overfat

Welham WC, Behnke AR. The specific gravity of healthy men; body weight/volume and other physical characteristics of exceptional athletes and of naval personnel. JAMA 1942;18:498.
> The Welham and Behnke research is one of the most frequently cited studies in the body composition and exercise physiology literature. These investigators tested the hypothesis that differences in body fat among men relate chiefly to the bodys specific gravity and not body mass per se. The hypothesis predicted that heavy but lean men would have higher body specific gravity values than counterparts of similar body mass, but with high body fat levels. If correct, a relatively large body mass may not always provide an appropriate measure of excessive fatness.

In 1942, the relation between the body density and estimates of body fatness remained undetermined, although scientists knew the specific gravity of the bodys fat and nonfat (fat-free) components. Twenty-five professional football players, most of whom had been designated All-Americans, were classified as unfit for military service because of excessive body weight according to standard height-weight tables. Measurements included stature, body mass, and whole-body density determined by hydrostatic weighing. A unique aspect of the body density assessment corrected body volume from estimates of residual lung volume.

The figure shows the relationship between body density and height-weight for the athletes. The vertical line at a height-weight ratio of 2.65 represents the upper limit for classification as fit for military service. Men of this age who fell to the right of the vertical line did not qualify for life insurance because of their excessive body weight; 17 of the players classified as overweight. However, the high body densities of 11 of these men indicated a low percentage body fat. Body mass of all the players averaged 90.9 kg (200 lb), and body density averaged $1.080 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$. For
the 6 heaviest men, body mass averaged $104.5 \mathrm{~kg}(230 \mathrm{lb})$, with body density at $1.059 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$.

Welham and Behnkes research was the first to show that variations in body density related mainly to individual differences in the bodys fat content. The research also pointed up the inadequacies of height-weight tables to infer body fatness or determine a desirable body weight, particularly among highly trained large athletes. The researchers suggested that a body density of $1.060 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ should serve as the demarcation for excessive fatness for men. With this criterion, 23 of the 25 lean but heavy football players qualified as fit (and not overly fat) for military service.


Relationship between body density and height weight ratio for 25 All-American football players.

## New Standards for Overweight and Obesity

In 1998, the expert panel of the National Heart, Lung and Blood Institute lowered the BMI demarcation point for overweight from 27 to 25 . Based on the association between excess body weight and disease, individuals with a BMI of 30 or more were categorized as obese. Persons with a BMI of 30 average 30 pounds overweight. For example, a $6^{\prime} 0^{\prime \prime}$ man
weighing 221 pounds and a woman weighing 186 pounds at $5^{\prime} 6^{\prime \prime}$ each have a BMI of 30 , and each is approximately 30 pounds overweight. These revised standards place nearly 130 million, or $62 \%$, of Americans in the overweight and obese categoriesup from 72 million under the previous standard. Of this total, $30.5 \%$ ( 59 million people) classify as obese. For the first time, overweight persons (BMI above 25) outnumber persons of desirable weight! More black, Mexican, Cuban, and Puerto Rican males and females


Figure 28.1 A. Multivariate relative risk of death from all causes among men and women according to body mass index (BMI), smoking status, and disease status. Data are from four mutually exclusive subgroups. Nonsmokers had never smoked. B. Multivariate relative risk of death from cardiovascular disease, cancer, and all other causes according to BMI among men and women who had never smoked and had no history of disease at enrollment. Subjects with BMIs of 23.5 to 24.9 composed the reference category in both figures. (From Calle EE, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097.)
classify as overweight than their white counterparts. FigURE 28.2 shows the computed BMI and accompanying weight classifications with associated health risks.

Figure 28.3 presents the revised (2000) growth charts for the United States for boys and girls ages 2 to 20 years. No absolute BMI standard exists to classify children and adolescents as overweight and obese. Expert panels recommend BMI-for-age to identify the increasing number of children and adolescents at the upper end of the distribution who are either overweight ( $\geq 95$ th percentile) or at risk for overweight ( $\geq 85$ th percentile and $\leq 95$ th percentile; see Chapter 30 ). Less specific recommendations exist for the lower end of the distributions, but BMIs in this lower range may indicate underweight or at risk for underweight. ${ }^{46,171}$

## BMI Limitations

Current classification for overweight (and obesity) assumes that the relationship between BMI and percentage
body fat (and disease risk) remains independent of age, gender, ethnicity, and race, but this is not the case. ${ }^{34,49}$ For example, at a given BMI Asians have a higher body fat content than Caucasians and thus show greater risk for fat-related illness. A higher body fat percentage for a given BMI also exists among Hispanic American women compared with European American and African American women. ${ }^{41}$ Failure to consider these sources of bias alters the proportion of individuals defined as obese by measured percentage body fat. ${ }^{70,111}$ The accuracy of BMI in diagnosing obesity is limited for individuals in the intermediate BMI ranges, particularly in men and in the elderly. ${ }^{138}$

The BMI, like the height-weight tables, fails to consider the bodys proportional composition or the allimportant component of body fat distribution, referred to as fat patterning. In addition, factors other than excess body fatbene, muscle mass, and even increased plasma volume induced by exercise trainingaffect the numerator of the BMI equation. A high BMI could lead to an incorrect


Weight Classification
Underweight Healthy weightOverweightObese


Moderately to morbidly obese

Figure 28.2 Body mass index (BMI), weight classifications, and associated health risks.


Figure 28.3 Body mass index-for-age percentiles for boys and girls ages 2 to 20 years. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). (From Kuczmarski RJ, et al. CDC growth charts: United States. Advance Data 2000;314. From Vital and Health Statistics of the Centers for Disease Control and Prevention/National Center for Health Statistics.)
interpretation of overfatness in lean individuals with excessive muscle mass because of genetic makeup or exercise training. ${ }^{127}$

The possibility of misclassifying someone as overweight by applying BMI standards pertains particularly to large-sized field athletes, bodybuilders, weightlifters, heavier wrestlers, and most professional American football players. Figure 28.4 plots the average BMI for all National Football League (NFL) roster players at each 5-year interval between 1920 and 1996 based on 53,333 players. Average body fat content of players measured during the late 1970s through the 1990s fell below the range typically associated with population data for men. Those with body fat evaluated by densitometry during this era included all roster players of the New York Jets, Washington Redskins, New Orleans Saints, and Dallas Cowboys. Almost all players from 1960 onward classify as overweight based on standard height-weight tables. For the BMI data up to 1989, values for linebackers, skill players, and defensive backs represent the low category for disease risk, while the BMIs for offensive and defensive linemen place them at moderate risk. After 1989, risk for linebackers increased from the low to moderate category. The BMIs for offensive and defensive linemen, the largest NFL players, quickly approached a high risk and remained in that category. This does not bode well from a health perspective for these
large-size players, at least based on BMI risk predictions for the general population.

In contrast to professional football players, the BMI for the National Basketball Association (NBA) players for the 1993-1994 season averaged only 24.5. This relatively low BMI places them in the very low risk category, yet heightweight standards would classify them as overweight.

Another category of world-class athletesfacing cyclists who participated in the Tour de Francehad remarkably low BMIs. In the 1997 race, the BMI for 170 competitors averaged $21.5(1.79 \mathrm{~m}$ stature, 68.75 kg body mass). Three years later in the 2000 race, the BMI for 162 competitors remained essentially unchanged (21.5; 1.79 m stature, 69.1 kg body mass). On average, stature among cycling teams was within $0.2 \mathrm{~m}(1.78$ to 1.80 m$)$ and body mass ranged from 66.8 kg (Swiss) to 72.1 kg (U.S.). The homogeneity in body size variables among these toplevel performers makes it unlikely that body composition variables per se determine individual differences in cycling performance.

## Miss America and BMI: Undernourished Role Models?

Many consider Miss America beauty pageant contestants to possess the ideal combination of beauty, grace, and


Figure 28.4 BMIs for all players in the National Football League between 1920 and 1996 ( $n=53,333$ ). Categories include offensive and defensive linemen, linebackers, skill players (quarterbacks, receivers, backfield), and defensive backs. (Data compiled by K. Monahan and F. Katch, Exercise Science Department, University of Massachusetts, Amherst, 1996.)
talent. Each competitor survives the rigors of local and state contests, thus satisfying judges that finalists have ideal qualities worthy of role-model status. The consummate image of the Miss America physique to some extent shapes societys generalized ideal for female size and shape. An important question concerns whether such images, televised worldwide to millions of viewers, reinforce an unhealthful message to young women who attempt to emulate such ideal physiques.

Figure 28.5 shows the BMIs and accompanying anthropometric data of Miss America contestants from available data between 1922 and 1999 (excluding 1927-1933, when the pageant was not held, and from 2000 on, when data were no longer available). Also included for comparison about body size is Behnkes standard for the reference woman (Fig. 28.5C; see p. 735). The bottom horizontal white dashed line in Figure 28.5A designates the World Health Organization (WHO) cutoff for undernutrition established at a BMI of 18.5. ${ }^{188}$ The top horizontal black dashed line represents the BMI for the reference woman (see Fig. 28.6; stature: 1.638 m ; body mass: 56.7 kg ; BMI: 21.1). The downward slope of the regression line from 1922 to 1999 shows a clear tendency for relative undernutrition from the mid-1960s to approximately 1990. Using the WHO cutoff, the BMIs of $30 \%$ ( $n=14$ ) of the 47 Miss America winners fell below 18.5. Raising the BMI cutoff to 19.0 adds another 18 women, or a
total of $48 \%$ of the winners with undesirable values. Approximately $24 \%$ of contest winners had BMIs between 20.0 and 21.0, and no winner after 1924 had a BMI equaling that of the reference woman!

Interestingly, 1965 was the last year we could locate girth measurements from official press releases or newspaper coverage of the contest. We compared the percentage difference between the Miss America girth averages with the corresponding measurements for the reference woman (bottom yellow row of Fig. 28.5C). For the average bust, waist, and hip values (35.1, 24.0, 35.4 in, respectively), Miss Americas measurement exceeded the reference womans bust measurement by 2.6 inches ( $8 \%$ ) but fell $7 \%$ below for the waist value ( -1.8 in .) and $5 \%(-1.7 \mathrm{in}$.) for the hips. Unfortunately, no contemporary data exist from 1966 through 2010, so we cannot compare the current Miss Americas physique with historical data.

## COMPOSITION OF THE HUMAN BODY

In 1921, Czech anthropologist J. Matiega described a fourcomponent model consisting of the weight of the skeleton (S), skin plus subcutaneous tissue ( $\mathrm{Sk}+\mathrm{St}$ ), skeletal muscle ( M ), and a remainder (R). ${ }^{105}$ The sum of the four components equaled the body mass.


| B |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 1922-1948 |  |  | 1951-1968 |  |  |  |  | 1970-1999 |  |  |
|  | Age | Ht | Wt |  | Age | Ht | Wt |  | Age | Ht | Wt |
| 1922 | 18 | 65 | 135 | 1951 | 20 | 65.5 | 119 | 1970 | 21 | 65.5 | 110 |
| 1923 | 19 | 65 | 140 | 1952 | 25 | 70 | 143 | 1971 | 21 | 68 | 121 |
| 1924 | 18 | 66 | 132 | 1953 | 19 | 66.5 | 128 | 1972 | 22 | 67 | 118 |
| 1926 | 18 | 52.5 | 118 | 1954 | 20 | 68 | 132 | 1973 | 23 | 68 | 120 |
| 1936 | 22 | 66 | 114 | 1955 | 19 | 68.5 | 124 | 1974 | 23 | 69 | 125 |
| 1937 | 17 | 66.5 | 120 | 1957 | 19 | 67 | 120 | 1976 | 18 | 70.5 | 128 |
| 1939 | 19 | 67 | 126 | 1958 | 20 | 68.5 | 130 | 1979 | 22 | 64 | 121 |
| 1941 | 19 | 65.5 | 120 | 1959 | 21 | 65 | 114 | 1980 | 22 | 67 | 114 |
| 1942 | 21 | 65 | 118 | 1960 | 21 | 67 | 120 | 1983 | 25 | 67 | 115 |
| 1943 | 21 | 68 | 130 | 1961 | 18 | 66 | 116 | 1984 | 20 | 66 | 110 |
| 1944 | 21 | 67 | 125 | 1962 | 19 | 65.5 | 118 | 1985 | 20 | 68 | 120 |
| 1945 | 18 | 70 | 136 | 1964 | 21 | 66.5 | 124 | 1986 | 21 | 69 | 114 |
| 1946 | 21 | 68 | 123 | 1965 | 22 | 124 | 124 | 1987 | 21 | 68.5 | 116 |
| 1947 | 21 | 67 | 130 | 1966 | 19 | 115 | 115 | 1988 | 24 | 70 | 131 |
| 1948 | 18 | 69 | 138 | 1967 | 19 | 116 | 116 | 1990 | 24 | 67.5 | 118 |
|  |  |  |  | 1968 | 19 | 135 | 135 | 1999 | 24 | 69 | 133 |

C

| Girths (in) |  |  |  |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
|  | Bust | Waist | Hips | Calf | Thigh | Ankle | Biceps | Wrist |
| $\mathbf{1 9 2 6}$ | 33 | 24.5 | 33.5 | 12.5 | 19.5 | 7 | - | - |
| $\mathbf{1 9 3 5}$ | 33 | 23 | 35.5 | - | - | - | - | - |
| $\mathbf{1 9 2 6}$ | 34 | 23.5 | 34.5 | 13 | 19 | 8.5 | 9.5 | 5.5 |
| $\mathbf{1 9 4 1}$ | 34 | 24 | 36 | 14 | 23 | 8 | 11 | 6 |
| $\mathbf{1 9 4 2}$ | 34 | 24 | 34.5 | - | - | - | - | - |
| $\mathbf{1 9 4 3}$ | 36 | 23 | 35 | - | - | - | - | - |
| $\mathbf{1 9 4 4}$ | 36.5 | 25 | 37.5 | 13 | 19.5 | 8 | - | - |
| $\mathbf{1 9 4 5}$ | 35.5 | 25 | 35 | 14.5 | 20 | 8.5 | - | - |
| $\mathbf{1 9 4 6}$ | 35.5 | 25.5 | 36 | 13.5 | 22 | 8.5 | - | - |
| $\mathbf{1 9 4 7}$ | 35 | 35 | - | - | - | - | - | - |
| $\mathbf{1 9 4 8}$ | 37 | 37 | - | - | - | - | - | - |
| $\mathbf{1 9 5 1}$ | 35 | 35 | - | - | - | - | - | - |
| $\mathbf{1 9 5 2}$ | 36 | 24 | 36 | - | - | - | - | - |
| $\mathbf{1 9 5 3}$ | 35 | 23 | 35 | - | - | - | - | - |
| $\mathbf{1 9 5 4}$ | 37 | 24 | 36 | - | - | - | - | - |
| $\mathbf{1 9 5 5}$ | 34.5 | 22 | 35 | - | - | - | - | - |
| $\mathbf{1 9 5 7}$ | 35 | 23 | 35 | - | - | - | - | - |
| $\mathbf{1 9 5 8}$ | 35 | 25 | 36 | - | - | - | - | - |
| $\mathbf{1 9 5 9}$ | 34 | 22 | 35 | - | - | - | - | - |
| $\mathbf{1 9 6 0}$ | 36 | 24 | 36 | - | - | - | - | - |
| $\mathbf{1 9 6 1}$ | 35 | 22 | 35 | - | - | - | - | - |
| $\mathbf{1 9 6 2}$ | 35 | 24 | 35 | - | - | - | - | - |
| $\mathbf{1 9 6 4}$ | 35 | 23 | 35 | - | - | - | - | - |
| $\mathbf{1 9 6 5}$ | 36 | 24 | 36 | - | - | - | - | - |
| Ref W* $^{*}$ | 36.1 | 30.3 | 36.8 | 14.1 | 21.6 | 8.9 | 12.5 | 6.8 |

Ref W* $=$ Behnke's reference woman; stature $=163.8 \mathrm{~cm}$, body mass $=56.7 \mathrm{~kg}$

Figure 28.5 A. Body mass index (BMI) of 47 Miss America pageant contestants from 1922 to 1999. The top horizontal black dashed line represents the BMI for Behnkes reference woman ( $21.1 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ ). The bottom horizontal white dashed line designates the World Health Organizations (WHO) BMI demarcation for undernutrition ( $18.5 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ ). B. Available data for age, height (in.), and weight (lb) for the contest winners. C. Selected girths for 24 Miss America winners from 1926 to 1965. Despite our best efforts, we were unable to locate height or weight data for Miss America winners from 2000 on.

Over the past 85 years, studies have focused on body composition and how best to measure the various components. One methodology partitions the body into two distinct compartments: (1) fat-free body mass and (2) fat mass. The density of homogenized samples of fat-free body tissues in small mammals equals $1.100 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ at $37 \mathrm{C} .{ }^{137}$ Fat-free
tissue maintains water content of $73.2 \%,{ }^{120}$ with potassium at 60 to $70 \mathrm{mmol} \cdot \mathrm{kg}^{-1}$ in men and 50 to $60 \mathrm{mmol} \cdot \mathrm{kg}^{-1}$ in women. ${ }^{16}$ Fat stored in adipose tissue has a density of 0.900 g . $\mathrm{cm}^{-3}$ at $37 \mathrm{C} .{ }^{112}$ Subsequent body composition studies expanded the two-component model to account for biologic variability in three (water, protein, fat) or four (water, protein,
bone mineral, fat) distinct components. ${ }^{184,186}$ Women and men differ in relative quantities of specific body composition components. Consequently, gender-specific reference standards provide a framework to evaluate on a relative basis what constitutes normal body composition. Behnkes model for the reference man and reference woman proves useful for such purposes. ${ }^{12}$

## Reference Man and Reference Woman

Figure 28.6 shows the body composition compartments for the reference man and reference woman. This schema partitions body mass into lean body mass, muscle, and bone, with total body fat subdivided into storage and essential fat components. This model integrates the average physical dimensions
from thousands of individuals measured in large-scale civilian and military anthropometric surveys with data from laboratory studies of tissue composition and structure.

The reference man is taller and heavier, his skeleton weighs more, and he possesses a larger muscle mass and lower body fat content than the reference woman. These differences exist even when expressing fat, muscle, and bone as a percentage of body mass. Just how much of the gender difference in body fat relates to biologic and behavioral factors, perhaps from lifestyle differences, remains unclear. Undoubtedly, hormonal differences play an important role. The concept of reference standards does not mean that men and women should strive to achieve this body composition or that the reference man and woman reflect some healthful standard. Instead, the reference model proves useful for statistical


Figure 28.6 Behnkes theoretical model for the body composition of the reference man (A) and reference woman (B). Values in parenthesis indicate percentage of total body mass.


Figure 28.7 Theoretical model for body fat distribution for the reference woman with body mass of 56.7 kg , stature of 163.8 cm , and $27 \%$ body fat. (From Katch VL, et al. Contribution of breast volume and weight to body fat distribution in females. Am J Phys Anthropol 1980;53:93.)
comparisons and interpretations of data from other studies of elite athletes, individuals involved in exercise training, different racial and ethnic groups, and the underweight and the obese.

## Essential and Storage Fat

In the reference model, total body fat exists in two storage sites or depotsessential fat and storage fat. Essential fat consists of the fat in heart, lungs, liver, spleen, kidneys, intestines, muscles, and lipid-rich tissues of the central nervous system and bone marrow. Normal physiologic functioning requires this fat. In the heart, for example, dissectible fat from cadavers represents approximately 18.4 g , or $5.3 \%$, of an average heart weighing 349 g in males and 22.7 g , or $8.6 \%$, of a heart weighing 256 g in females. ${ }^{187}$ Importantly, essential fat in the female includes additional sex-specific essential fat. Whether this fat provides reserve storage for metabolic fuel is unclear.

The storage fat depot includes fat primarily in adipose tissue. The adipose tissue energy reserve contains approximately $83 \%$ pure fat, $2 \%$ protein, and $15 \%$ water within its supporting structures. Storage fat includes the visceral fatty tissues that protect the organs within the thoracic and abdominal cavities from trauma, and the larger adipose tissue volume deposited beneath the skins surface. A similar proportional distribution of storage fat exists in men and women ( $12 \%$ of body mass in men, $15 \%$ in women), but the total percentage of essential fat in women that includes the sexspecific fat averages four times the value in men. The additional essential fat most likely serves biologically important functions for child bearing and other hormone-related functions. Considering the reference bodys total quantity of storage fat (approximately 8.5 kg ), this depot theoretically represents $63,500 \mathrm{kCal}$ of available energy, or the energy
equivalent of playing pickup basketball nonstop for 107 hours, golfing without a cart or walking at a normal pace on a track for 176-180 continuous hours, or treading water in a swimming pool without a break for 10 days straight!

Figure 28.7 partitions the distribution of body fat for the reference woman. As part of the 5 to $9 \%$ sex-specific fat reserves, breast fat probably contributes no more than $4 \%$ of body mass for women whose total fat content ranges between 14 and $35 \% .{ }^{80}$ We interpret this to mean that other substantial sex-specific fat depots exist (e.g., pelvic, buttock, and thigh regions) that contribute to the females body fat stores.

Fat-Free Body Mass and Lean Body Mass. The terms fat-free body mass (FFM) and lean body mass refer to specific entities. Lean body mass contains the small percentage of non-sex-specific essential fat equivalent to approximately $3 \%$ of body mass. In contrast, FFM represents the body mass devoid of all extractable fat (FFM = body mass - fat mass). Behnke points out that FFM refers to an in vitro entity appropriate to carcass analysis. He considered lean body mass as an in vivo entity relatively constant in water, organic matter, and mineral content throughout the active adults life span. In normally hydrated, healthy adults, the FFM and lean body mass differ only in the essential fat component.

Figure 28.6 showed that lean body mass in men and minimal body mass in women consist chiefly of essential fat (plus sex-specific essential fat for women), muscle, water, and bone. The whole-body density of the reference man with $12 \%$ storage fat and $3 \%$ essential fat is $1.070 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$; the density of his FFM is $1.094 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$. If the reference mans total body fat percentage equals $15.0 \%$ (storage fat plus essential fat), the density of a hypothetical fat-free body attains the upper limit of $1.100 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$.

In the reference woman, the average whole-body density of $1.040 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ represents a body fat percentage of $27 \%$; of
this, approximately $12 \%$ consists of essential body fat. A density of $1.072 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ represents the minimal body mass of 48.5 kg . In actual practice, density values that exceed 1.068 for women ( $14.8 \%$ body fat) and $1.088 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ for men ( $5 \%$ body fat) rarely occur except in young, lean athletes.

## Minimal Leanness Standards

A biologic lower limit exists beyond which a persons body mass cannot decrease without impairing health status or altering normal physiologic functions.

## Men

To estimate the lower body fat limit in men (i.e., lean body mass), subtract storage fat from body mass. For the reference man, the lean body mass ( 61.7 kg ) includes approximately $3 \%(2.1 \mathrm{~kg})$ essential body fat. Encroachment into this reserve may impair optimal health and capacity for vigorous exercise.

Low body fat values exist for male world-class endurance athletes and some conscientious objectors to military service who voluntarily reduced body fat stores during a prolonged experiment with semistarvation. The low fat levels of marathon runners, which ranges from 1 to $8 \%$ of body mass, probably reflect adaptation to severe training for distance running. ${ }^{92}$ A low body fat level reduces the energy cost of weight-bearing exercise; it also provides a more effective gradient to dissipate metabolic heat generated during prolonged, intense exercise.

Considerable variation exists in the FFM of different athletes, with values ranging from a low of 48.1 kg in some jockeys to over 100 kg in football linemen and field-event athletes. Seven elite sumo wrestlers (seki-tori) possessed an average FFM of 109 kg . ${ }^{85}$

## Women

In comparison to the lower limit of body mass for the reference man (with 3\% essential fat), the lower limit for the reference woman includes approximately $12 \%$ essential fat. This theoretical lower limit developed by Dr. Behnke, termed minimal body mass, is 48.5 kg for the reference woman. Generally, the leanest women in the population do not possess less than 10 to $12 \%$ body fat, a narrow range at the lower limit for most women in good health. Behnkes theoretical concept of minimal body mass in women that incorporates $12 \%$ essential fat, corresponds to the lean body mass in men that includes 3\% essential fat.

## Leanness, Regular Exercise, and Menstrual Irregularity

Physically active women, mainly participants in the low weight or appearance sports (e.g., distance running, bodybuilding, figure skating, diving, ballet, and gymnastics), increase their likelihood for one of three maladies: (1) delayed
onset of menstruation, (2) irregular menstrual cycle (oligomenorrhea), or (3) complete cessation of menses (amenorrhea). Menstrual and ovarian dysfunction results largely from changes in the pituitary glands normal pulsatile secretion of luteinizing hormone regulated by gonadotropin-releasing hormone from the hypothalamus.

Amenorrhea occurs in 2 to 5\% of women of reproductive age in the general population, but it can reach $40 \%$ in some athletic groups. As a group, ballet dancers remain lean, with a greater incidence of menstrual dysfunction and eating disorders and a higher mean age at menarche than age-matched, nondance counterparts. ${ }^{47}$ One-third to one-half of female endurance athletes exhibit some menstrual irregularity. In premenopausal women, irregularity or absence of menstrual function accelerates bone loss and increases risk of musculoskeletal injury during exercise and causes a longer interruption of training (see Chapter 2). ${ }^{11,122}$

A prolonged level of physical stress may disrupt the hy-pothalamic-pituitary-adrenal axis and modify the output of gonadotropin-releasing hormone, which results in irregular menstruation (exercise stress hypothesis). A concurrent hypothesis maintains that energy (fat) reserves inadequate to sustain pregnancy induce cessation of ovulation (energy availability hypothesis).

## 10 <br> INTEGRATIVE QUESTION <br> What arguments counter the following position? No true sex difference exists in body fat level, but only a difference caused by gender-related patterns of regular physical activity and caloric intake.

## Lean-to-Fat Ratio

An optimal lean-to-fat ratio is important to normal menstrual function, perhaps through peripheral fats role that converts androgens to estrogens or through adipose tissues production of leptin, a hormone intimately linked to body fat levels and appetite control (see Chapter 30) and initiation of puberty. ${ }^{155}$ Thus, linkage exists between hormonal regulation of sexual maturity onset (and perhaps continued optimal sexual function) and level of stored energy from accumulated body fat.

Some researchers assert that $17 \%$ body fat represents a lower-end critical level for the onset of menstruation, with $22 \%$ fat needed to sustain a normal menstrual cycle. ${ }^{47,48}$ They reason that lower body fat levels trigger hormonal and metabolic disturbances that affect menses. Objective data indicate that many physically active females who are below the supposedly critical $17 \%$ body fat level have normal menstrual cycles with high levels of physiologic and exercise capacity. Conversely, some amenorrheic athletes maintain body fat levels considered average for the population. One of our laboratories compared 30 athletes and 30 nonathletes, all with less
than $20 \%$ body fat, for menstrual cycle regularity. ${ }^{78}$ Four athletes and 3 nonathletes, ranging from 11 to $15 \%$ body fat, maintained regular cycles, whereas 7 athletes and 2 nonathletes had irregular cycles or were amenorrheic. For the total sample, 14 athletes and 21 nonathletes maintained regular menstrual cycles. These data indicate that normal menstrual function does not require a critical body fat level of 17 to $22 \%$.

Potential causes of menstrual dysfunction include the complex interplay of physical, nutritional, genetic, hormonal, regional fat distribution, psychologic, and environmental factors. ${ }^{84}$ An intense exercise bout triggers the release of an array of hormones, some of which disrupt normal reproductive function. ${ }^{56,181}$ Intense and/or prolonged exercise that releases cortisol and other stress-related hormones also can alter ovarian function via the hypothalamic-pituitary-adrenal axis. ${ }^{31,101}$

Consuming well-balanced, nutritious meals prevents or reverses athletic amenorrhea without requiring the athlete to reduce exercise training volume or intensity. ${ }^{100}$ In this regard, when injuries to young amenorrheic ballet dancers prevent them from exercising regularly, normal menstruation resumes even though body weight remains low. ${ }^{72,191}$ Proponents of this energy deficit explanation maintain that exercise per se exerts no deleterious effect on the reproductive system other than the potential impact of its additional energy cost on creating a negative energy balance. ${ }^{5,98,99,102,180}$

The effects and risks of sustained amenorrhea on the reproductive system remain unknown. A gynecologist/endocrinologist should evaluate failure to menstruate or cessation of the normal cycle because it may reflect pituitary or thyroid gland malfunction or premature menopause. ${ }^{10,97}$ As we point out in Chapter 2, prolonged menstrual dysfunction affects bone mass profoundly and negatively.

## Delayed Onset of Menstruation and Cancer Risk

The delayed onset of menarche in chronically active young females may offer positive health benefits. Female athletes who start training in high school or earlier show a lower lifetime occurrence of cancers of the breast and reproductive organs, and non-reproductive-system cancers than lessactive counterparts. ${ }^{48}$ Even among older women, regular exercise protects against reproductive cancers. Swedish researchers studied the countrys entire female population ages 50 to 74 years in 1994-1995. ${ }^{119}$ Higher levels of occupational and leisure-time physical activity in normal-weight nonsmokers during ages 18 to 30 years related to lower postmenopausal endometrial cancer risk. Women who exercise an average of 4 hours a week after menarche reduce breast cancer risk by $50 \%$ compared with age-matched inactive women. ${ }^{14}$ One proposed mechanism for reduced cancer risk links lower total estrogen production (or a less potent estrogen form) over the athletes lifetime with fewer ovulatory cycles because of the delayed onset of menstruation. ${ }^{93,176}$ Lower body fat levels in physically active individuals also may contribute to lowered cancer risk because peripheral fatty tissues convert androgens to estrogen.

## COMMON TECHNIQUES TO ASSESS BODY COMPOSITION

Two procedures evaluate body composition:

1. Direct measurement by chemical analysis of the animal carcass or human cadaver
2. Indirect estimation by hydrostatic weighing, simple anthropometric measurements, and other clinical and laboratory procedures

## Direct Assessment

Two approaches directly assess body composition. One technique dissolves the body in a chemical solution to determine its mixture of fat and fat-free components. The other physically dissects fat, fat-free adipose tissue, muscle, and bone. Considerable research has chemically assessed body composition in various animal species, but few studies have directly determined human fat content. ${ }^{25,26,27}$ These labor-intensive and tedious analyses require specialized laboratory equipment and involve ethical questions and legal hurdles in obtaining cadavers for research purposes.

Direct body composition assessment suggests that while considerable individual differences exist in total body fatness, the compositions of skeletal mass and the fat-free and fat tissues remain relatively stable. Researchers have developed mathematical equations to indirectly predict the bodys fat percentage on the basis of the assumed constancy of these tissues.

## Indirect Assessment

Diverse indirect procedures assess body composition. One involves Archimedes principle applied to hydrostatic weighing (also referred to as hydrodensitometry, or underwater weighing). This method computes percentage body fat from body density (ratio of body mass to body volume). Other procedures predict body fat from skinfold thickness and girth measurements, X-ray, total body electrical conductivity or bioimpedance (including segmental impedance), near-infrared interactance, ultrasound, computed tomography, air plethysmography, and magnetic resonance imaging.

## Hydrostatic Weighing: Archimedes Principle

The Greek mathematician and inventor Archimedes (287-212 BC) discovered a fundamental principle currently applied to evaluate human body composition. An itinerant scholar of that time described the circumstances surrounding the event:

King Hieron of Syracuse suspected that his pure gold crown had been altered by substitution of silver for gold. The King directed Archimedes to devise a method for testing the crown for its gold content without dismantling it. Archimedes pondered over this problem for many weeks without succeeding, until one day, he stepped into a bath filled to the top with water and observed the overflow. He thought about this for a moment,
and then, wild with joy, jumped from the bath and ran naked through the streets of Syracuse shouting, Eureka, Eureka! I have discovered a way to solve the mystery of the Kings crown.

Archimedes reasoned that a substance such as gold must have a volume proportional to its mass; measuring the volume of an irregularly shaped object would require submersion in water with collection of the overflow. To apply his reasoning, Archimedes took lumps of gold and silver of the same mass as the crown and submerged each in a water-filled container. He discovered the crown displaced more water than the lump of gold and less than the lump of silver. This could only mean that the crown consisted of both silver and gold as the king suspected.

Essentially, Archimedes compared the specific gravity of the crown with the specific gravities for gold and silver. He also reasoned that an object submerged or floating in water becomes buoyed up by a counterforce that equals the weight of the volume of water it displaces. This buoyant force supports an immersed object against gravitys downward pull. Thus, an object loses weight in water. Because the objects loss of weight in water equals the weight of the volume of water it displaces, its specific gravity refers to the mass of an object in air divided by its loss of weight in water. The loss equals the weight in air minus the weight in water.

$$
\text { Specific gravity }=\text { Weight in air } \div \text { Loss of weight in water }
$$

In practical terms, suppose a crown weighed 2.27 kg in air and 0.13 kg less, or 2.14 kg , when weighed underwater (Fig. 28.8). Dividing the crowns mass ( 2.27 kg ) by its weight loss in water $(0.13 \mathrm{~kg})$ yields a specific gravity of 17.5 . Because this ratio differs considerably from golds specific gravity of 19.3, we too can conclude: Eureka, the crown is
a fraud! The physical principle Archimedes discovered allows us to use water submersion to determine the bodys volume. Dividing body mass by its volume yields body density (density $=$ mass $\div$ volume), and from this, an estimate of percentage body fat.

One can think of specific gravity as an objects heaviness related to its volume. Objects of the same volume may vary considerably in density defined as mass per unit volume. One gram of water occupies exactly $1 \mathrm{~cm}^{3}$ at a temperature of $4 \mathrm{C}(39.2 \mathrm{~F})$; the density equals $1 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$. Water achieves its greatest density at 4 C ; thus, increasing water temperature increases the volume of 1 g of water and decreases its density. One must correct the volume of an object weighed in water for water density at the weighing temperature (see Appendix A, available online at http://thepoint.lww.com/mkk7e). The temperature effect distinguishes density from specific gravity.

INTEGRATIVE QUESTION
Why does a solid piece of steel or concrete sink rapidly when placed in water while a ship made of either substance readily floats?

## Body Volume Measurement

The principle discovered by Archimedes applies body volume measurement in one of two ways: (1) water displacement or (2) hydrostatic weighing. Body volume requires accurate measurement because small volume variations substantially affect the density calculation and computed percentage body fat and FFM.


Figure 28.8 Archimedes principle of buoyant force to determine the volume and, subsequently, specific gravity of the kings crown.

## Water Displacement

One can measure the volume of an object submerged in water by the corresponding rise in the level of water within a container. With this technique, a finely calibrated tube, secured to the side of the container, that measures the rise of water permits accurate volume measurements. With this method, one must account for the volume of air remaining in the lungs during submersion. The usual protocol assesses this lung volume before the subject enters the tank and subtracts it from the total body volume determined by water displacement. Water displacement has proved effective in assessing arm and leg volumes and their corresponding changes with exercise training, weight gain or loss, or physical inactivity.

## Hydrostatic Weighing

Hydrostatic weighing provides the most common application of Archimedes principle to determine body volume. It
computes body volume as the difference between body mass measured in air $\left(\mathrm{M}_{\mathrm{a}}\right)$ and body weight measured during water submersion $\left(\mathrm{W}_{\mathrm{w}}\right.$; the correct term because body mass remains unchanged under water). Body volume equals loss of weight in water with the appropriate temperature correction for waters density.

Figure 28.9 illustrates measurement of body volume by hydrostatic weighing under four different conditions. The first step in each condition accurately assesses the subjects body mass in air, usually within 50 g . The subject, who wears a thin nylon swimsuit, sits in a lightweight, plastic tubular chair suspended from the scale and submerged beneath the waters surface. A swimming pool serves the same purpose as the tank, with the scale and chair assembly suspended from a support at the side of the pool or diving board. The tank maintains a comfortable water temperature near 95 F , similar to skin temperature. Water temperature provides the correction factor to determine water density at the weighing temperature. A divers belt secured around the waist (or placed across the lap) stabilizes the subject from floating toward the surface


Figure 28.9 Measuring body volume by underwater weighing. Prone and supine underwater weighing methods provide the same values with residual lung volume measured before, during, or after the underwater weighing. Measurements taken (A) prone in a swimming pool, (B) seated in a swimming pool, (C) seated in a therapy pool, and (D) seated in a stainless steel tank with Plexiglas front in the laboratory. For any of the methods, subjects can use a snorkel with nose clip if they express apprehension about submersion. The final calculation of underwater weight must account for these added objects.
during submersion. The underwater weight of this belt and chair (tare weight) is subtracted from the subjects total weight under water.

Seated with the head above water, the subject makes a forced maximal exhalation while slowly lowering the head under the water. The breath is held for 5 to 8 seconds to allow the scale pointer to stabilize before recording the reading at the midpoint of the oscillations. The subject repeats the procedure 8 to 12 times to obtain a dependable underwater weight score. Even when achieving a full exhalation, a small volume of air, the residual lung volume, remains in the lungs. Body volume calculation requires subtracting the buoyant effect of the residual lung volume measured immediately before, during, or following the underwater weighing. Failure to account for residual lung volume underestimates whole-body density because the lungs air volume contributes to buoyancy. This omission creates a fatter person when converting body density to percentage body fat.

Variations with Menstruation. Normal fluctuations in body mass (chiefly body water) related to the menstrual cycle generally do not affect body density and body fat assessed by hydrostatic weighing. However, some females experience noticeable increases in body water $(>1.0 \mathrm{~kg})$ during menstruation. Water retention of this magnitude affects body density and introduces a small error in computing percentage body fat. ${ }^{21}$

Calculating Body Composition from Body Mass, Body Volume, and Residual Lung Volume. Data for two professional football players, an offensive guard and a quarterback, illustrate the sequence of steps in computing body density, percentage fat, fat mass, and FFM (Table 28.2). Mass $\div$ volume is the conventional formula for computing density, with density expressed in grams per cubic centimeter ( $\mathrm{g} \cdot \mathrm{cm}^{-3}$ ), mass in kilograms, and volume in liters. The difference between $M_{a}$ and $W_{w}$ equals body volume after applying the appropriate water temperature correction $\left(D_{w}\right)$. Air remaining in the lungs and other body spaces (abdominal viscera, sinuses) contributes some buoyancy at the time of underwater weighing. In the extreme, consuming 800 mL of a carbonated beverage increases gastric gas volume by approximately 600 mL . This underestimates body density by hydrostatic weighing by $0.7 \%$ and overestimates percentage body fat by $11 \%$ compared with measures made before drinking the beverage. ${ }^{135}$ In most subjects, abdominal gas and sinus air volume remain small $(<100 \mathrm{~mL})$ and can be ignored. This contrasts with the relatively large and variable residual lung volume, which requires measurement and subsequent subtraction from total body volume.

Whereas the residual lung volume decreases slightly in a person immersed in water compared with residual volume in air (from waters compressive force against the thoracic cavity), the difference exerts only a small effect on computed percentage body fat. ${ }^{64}$ Consequently, most laboratories measure residual lung volume in air just prior to underwater weighing.
TABLE 28.2 Measurements of Two Professional Football Players from Underwater Weighing

| Variable | Symbol | Defensive <br> Lineman | Running <br> Back |
| :---: | :---: | :---: | :---: |
| Body mass $(\mathrm{kg})$ <br> Net underwater <br> weight $(\mathrm{kg})$ | $\mathrm{M}_{\mathrm{a}}$ | 121.73 | 97.37 |
| Water temperature <br> correction | $\mathrm{D}_{\mathrm{w}}$ | 7.30 | 6.52 |
| Residual lung <br> volume $(\mathrm{L})$ | RLV | 1.213 | 1.374 |
| Total body <br> volume $(\mathrm{L})$ <br> Body density <br> $\left(\mathrm{g} \cdot \mathrm{cm}^{-3}\right)$ | TBV | 113.89 | 90.08 |


| Body Composition |  |  |  |
| :--- | ---: | ---: | ---: |
| Relative percentage <br> body fat (\%) | \%Fat | 13.1 | 8.0 |
| Absolute body <br> fat (kg) | FM | 15.9 | 7.2 |
| Fat-free body <br> mass (kg) | FFM | 105.8 | 90.2 |

${ }^{a}$ Siri equation, \%fat $=(495 /$ density $) \div 450$.

The following formula computes body density $\left(D_{b}\right)$ from underwater weighing variables:

$$
\begin{aligned}
D_{b} & =\text { mass } \div \text { volume } \\
& =M_{a} \div\left[\left(M_{a} \times W_{w}\right) \div D_{w}\right]-R L V
\end{aligned}
$$

For ease in computation, the following formula can be used to compute body density:

$$
\mathrm{D}_{\mathrm{b}}=\mathrm{M}_{\mathrm{a}} \times \mathrm{D}_{\mathrm{w}} /\left(\mathrm{M}_{\mathrm{a}}-\mathrm{W}_{\mathrm{w}}-\mathrm{RLV} \times \mathrm{D}_{\mathrm{w}}\right)
$$

The lower part of Table 28.2 presents body composition results for the two football players based on body density.

Validity of Hydrostatic Weighing to Estimate Body Fat. Experimental evidence supports the validity of hydrostatic weighing to estimate the bodys fat content. Behnkes early studies of Navy divers placed 64 subjects into two groups based on their body density. The mean difference between the groups in body mass ( 12.4 kg ) and body volume (13.3 L) allowed Behnke to easily discern body composition differences between the groups. The ratio of the average differences ( $\Delta$ mass $\div \Delta$ volume) equaled $0.933 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$, a value within the density range of 0.92 to $0.96 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ for human adipose tissue. The difference in body mass between the high- and low-density groups represented the density of adipose tissue. Body density for a group of heavy but lean professional football players (lean body mass 20 kg higher than the Navy divers) averaged $1.080 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$. Behnke stated, Here indeed was a presumptive demonstration that fat
could be separated from bone and muscle in vivo or the silver from the gold by application of a principle renowned in antiquity. ${ }^{12}$

The lower and upper limits of body density among humans range from $0.93 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ in the massively obese to nearly $1.10 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ in the leanest males. This coincides nicely with the 1.10 density of fat-free tissue and 0.90 for homogenized samples of fat tissue from small mammals at 37 C .

Computing Body Density. For illustrative purposes, suppose a $50-\mathrm{kg}$ person weighs 2 kg submerged in water. According to Archimedes principle, loss of weight in water of 48 kg equals the weight of the displaced water. One can easily compute the volume of water displaced by correcting for the density of water at the weighing temperature. In this example, 48 kg of water equals 48 L , or $48,000 \mathrm{~cm}^{3}(1 \mathrm{~g}$ of water $=1 \mathrm{~cm}^{3}$ by volume at $\left.39.2 \mathrm{~F}[4 \mathrm{C}]\right)$. Measuring the person at a water temperature of 39.2 F requires no density correction for water temperature. In practice, researchers use warmer water and apply the appropriate density value for water at the weighing temperature.

The density of this person, computed as mass divided by volume, equals $50,000 \mathrm{~g}(50 \mathrm{~kg}) \div 48,000 \mathrm{~cm}^{3}$, or 1.0417 g . $\mathrm{cm}^{-3}$. The total volume of any body segment can be determined using densitometry, for example, the volume of the hands. ${ }^{66}$ The next step estimates percentage body fat and mass of the fat and fat-free tissues.

Computing Percentage Body Fat. An equation that incorporates whole-body density estimates the bodys fat percentage. The simplified equation derived by UC Berkeley scientist William Siri (1919-1998) substitutes $0.90 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ for the density of fat and $1.10 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ for the density of the fat-free tissues. ${ }^{145}$ The final derivation, referred to as the Siri equation, computes percentage body fat as:

$$
\text { Percentage body fat }=(495 \div \text { body density })-450
$$

This equation assumes the two-component model of body composition; the density of fat extracted from adipose tissue equals $0.90 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ and $1.10 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ for fat-free tissue at 37 C . The pioneer researchers in this area maintained that each of these densities remains relatively constant among individuals despite large individual variations in total fat and FFM. They also assumed that the densities of the lean tissue components of bone and muscle remained the same among individuals.

In the previous example (body mass: 50 kg ; body volume: 48 L ), the whole-body density of $1.0417 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ converted to percentage fat by the Siri equation equaled $25.2 \%$.

$$
\begin{aligned}
\text { Percentage body fat } & =(495 \div 1.0417)-450 \\
& =25.2 \%
\end{aligned}
$$

Several formulas other than Siris equation also estimate percentage body fat from body density. ${ }^{20,82}$ The basic difference among the formulas in calculating body fat generally averages less than $1 \%$ body fat units for body fat levels between 4 and $30 \%$.

Limitations of Density Assumptions. The generalized density values for the fat-free $\left(1.10 \mathrm{~g} \cdot \mathrm{~cm}^{-3}\right)$ and fat $\left(0.90 \mathrm{~g} \cdot \mathrm{~cm}^{-3}\right)$ tissue compartments represent averages for young and middle-aged adults. These constants vary among individuals and groups, particularly the density and chemical composition of the FFM. Such variation places some limitation in partitioning body mass into fat and fatfree components and predicting percentage body fat from whole-body density. ${ }^{50}$ More specifically, average density of the FFM is higher for blacks and Hispanics than for whites ( $1.113 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ blacks, $1.105 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ Hispanics, and $1.100 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ whites). ${ }^{128,141,150}$ Racial differences also exist among adolescents. ${ }^{157,189}$ Consequently, existing equations formulated from assumptions for whites to calculate body composition from body density in blacks or Hispanics overestimates FFM and underestimates percentage body fat. The following modification of the Siri equation computes percentage body fat from body density for blacks:

$$
\text { Percentage body fat }=(437.4 \div \text { body density })-392.8
$$

Applying constant density values for the different tissues in growing children or aging adults also introduces errors in predicting body composition. For example, the water and mineral contents of the FFM continually change during the growth period including the demineralization of osteoporosis with aging. Reduced bone density makes the density of the fat-free tissue of young children and the elderly lower than the assumed $1.10 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ constant. This invalidates assumptions of constant densities of fat and fat-free masses in the two-compartment model and overestimates relative body fat calculated from densitometry. For this reason, many researchers do not convert body density to percentage body fat in children and aging adults. Others apply a multicompartment model to adjust for such factors to compute percentage body fat from body density in prepubertal children. ${ }^{146,178}$ Table 28.3 gives equations adjusted to maturation level to predict percentage body fat from whole-body density of boys and girls ages 7 to 17 .

## Adjust for Large Musculoskeletal Development.

 Chronic resistance training affects the density of the FFM, altering body fat estimation from whole-body density determinations. White male weightlifters with considerable muscular development and nontrained controls were assessed for body density, total body water, and bone mineral content. ${ }^{117}$ Comparisons included estimations of percentage body fat with both the two-compartment model and a four-compartment model using the bodys fat, water, mineral, and protein content and corresponding densities. Percentage body fat estimated from body density (two-compartment Siri equation) produced higher values than percentage body fat from the four-compartment model for the weight trainers but not for untrained controls. A lower FFM density in weight trainers than in controls ( 1.089 vs. $1.099 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ ) explained this discrepancy; it resulted from larger water and smaller mineral and protein fractions of the FFM in the resistance-trained| TABLE 28.3 | Percentage Body Fat Estimated from Body Density (BD) Using Age- and Gender-Specific Conversion Constants to Account for Changes in the Density of the Fat-Free Body Mass as a Child Matures |  |
| :---: | :---: | :---: |
| Age (y) | Boys | Girls |
| 7-9 | \% Fat $=(5.38 / \mathrm{BD}-4.97) \times 100$ | $\%$ Fat $=(5.43 / \mathrm{BD}-5.03) \times 100$ |
| 9-11 | $\%$ Fat $=(5.30 / \mathrm{BD}-4.89) \times 100$ | $\%$ Fat $=(5.35 / \mathrm{BD}-4.95) \times 100$ |
| 11-13 | $\%$ Fat $=(5.23 / \mathrm{BD}-4.81) \times 100$ | $\%$ Fat $=(5.25 / \mathrm{BD}-4.84) \times 100$ |
| 13-15 | $\%$ Fat $=(5.08 / \mathrm{BD}-4.64) \times 100$ | $\%$ Fat $=(5.12 / \mathrm{BD}-4.69) \times 100$ |
| 15-17 | $\%$ Fat $=(5.03 / \mathrm{BD}-4.59) \times 100$ | $\%$ Fat $=(5.07 / \mathrm{BD}-4.64) \times 100$ |
| From Lohman T Sports Sci Rev | cability of body composition techniq :325. | stants for children and youth. Exerc |

men. For them, incorrect assumptions underlying the Siri equation overestimated percentage body fat.

For the weightlifters, muscularity increased disproportionately to changes in bone mass. A lower FFM density occurred because the density of their fat-free muscle $\left(1.066 \mathrm{~g} \cdot \mathrm{~cm}^{-3}\right.$ at 37 C ) was below the $1.1 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ value assumed in the Siri equation. Disproportionate increases in muscle mass relative to increases in bone mass accounted for the reduced density of the FFM below $1.1 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$, overpredicting percentage body fat from the two-compartment model. If resistance training does indeed progressively lower FFM density, then applying the Siri equation fails to accurately reflect true body composition changes from this training mode.

Based on revised densities of the FFM ( $1.089 \mathrm{~g} \cdot \mathrm{~cm}^{-3}$ ) and fat mass $\left(0.9007 \mathrm{~g} \cdot \mathrm{~cm}^{-3}\right)$, a modified equation more accurately appraises resistance-trained white males: ${ }^{117}$

$$
\text { Percentage body fat }=(521 \div \text { body density })-478
$$

Computing Fat Mass. Using data from the example on page 742 , fat mass computes by multiplying body mass by percentage body fat as follows:

$$
\begin{aligned}
\text { Fat mass } & =\text { body mass } \times(\% \text { fat } / 100) \\
& =50 \mathrm{~kg} \times 0.252 \\
& =12.5 \mathrm{~kg}
\end{aligned}
$$

Further computations subdivide this persons fat mass into essential and storage fat. A female with $25.2 \%$ body fat has approximately $12 \%$ essential fat, or $6.0 \mathrm{~kg}(0.12 \times 50 \mathrm{~kg})$; the remaining $13.2 \%(6.6 \mathrm{~kg})$ exists as storage fat $(0.132 \times 50 \mathrm{~kg})$. For a male with $3 \%$ essential fat and $22.2 \%$ storage fat (based on $25.2 \%$ body fat), the corresponding values equal 1.5 kg for essential fat and 11.1 kg for storage fat. Clearly, for a man and woman with identical percentage body fat, the man rates fatter because storage fat represents a larger percentage of total body fat. Each gram of body fat ( $83 \%$ pure fat) contains approximately $7.5 \mathrm{kCal}(7500 \mathrm{kCal}$ per kg ). One can compute the approximate potential energy stored in each fat depot. For storage fat in this example, the values are $49,500 \mathrm{kCal}$ for the woman and $83,260 \mathrm{kCal}$ for the man; for essential fat, including
a females sex-specific fat, the values are $45,000 \mathrm{kCal}$ for the woman and $11,250 \mathrm{kCal}$ for the man.

Computing Fat-Free Body Mass. Compute FFM by subtracting fat mass from body mass.

$$
\begin{aligned}
\text { Fat-free body mass } & =\text { body mass } \times \text { fat mass } \\
& =50 \mathrm{~kg} \times 12.5 \mathrm{~kg} \\
& =37.5 \mathrm{~kg}
\end{aligned}
$$

## BOD POD Measurement of Body Volume

A procedure has been perfected to assess body volume and its changes for groups that range from infants to the elderly, to collegiate wrestlers and exceptionally large athletes like American professional football and basketball players. ${ }^{45,162,190}$ The method has adapted helium-displacement plethysmography first reported in the late 1800s. The subject sits inside a small chamber marketed commercially as BOD POD (Fig. 28.10A). Measurement requires only 3 to 5 minutes, with high reproducibility of test scores $(r>0.90)$ within and across days. After being weighed to the nearest $\pm 5 \mathrm{~g}$ on an electronic scale (bottom left of BOD POD illustration), the subject sits comfortably in the 750-L volume, dual-chamber fiberglass shell. The molded front seat separates the unit into front and rear chambers. The electronics, housed in the rear chamber, contain the pressure transducers, breathing circuit, and air circulation system.

The BOD POD determines body volume by measuring the initial volume of the empty chamber and then the volume with the person inside. To ensure measurement reliability and accuracy, the person wears a tight-fitting swimsuit. ${ }^{169}$ Body volume represents the initial volume minus the reduced chamber volume with the subject inside. The subject breathes several breaths into an air circuit to assess pulmonary gas volume, which when subtracted from measured body volume yields body volume. Body density computes as body mass (measured in air) divided by body volume (measured in BOD POD, including a correction for a small negative volume caused by isothermal effects related to skin


Figure 28.10 A. BOD POD for measuring human body volume. (Photo courtesy of Dr. Megan McCrory, Purdue University, West Lafayette, IN.) B. Regression of percentage body fat by hydrostatic weighing (HW) versus percentage body fat by BOD POD (BP). (Data from McCrory MA, et al. Evaluation of a new air displacement plethysmograph for measuring human body composition. Med Sci Sports Exerc 1995;27:1686.)
surface area). The Siri equation converts body density to percentage body fat.

## Some Discrepancies in the Literature

Figure 28.10B shows the regression of percentage body fat assessed by hydrostatic weighing versus percentage body fat assessed by BOD POD in an ethnically diverse group of adult women and men. A difference of only $0.3 \% ~(0.2 \%$ fat units) occurred between body fat determined by the two methods, with a validity coefficient of $r=0.96$. In contrast to these rather impressive findings, BOD POD assessments of collegiate football players, although producing reliable scores, underpredicted percentage body fat compared with hydrostatic weighing and DXA. ${ }^{29}$ Underprediction of body fat also occurred in a heterogeneous sample of black men who varied considerably in age, stature, body mass, percentage body fat, and self-reported physical activity level and socioeconomic status. ${ }^{174}$ The method underpredicted percentage body fat compared with densitometry ( $-1.9 \%$ fat units) and DXA( $-1.6 \%$ fat units). Similar underpredictions compared with DXA-derived body fat ( $-2.9 \%$ fat units) occurred in 54 boys and girls 10 to 18 years of age. ${ }^{95}$ BOD POD also underestimated body fat of young adults compared with body fat predictions from a four-component model. ${ }^{44,115}$ The method overestimated percentage body fat among lean individuals in a heterogeneous group of adults. ${ }^{168}$ A BOD POD validation study in children ages 9 to 14 concluded that compared with DXA, total body water, and densitometry, BOD POD precisely and accurately estimated fat mass without introducing bias estimates. ${ }^{42}$ The method has also been shown to accurately detect body composition changes from a small-to-moderate weight loss in overweight women and men. ${ }^{179}$ Numerous studies have assessed the efficacy of BOD POD compared with other body composition methods in children; young, middle-age, and elderly adults; obese persons; and athletes. 4 . $6,9,13,28,39,43,133,161,170$

## Skinfold and Girth Measurements

In field situations, two relatively simple procedures that measure either subcutaneous fat (skinfolds) or circumferences (girths) predict body fatness with reasonable accuracy.

## Subcutaneous Fat Measurement with Skinfolds

The rationale for using skinfolds to estimate body fat comes from the interrelationships among three factors: (1) adipose tissue directly beneath the skin (subcutaneous fat), (2) internal fat, and (3) whole-body density.

The Caliper. By 1930, a pincer-type caliper accurately measured subcutaneous fat at selected anatomic sites. The three calipers shown in Figure 28.11 operate on a principle similar to a micrometer that measures distance between two points. Measuring skinfold thickness requires firmly grasping a fold of skin and subcutaneous fat with the thumb and


Figure 28.11 Common calipers for skinfold measurements. The Harpenden and Lange calipers provide constant tension at all jaw openings.
forefingers, pulling it away from the underlying muscle tissue following the natural contour of the skinfold. When calibrated, the pincer jaws exert a relatively constant tension of $10 \mathrm{~g} \cdot \mathrm{~mm}^{-2}$ at the point of contact with the double layer of skin plus subcutaneous adipose tissue. The caliper dial indicates skinfold thickness in mm recorded within 2 seconds after applying the full force of the caliper. This time limitation avoids skinfold compression when taking the measurement. For research purposes, the investigator has considerable experience in taking measurements and demonstrates consistency in duplicating values for the same subjects on the same day, consecutive days, or weeks apart. A rule of thumb to achieve consistency requires duplicate or triplicate practice measurements on approximately 50 individuals who vary in body fat. Careful attention to detail usually ensures high measurement reproducibility.

Measurement Sites. Common anatomic sites for skinfold measurements include triceps, subscapular, suprailiac, abdominal, and upper thigh sites. The investigator should take a minimum of two or three measurements in rotational order at each site on the right side of the body with the subject standing. The average value represents the skinfold score. Figure 28.12 shows the anatomic location of five of the more frequently measured sites:

Triceps: Vertical fold at the posterior midline of the right upper arm, halfway between the tip of the
shoulder and tip of the elbow; elbow remains in an extended, relaxed position
Subscapular: Oblique fold, just below the bottom tip of the right scapula
Iliac (iliac crest): Slightly oblique fold, just above the right hipbone (crest of ileum); the fold follows the natural diagonal line
Abdominal: Vertical fold 1 inch to the right of the umbilicus
Thigh: Vertical fold at the midline of the right thigh, two thirds the distance from the middle of the patella (kneecap) to the hip

## Other sites include:

Chest: Diagonal fold with long axis directed toward the right nipple; on the anterior axillary fold as high as possible
Biceps: Vertical fold at the posterior midline of the right upper arm

## Usefulness of Skinfold Scores

Skinfold measurements provide meaningful information about body fat and its distribution. We recommend two ways to use skinfolds. The first sums the skinfold scores to indicate relative fatness among individuals. The sum-of-skinfolds and individual values reflect either absolute or percentage skinfold changes before and after an intervention program.

One can draw the following conclusions from the skinfold data in Table 28.4 obtained from a 22 -year-old female college student before and after a 16 -week aerobic exercise program:

Largest changes in skinfold thickness occurred at the iliac and abdomen sites
Triceps showed the largest percentage decrease and the subscapular the smallest percentage decrease Total reduction in subcutaneous skinfolds at the five sites was 16.6 mm or $12.6 \%$ below the before condition

A second use of skinfolds incorporates populationspecific mathematical equations to predict body density or percentage body fat. The equations prove accurate for subjects similar in age, gender, training status, fatness, and race to the group from which they were derived. ${ }^{18,38,124,132,165}$ When meeting these criteria, predicted body fat for an individual usually ranges between 3 and 5\% body fat units computed from body density with hydrostatic weighing.

Our laboratories developed the following equations to predict percentage body fat from triceps and subscapular skinfolds in young women and men: ${ }^{75-77}$

Young women, ages 17 to 26 years

$$
\% \text { Body fat }=0.55 A+0.31 B+6.13
$$

Young men, ages 17 to 26 years

$$
\% \text { Body fat }=0.43 A+0.58 B+1.47
$$



Figure 28.12 Anatomic location of five common skinfold sites: A. Triceps. B. Subscapular. C. Iliac. D. Abdomen.
E. Thigh. Measurements taken on the right side of the body in the vertical plane except diagonally at subscapular and iliac sites.

TABLE 28.4 Changes in Selected Skinfolds of a Young Woman During a 16-Week Exercise Program

| Skinfolds <br> $(\mathbf{m m})$ | Before | After | Absolute <br> Change | Percentage <br> Change |
| :--- | :---: | :---: | :---: | :---: |
| Triceps | 22.5 | 19.4 | -3.1 | -13.8 |
| Subscapular | 19.0 | 17.0 | -2.0 | -10.5 |
| Suprailiac | 34.5 | 30.2 | -4.3 | -12.8 |
| Abdomen | 33.7 | 29.4 | -4.3 | -12.8 |
| Thigh | $\underline{21.6}$ | $\underline{18.7}$ | $\underline{-2.9}$ | $\underline{-13.4}$ |
| Sum | 131.3 | 114.7 | $\underline{-16.6}$ | $\underline{-12.6}$ |

In both equations, $A$ is triceps skinfold (mm) and $B$ is subscapular skinfold (mm).

We computed the before and after percentage body fat of the woman who participated in the 16 -week physical conditioning program (Table 28.4). Percentage body fat equals $24.4 \%$ by substituting the pretraining values for triceps ( 22.5 mm ) and subscapular ( 19.0 mm ) skinfolds into the equation.

$$
\begin{aligned}
\% \text { Body fat } & =0.55 A+0.31 B+6.13 \\
& =0.55(22.5)+0.31(19.0)+6.13 \\
& =12.38+5.89+6.13 \\
& =24.4 \%
\end{aligned}
$$

Substituting posttraining values for triceps ( 19.4 mm ) and subscapular ( 17.0 mm ) skinfolds produced a body fat value of $22.1 \%$.

$$
\begin{aligned}
\% \text { Body fat } & =0.55(19.4)+0.31(17.0)+6.13 \\
& =10.67+5.27+6.13 \\
& =22.1 \%
\end{aligned}
$$

Percentage body fat determined before and after a physical conditioning or weight-loss program provides a convenient way to evaluate alterations in body composition, independent of body weight changes.

## Skinfold Prediction for Athletes

Predict body fat in athletes from an equation validated against a 4-component model (total body water, bone mineral by DXA, and body density by underwater weighing).
\% Body fat $=8.997+0.24658(3$ SKF $)-6.343$
(gender) - 1.998 (race)
Where $3 \mathrm{SKF}=$ sum of skinfolds in mm at ab domen, thigh, and triceps; gender $=0$ for female, 1 for male; race $=0$ for white, 1 for black.

From Evans EM, et al. Skinfold prediction equation for athletes developed using a four-component model. Med Sci Sports Exerc 2005;37: 2006.

## Skinfolds and Age

In young adults, approximately one-half of total fat consists of subcutaneous fat, with the remainder visceral and organ fat. With advancing age, proportionately more fat deposits internally than subcutaneously. Thus, the same skinfold score reflects a greater total percentage of body fat as one ages. For this reason, use age-adjusted generalized equations to predict body fat from skinfolds or girths in older men and women. ${ }^{68,69,136,159}$

## User Beware

The person taking skinfold measurements must develop expertise with the proper techniques. Also, with extremely obese people, the skinfold thickness often exceeds the width of the calipers jaws. The particular caliper also contributes to errors of measurement. ${ }^{53}$ Under these conditions, girth becomes the measure of choice (see next section).

## INTEGRATIVE QUESTION

A friend complains that three different fitness centers determined her percentage body fat from skinfolds as follows: $25 \%$, $29 \%$, and $21 \%$. How can you reconcile the differences in these values?

## Measurement of Girths

Apply a linen or plastic measuring tape (not a metal tape) lightly to the skin surface so the tape remains taut but not tight. This avoids skin compression, which produces below-normal scores. Make duplicate measurements at each site and average the scores. Figure 28.13 shows six common anatomic landmarks for anthropometric measurement:

1. Right upper arm (biceps): arm straight and extended in front of the body; measurement taken at midpoint between the shoulder and the elbow
2. Right forearm: maximum girth with arm extended in front of the body
3. Abdomen: 1 inch above the umbilicus
4. Buttocks: maximum protrusion with heels together
5. Right thigh: upper thigh, just below the buttocks
6. Right calf: widest girth midway between ankle and knee

Prediction equations based on girths exist for each gender and different age groups. ${ }^{75,114,160}$ The equations for these subgroups show considerable population specificity. They do not apply to individuals who (1) appear overly thin or excessively fat, (2) train regularly in strenuous endurance sports or activities with a substantial resistance-training (and subsequent muscular-enlargement) component, and (3) differ in race from the specific group used to derive the original equations.

## Usefulness of Girth Scores

Girths prove most useful in ranking individuals within a group according to relative fatness. As with skinfolds, girthbased equations predict body density and/or percentage body fat with a certain degree of error. The equations and constants presented in Body Composition on this books companion website at http://thepoint.lww.com/mkk7e for young and older men and women predict body fat to within $\pm 2.5$ to $4.0 \%$ body fat units of the actual value. The prediction error depends on whether the individual portrays physical characteristics similar to the original validation group. Such relatively small errors make girth predictions particularly useful in nonlaboratory settings. Specific equations based on girths also estimate body composition of obese adult men and women. ${ }^{17,159,177}$

Along with predicting percentage body fat, girths can analyze patterns of body fat distribution, including changes in fat patterning during weight loss. ${ }^{57,173}$ Not surprisingly, those equations that use the more labile sites of fat deposition (e.g., waist and hips instead of upper arm or thigh in females and abdomen in males) provide the greatest accuracy to predict changes in body composition. ${ }^{46}$

## Body Fat Predictions from Girths

From the appropriate tables on http://thepoint. lww.com/mkk7e, substitute the corresponding constants $A, B$, and $C$ in the formula shown at the bottom of each table. This


Figure 28.13 Landmarks for measuring various girths at six common anatomic sites.
requires one addition and two subtraction steps. The following five-step example shows how to compute percentage fat, fat mass, and FFM for a 21-year-old man who weighs 79.1 kg :

Step 1. Measure upper arm, abdomen, and right forearm girths with a cloth tape to the nearest 0.25 in . $(0.6 \mathrm{~cm})$ : upper arm $=11.5 \mathrm{in} .(29.21 \mathrm{~cm})$; abdomen $=31.0 \mathrm{in} .(78.74 \mathrm{~cm})$; right forearm $=$ 10.75 in. ( 27.30 cm )

Step 2. Determine the three constants $A, B$, and $C$ corresponding to the three girths from the table: $A$, corresponding to 11.5 in $=42.56 ; B$, corresponding to 31.0 in $=40.68$; and $C$, corresponding to 10.75 in $=58.37$.

Step 3. Compute percentage body fat by substituting the constants from step 2 in the formula for young men as follows:

$$
\begin{aligned}
\text { Percentage fat } & =A+B-C-10.2 \\
& =42.56+40.68-58.37-10.2 \\
& =83.24-58.37-10.2 \\
& =24.87-10.2 \\
& =14.7 \%
\end{aligned}
$$

Step 4. Determine fat mass

$$
\begin{aligned}
\text { Fat mass } & =\text { Body mass } \times(\% \text { fat } \div 100) \\
& =79.1 \mathrm{~kg} \times(14.7 \div 100) \\
& =79.1 \mathrm{~kg} \times 0.147 \\
& =11.6 \mathrm{~kg}
\end{aligned}
$$

Step 5. Determine FFM

$$
\begin{aligned}
\text { FFM } & =\text { Body mass }- \text { fat mass } \\
& =79.1 \mathrm{~kg}-11.6 \mathrm{~kg} \\
& =67.5 \mathrm{~kg}
\end{aligned}
$$

## Bioelectrical Impedance Analysis

In the single mode of low-frequency bioelectrical impedance analysis (BIA), a small alternating current flowing between two electrodes passes more rapidly through hydrated fat-free body tissues and extracellular water than through fat or bone tissues because of the greater electrolyte content (lower electrical resistance) of the fat-free component. In essence, the bodys water content conducts the flow of electrical charges, so when current flows through the fluid, sensitive
instrumentation can detect the waters impedance. Impedance to electric current flow, calculated by measuring current and voltage, is based on Ohms law ( $\mathrm{R}=\mathrm{V} / \mathrm{I}$, where $\mathrm{R}=$ resistance, $\mathrm{V}=$ volume, and $\mathrm{I}=$ current). These relationships can quantify the volume of water within the body, and from this, percentage body fat and FFM.

Figure 28.14 A and B show an example for singlefrequency BIA. A person lies on a flat, nonconducting surface with injector (source) electrodes attached on the dorsal surfaces of the foot and wrist and detector (sink) electrodes attached between the radius and ulna (styloid process) and at the ankle between the medial and lateral malleoli. A painless,



Right Arm


Trunk


Impedance

Figure 28.14 Method to assess body composition by bioelectrical impedance analysis. A. Four-surface electrode technique (whole-body impedance) applies current via one pair of distal (injector) electrodes, while the proximal (detector) electrode pair measures electrical potential across the conducting segment. B. Standard placement of electrodes and body position during whole-body impedance measurement. C. Segmental measurement illustrating assessment of current (I) and voltage ( $V$ ) for the right arm, trunk, and right leg.
localized electrical current (approximately $800 \mu \mathrm{~A}$ at a frequency of 50 kHz ) is introduced, and the impedance (resistance) to current flow between the source and detector electrodes determined. Conversion of the impedance value to body densityadding body mass and stature; gender, age, and sometimes race; level of fatness; and several girths to the equationeemputes percentage body fat from the Siri equation or other density conversion equations. Body composition prediction with such a system depends on the additional input data as part of the BIA equation. Thus, any unreliability of data input produces different prediction results. This becomes more pronounced for individuals at the extremes of body composition. For example, a difference of only 5 mm in a girth measurement or difference of 1.5 cm in true stature from measurement to measurement can produce up to a $2 \%$ change in an output variabletmrelated to any real change in a computed body composition variable such as fat mass or FFM. Figure 28.14C illustrates the segmental measurement approach including electrode configuration and how current (I) and voltage (V) are assessed for the right arm, trunk, and right leg.

## Influence of Hydration Level and Ambient Temperature

Hydration level affects the accuracy of BIA and may give incorrect information about an individuals body fat content. ${ }^{86,126}$ Hypohydration and hyperhydration alter the bodys normal electrolyte concentrations; this in turn affects current flow independent of real body composition changes. For example, voluntary fluid restriction decreases the impedance measure. This lowers the percentage body fat estimate; hyperhydration produces the opposite effect (higher body fat estimate). Skin temperature, influenced by ambient conditions, also affects whole-body resistance and BIA prediction of body fat. Predicted body fat is lower in a warm environment (moist skin produces less impedance to electrical flow) than in a cold one.

Even with normal hydration and environmental temperature, body fat predictions with BIA prove less valid than with hydrostatic weighing. BIA tends to overpredict body fat in lean and athletic subjects and underpredict body fat in obese subjects. ${ }^{103,142}$ BIA often predicts body fat less accurately than do girths and skinfolds. ${ }^{19,37,79,151}$ Whether BIA detects small changes in body composition during weight loss remains unclear. ${ }^{88,123,134}$ Conventional BIA technology cannot determine regional fat distribution.

At best, BIA represents a noninvasive, safe, relatively easy, and reliable means to assess total body water. The technique requires that experienced personnel make measurements under standardized conditions. Particularly important are electrode placement and the subjects body position, hydration status, plasma osmolality and sodium concentration, skin temperature, recent physical activity, and previous food and beverage intake. ${ }^{15,87,88}$ For example, ingestion of consecutive meals progressively decreases bioelectrical impedance (possibly the combined effect of increased electrolytes and a
redistribution of extracellular fluid), which decreases computed percentage body fat. ${ }^{147}$ Body fatness and racial characteristics also influence BIAs predictive accuracy. ${ }^{3,129,152,189}$ The tendency to overestimate percentage body fat increases among black athletes ${ }^{61,142}$ and lean subjects. ${ }^{153}$ Fatnessspecific BIA equations exist that predict body fat for obese and nonobese American Indian, Hispanic, and white men and women. ${ }^{151}$ With proper measurement standardization, the menstrual cycle does not affect body composition assessment by BIA. ${ }^{108}$

## Applicability of BIA in Sports and Exercise Training

Coaches and athletes require a safe, easily administered, and valid tool to assess body composition and detect changes with caloric restriction or exercise training. A major limitation in achieving these goals concerns BIAs lack of sensitivity to detect small body-compositional changes, particularly without appropriate control over factors that affect measurement accuracy and reliability. For example, sweat-loss dehydration from prior exercise or reduced glycogen reserves (and associated loss of glycogen-bound water) from an intense training session reduces body resistance (impedance) to electrical current flow. This overestimates FFM and underestimates percentage body fat.

Chapter 29 (In a Practical Sense) includes BIA equations (in addition to equations using skinfolds and girths) to estimate body density and percentage body fat for athletes in general and athletes in specific sports. Without sport-specific equations, population-based generalized equations that account for age and gender usually provide an acceptable alternative to estimate body fat. ${ }^{68,144,156}$

## Near-Infrared Interactance

Near-infrared interactance (NIR) applies technology developed by the U.S. Department of Agriculture to assess body composition of livestock and the lipid content of various grains. The commercial versions to assess human body composition use principles of light absorption and reflection. A fiber optic probe or light wand emits a low-energy beam of near-infrared light into the single measuring site at the anterior midline surface of the dominant biceps. A detector within the same probe measures the intensity of the reemitted light, expressed as optical density. Shifts in wavelength of the reflected beam as it interacts with organic material in the arm inserted into the manufacturers prediction equation (including adjustments for subjects body mass and stature, estimated frame size, gender, and physical activity level) computes percentage body fat and FFM. The safe, portable, lightweight equipment requires minimal training to use and necessitates little physical contact with the subject during measurement. These test administration aspects make NIR popular for body composition assessment in health clubs, hospitals, and weight-loss centers. The important question about the usefulness of NIR concerns its validity.

## Questionable Validity

Early research indicated a relationship between spectrophotometric measures of light interactance at various body sites and body composition assessed by total body water. ${ }^{32}$ Subsequent studies with humans have not confirmed NIRs validity versus hydrostatic weighing or skinfold measurements. NIR does not accurately predict body fat across a broad range of body fat levels; it often provides less accuracy than skinfolds. ${ }^{19,60,167}$ It overestimates body fat in lean men and women and underestimates it in fatter subjects. ${ }^{109}$ Figure 28.15 shows the inadequacy of NIR compared with skinfold measurements to predict body fat compared to hydrostatic weighing. In more than $47 \%$ of the subjects, an error greater than $4 \%$ body fat units occurred with NIR, with the largest errors at the extremes of body fatness. NIR produced large errors when estimating body fat for children ${ }^{24}$ and youth wrestlers, ${ }^{63}$ and underestimated body fat in collegiate football players. ${ }^{62}$ NIR did not accurately assess body composition changes from resistance training. ${ }^{19}$ At this time, research does not support NIR as a robust, valid method to assess human body composition.


Figure 28.15 Comparison of near-infrared interactance (Futrex-5000) (top) and skinfolds (bottom) for assessing percentage body fat. Shaded area around line incorporates $\pm 4 \%$ body fat units. (From McLean K, Skinner JS. Validity of Futrex5000 for body composition determination. Med Sci Sports Exerc 1992;24:253.)

## Ultrasound Assessment of Fat

Ultrasound technology can assess the thickness of different tissues (fat and muscle) and image the deeper tissues such as a muscles cross-sectional area. The method converts electrical energy through a probe into high-frequency (pulsed) sound waves that penetrate the skin surface into the underlying tissues. The sound waves pass through adipose tissue to penetrate the muscle layer. They then reflect from the fat-muscle interface (after reflection from a bony surface) to produce an echo, which returns to a receiver within the probe. The simplest type of ultrasound (A-mode) does not produce an image of the underlying tissues. Rather, the time required for sound wave transmission through the tissues and back to the transducer converts to a distance score that indicates fat or muscle thickness. With the more expensive and technically demanding B-mode ultrasound, a 2-dimensional image provides considerable detail and tissue differentiation.

Ultrasound exhibits high reliability for repeat measurements of subcutaneous fat thickness at multiple sites in the lying and standing positions on the same day and different days. ${ }^{67,74}$ The technique can determine total and segmental subcutaneous adipose tissue volume. ${ }^{2}$ It has also shown validity for assessing FFM of high school wrestlers, which may prove useful as a field-based body composition assessment method. ${ }^{163}$ Ultrasound proves particularly useful with obese persons who show considerable variation and compression of subcutaneous body fat with skinfold measures. When used to map muscle and fat thickness at different body regions and quantify changes in topographic fat patterns, ultrasound serves as a valuable adjunct to body composition assessment. In hospitalized patients, ultrasonic fat and muscle thickness determinations aid in nutritional assessment during weight loss and weight gain. Ultrasonic imaging also serves a clinical role in assessing tissue growth and development, including fetal development and structure and function of the heart and other organs. With imaging devices, reflected sound waves from the soft tissues convert to a real-time image for convenient visualization or for computer digitization (area, volume, and diameter) directly from the image. Color and multiple-frequency imaging allows clinicians to trace blood flow through organs and tissues or, with the use of miniaturized probes, identify internal tissues, vessels, and organs. In consumer-oriented research, ultrasonic imaging of thigh fat depth provided evidence that treatments using two topical cream applications to the thighs and buttocks to reduce cellulite (dimpled fat) failed to reduce local fat thickness compared with control conditions. ${ }^{30}$

## Computed Tomography, Magnetic Resonance Imaging, and Dual-Energy X-Ray Absorptiometry <br> Computed Tomography

Computed tomography (CT) generates detailed crosssectional, 2-dimensional radiographic images of body segments when an X-ray beam (ionizing radiation) passes through
tissues of different densities. The CT scan produces pictorial and quantitative information about total tissue area, total fat and muscle area, and thickness and volume of tissues within an organ. ${ }^{52,116,172}$

Figure 28.16A-C shows CT scans of the upper legs and a cross section at the midthigh of a professional walker who walked 11,200 miles through the 50 United States in 50 weeks. Total cross section and muscle cross section increased and subcutaneous fat decreased correspondingly in the midthigh region in the after scans (not shown). Studies have demonstrated the efficacy of CT scans to establish the relationship between simple anthropometric measures (skinfolds and girths) at the abdomen and total abdominal fat volume measured from single or multiple pictorial slices through this region. ${ }^{143}$ The single cut through the L4 to L5 region minimizes radiation dose and provides the best view of visceral and subcutaneous fat. Figure 28.17 illustrates the high association between waist circumference and deep visceral adipose tissue (VAT) area; men with larger waist girth also possessed greater VAT. The relationship exceeded the association between subcutaneous fat thickness (skinfolds) and VAT. An increased amount of deep abdominal adipose tissue relates to increased risk for type 2 diabetes, blood lipid profile disorders, and hypertension, including the metabolic syndrome and cardiovascular disease. Chapter 30 discusses health risks from the deep type of abdominal obesity.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), originally discovered by physician and research scientist R. V. Damadian (1936-) in 1971, patented in 1974, and first constructed in 1977, provides an invaluable, noninvasive assessment of the bodys tissue compartments. ${ }^{1,73,91}$ Figure 28.18 shows a colorenhanced MRI transaxial image of the midthigh of a 30-yearold male middle-distance runner. Computer software subtracts fat and bony tissues (lighter-colored areas) to compute thigh muscle cross-sectional area (red area). With MRI, electromagnetic radiation (not ionizing radiation as in CT scans) in a strong magnetic field excites the hydrogen nuclei of the bodys water and lipid molecules. The nuclei then project a detectable signal that rearranges under computer control to visually represent the various body tissues. MRI can quantify total and subcutaneous adipose tissue in individuals of varying body fatness. Combined with muscle mass analysis, MRI assesses changes in a muscles lean and fat components following resistance training, changes in muscle volume in and out of training, or during different stages of growth and aging. ${ }^{71,158}$ MRI analysis has assessed postflight changes in muscle volume after a 17 -day space mission and 16- to 28 -week duration shuttle/MIR missions. ${ }^{90}$ MRI has wide acceptance for diagnosis in almost all fields of medicine and related disciplines, including muscular dystrophy. ${ }^{51}$ The latest MRI technologies allow imaging of pacemakers with fiber optic leads rather than wire leads, MRI compatible defibrillators, and FONAR stand-up MRI that scans patients in numerous weight-bearing positionsstanding, sitting, in flexion and


Figure 28.16 CT scans. A. Plot of pixel elements (CT scan) illustrating the extent of adipose and muscle tissue in a cross section of the thigh. The two other views show (B) a cross section of the midthigh and (C) an anterior view of the upper legs prior to a 1-year walk across the United States by a champion walker. (CT scans courtesy of Dr. Steven Heymsfeld, Obesity Research Center, St. Lukes-Roosevelt Hospital, Columbia University, College of Physicians and Surgeons, New York, NY.)


Figure 28.17 Relationship between deep visceral adipose tissue (VAT) determined by CT scanning and waist girth in 110 men, ages 18 to 42 years, who varied considerably in percentage body fat by densitometry ( $\bar{X}=22.9 \%$; range, 2.2-39.9\%). The best predictors of VAT included (a) abdominal skinfold thickness in mm , (b) waist girth in cm , and (c) waist-hip ratio. VAT $\left(\mathrm{cm}^{2}\right)=-363.12+(-1.113 a)+$ $3.478 b+186.7 c$. For example, if abdominal skinfold is 23.0 mm , waist girth is 92.0 cm , and waist hip ratio is 0.929 , then by substitution in the equation, VAT $=104.7 \mathrm{~cm}^{2}$. (Modified from $D$ pres J-P, et al. Estimation of deep abdominal adiposetissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr 1991;54:471.)


Figure 28.18 MRI scans of the midthigh of a 30-year-old male middle-distance runner. (MRI scans courtesy of J. Staab, Department of the Army, USARIEM, Natick, MA.)
extension, and the conventional lie-down position (www. invent.org/hall_of_fame/36.html; www.fonar.com/).

Figure 28.19 (top) shows a plot of percentage body fat determined by MRI scanning of 30 transaxial images along the length of the body and underwater weighing of 20 Swedish women, ages 23 to 40 years. Total fat from scans of the calves, thighs, lower- and upper-trunk, and lower- and upper-arms provided the basis for computing MRI percentage body fat. Good agreement emerged between the two body fat estimates
( $r=0.84$ ). Similar validity emerged between MRIdetermined total body fat and hydrostatic weighing and total body water estimates of body fat. ${ }^{110}$

The bottom of Figure 28.19 shows the distribution of total adipose tissue, subcutaneous adipose tissue, and nonsubcutaneous adipose tissue measures from different body regions. The bar graphs show the smallest to the largest adipose tissue depots. Of all body regions, adipose tissue in the lower trunk (both subcutaneous and nonsubcutaneous) contained the greatest percentage of total body fat ( $38.5 \%$ ); the lower arm region included $2.7 \%$, the smallest amount. The pie chart at the lower right of the figure shows the relative amounts of adipose tissue in each body compartment in relation to the MRI-determined total volume of body fat. Subcutaneous fat accounted for $75.2 \%$ of the total 21.8 L of body fat. Nonsubcutaneous fat accounts for the remaining 24.8\%, making it reasonable to conclude that excess fat deposits to the greatest extent in the subcutaneous tissues.

Comparison of Lean and Obese. Seventeen MRIderived tissue slices from groups of lean and obese females provided comparative data for total fat and VAT volume at four anatomic sites between the top of the patella and sternal notch. Body fat determined by densitometry for the light women (BMI: 20.6) averaged $25.4 \%$; the heavy womens BMI averaged 42.4 with about $42 \%$ body fat. The three graphs in Figure 28.20 display differences between the relatively light and heavy groups in total body tissue (sum of fat and nonfat tissues), total adipose tissue, and subcutaneous adipose tissue at the 17 sites. The results show a fairly consistent pattern in MRI-derived adipose tissue volumes. The overfat subjects possessed $165 \%$ more subcutaneous adipose tissue and $155 \%$ more total adipose tissue. Abdominal and upper-thigh regions showed the largest fat accretion. Interestingly, the light women had a greater amount of nonfat tissue (not shown) at the upper-thorax and lower-thigh regions. The inset graph shows the strong relationship between MRI-determined percentage of body adipose tissue (4 instead of 17 sites) and percentage body fat determined by densitometry. MRI yields a wealth of useful information for accurately assessing total and regional body composition.

Exercise Training. MRI and dual-energy X-ray absorptiometry (DXA, discussed in the next section) assessed changes in regional (trunk and extremities) and whole-body fat mass, lean body mass, and bone mineral content at 3 and 6 months of periodized resistance training in 31 women. ${ }^{125}$ MRI measured changes in thigh muscle morphology in a subset of 11 women exercisers. The women decreased fat mass by $10 \%$ and body mass and soft tissue lean mass by $2.2 \%$, but bone mineral content did not change compared with non-training groups of men and women. Soft tissue lean mass was distributed less in womens arms than in mens both before and after training. The most striking training-induced differences occurred in the tissue composition of the womens arms ( $31 \%$ loss in fat mass without change in lean mass) compared with the legs ( $5.5 \%$ gain in lean mass without change in fat mass).


Figure 28.19 Top. Percentage body fat determined by hydrostatic weighing (density) and MRI scanning (graph created from individual data points presented in the original article). Bottom bar graphs. Distribution of adipose tissue (total, subcutaneous, and nonsubcutaneous) within the various body compartments; arrangement progresses from smallest to largest. The right pie chart displays the relative distribution of adipose tissue in different body regions. (Modified from Sohlstrom A, et al. Adipose tissue distribution as assessed by magnetic resonance imaging and total body fat by magnetic resonance imaging, underwater weighing, and body-water dilution in healthy women. Am J Clin Nutr 1993;58:830.)


Figure 28.20 MRI-determined distribution of body tissues in seven lean (red) and seven obese (blue) females. A. Total body tissues (sum of fat and nonfat tissues). B. Total adipose tissue. C. Subcutaneous adipose tissue. Arrows to the right of the y -axis indicate the four anatomic markers in relation to position on the skeleton. The inset graph displays the relationship between percentage body adipose tissue (using 4 instead of 17 MRI sites) and percentage body fat determined by hydrostatic weighing in obese and lean subjects. (Modified from Fowler PA, et al. Total and subcutaneous adipose tissue in women: the measurement of distribution and accurate prediction of quantity by using magnetic resonance imaging. Am J Clin Nutr 1991;54:18.)

Fat decreased in the trunk by $12 \%$ without change in soft tissue lean mass. The changes for fat mass by MRI and DXA showed close relationships (range between $r=0.72$ and $r=$ 0.92 ). Both techniques also similarly assessed increases in lean leg tissue mass. This experiment reinforced the importance of apprising changes in regional tissue morphology (including total body changes) with an experimental treatmentin this case, the effects of periodized resistance training.

## Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) reliably and accurately quantifies fat and nonbone regional lean body mass, including the mineral content of the bodys deeper bony structures. ${ }^{81,83,96,131,139}$ It has become the accepted clinical tool to assess spinal osteoporosis and related bone disorders. ${ }^{40}$ When used for body composition assessment, DXA does not require
assumptions concerning the biologic constancy of the fat and fat-free components inherent with hydrostatic weighing.

With DXA, two distinct low-energy X-ray beams (short exposure with low radiation dosage) penetrate bone and soft tissue areas to a depth of approximately 30 cm . The subject lies supine on a table so that the source and detector probes slowly pass across the body over a 12 -minute period. Computer software reconstructs the attenuated X-ray beams to produce an image of the underlying tissues and quantify bone mineral content, total fat mass, and FFM. Analysis can include selected trunk and limb regions for detailed study of tissue composition and relation to disease risk, including the effects of exercise training and detraining. ${ }^{94,104,185}$

DXA shows excellent agreement with other independent estimates of bone mineral content. Strong relationships also exist between DXA-determined total body fat and body fat by either densitometry, ${ }^{58,106}$ segmental body composition (upper- and lower-extremity mass), total body potassium, or total body nitrogen ${ }^{107}$ and abdominal adiposity. ${ }^{50}$ Recent studies have focused on body fat estimation by DXA with other methods in young children, ${ }^{36}$ prepubertal children, ${ }^{23,65,149}$ younger and older men ${ }^{8}$ and women, ${ }^{7,118}$ the elderly, ${ }^{54,148}$ and changes during intense resistance training. ${ }^{166}$ Figure 28.21 shows the strong association between percentage body fat estimates by DXA and hydrostatic weighing over a broad age range in men and women. The strength of the prediction decreases for older and fatter subjects but remains within the typical range for comparisons among discrete methodologies. Using a more robust model of body composition assessment, the error is less than $2 \%$ body fat units between DXA and densitometry in the heterogeneous age group of adults shown in the figure. ${ }^{59}$

## INTEGRATIVE QUESTION

Outline your response to a student who asks: Why am I considered overfat by some criteria for obesity while my body fat assessment with other methods falls within normal limits?

## AVERAGE PERCENTAGE BODY FAT

TABLE 28.5 lists average values for percentage body fat in samples of men and women throughout the United States. The column headed $68 \%$ Variation Limits indicates the range of percentage body fat that includes approximately 68 of every 100 persons measured. As an example, the average percentage body fat of $15.0 \%$ for young men from the New York sample includes the $68 \%$ variation limits from 8.9 to $21.1 \%$ body fat. This means that for every 68 of 100 young men measured, percentage fat ranges between 8.9 and $21.1 \%$. Of the remaining 32 young men, 16 possess more than $21.1 \%$ body fat, while 16 other men have a body fat percentage below 8.9. In general, percentage body fat for young adult men averages between 12 and 15\%; the average value for women falls between 25 and $28 \%$.


Figure 28.21 Comparison of total body fat determined by hydrostatic weighing and DXA in men (top) and women (bottom). (Modified from Snead DB, et al. Age-related differences in body composition by hydrodensitometry and dual-energy absorptiometry. J Appl Physiol 1993;74:770.)

## Representative Samples are Lacking

Considerable data describe average body composition for many groups of men and women of different ages and fitness levels and athletic specialties (see Chapter 29). No systematic evaluation exists for the body composition of a representative sample of the general population to warrant establishing norms or precise recommended values for body composition. At this time, it seems appropriate to present average values from various studies of different age groups.

TABLE 28.5 Average Values of Body Fat for Younger and Older Women and Men from Selected Studies

| Study | Age Range | Stature (cm) | Mass (kg) | \% Fat | 68\% Variation Limits |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Younger women |  |  |  |  |  |
| North Carolina, 1962 | 17-25 | 165.0 | 55.5 | 22.9 | 17.5-28.5 |
| New York, 1962 | 16-30 | 167.5 | 59.0 | 28.7 | 24.6-32.9 |
| California, 1968 | 19-23 | 165.9 | 58.4 | 21.9 | 17.0-26.9 |
| California, 1970 | 17-29 | 164.9 | 58.6 | 25.5 | 21.0-30.1 |
| Air Force, 1972 | 17-22 | 164.1 | 55.8 | 28.7 | 22.3-35.3 |
| New York, 1973 | 17-26 | 160.4 | 59.0 | 26.2 | 23.4-33.3 |
| North Carolina, 1975 | - | 166.1 | 57.5 | 24.6 | - |
| Army Recruits, 1986 | 17-25 | 162.0 | 58.6 | 28.4 | 23.9-32.9 |
| Massachusetts, 1998 | 17-31 | 165.2 | 57.8 | 21.8 | 16.7-27.9 |
| Older women |  |  |  |  |  |
| Minnesota, 1953 | 31-45 | 163.3 | 60.7 | 28.9 | 25.1-32.8 |
|  | 43-68 | 160.0 | 60.9 | 34.2 | 28.0-40.5 |
| New York, 1963 | 30-40 | 164.9 | 59.6 | 28.6 | 22.1-35.3 |
|  | 40-50 | 163.1 | 56.4 | 34.4 | 29.5-39.5 |
| North Carolina, 1975 | 33-50 | - | - | 29.7 | 23.1-36.5 |
| Massachusetts, 1993 | 31-50 | 165.2 | 58.9 | 25.2 | 19.2-31.2 |
| Younger men |  |  |  |  |  |
| Minnesota, 1951 | 17-26 | 177.8 | 69.1 | 11.8 | 5.9-11.8 |
| Colorado, 1956 | $17-25$ | 172.4 | 68.3 | 13.5 | 8.3-18.8 |
| Indiana, 1966 | 18-23 | 180.1 | 75.5 | 12.6 | 8.7-16.5 |
| California, 1968 | 16-31 | 175.7 | 74.1 | 15.2 | 6.3-24.2 |
| New York, 1973 | 17-26 | 176.4 | 71.4 | 15.0 | 8.9-21.1 |
| Texas, 1977 | 18-24 | 179.9 | 74.6 | 13.4 | 7.4-19.4 |
| Army Recruits, 1986 | 17-25 | 174.7 | 70.5 | 15.6 | 10.0-21.2 |
| Massachusetts, 1998 | 17-31 | 178.1 | 76.4 | 12.9 | 7.8-19.0 |
| Older men |  |  |  |  |  |
| Indiana, 1966 | 24-38 | 179.0 | 76.6 | 17.8 | 11.3-24.3 |
|  | 40-48 | 177.0 | 80.5 | 22.3 | 16.3-28.3 |
| North Carolina, 1976 | 27-50 | - | - | 23.7 | 17.9-30.1 |
| Texas, 1977 | 27-59 | 180.0 | 85.3 | 27.1 | 23.7-30.5 |
| Massachusetts, 1993 | 31-50 | 177.1 | 77.5 | 19.9 | 13.2-26.5 |

The general trend of these data indicates a distinct tendency for percentage body fat to steadily increase with advancing age. The mechanisms that lead to increased body fat with age are poorly understood. It also remains unanswered to what extent additional fat in older age poses an increased health risk. The trend does not necessarily imply a desirable or normal aging process because participation in vigorous physical activity throughout life frequently blunts body fat accretion with age. ${ }^{164,182,183}$ Regular physical activity maintains or increases bone mass while preserving muscle mass. A sedentary lifestyle, in contrast, increases storage fat and reduces muscle mass. This occurs even if daily caloric intake remains unchanged.

## DETERMINING GOAL BODY WEIGHT

Average values for percentage body fat approximate $15 \%$ for young men and $25 \%$ for young women. In contact sports and activities that require muscular power (e.g., football, sprint swimming, and running), successful performance typically requires a large fat-free body mass with average or below-average body fat. Successful athletes in weight-bearing endurance activities generally possess a relatively light body mass with low body fat.

Proper assessment of body composition, not body weight, determines a persons ideal body weight. For athletes, goal body weight must coincide with optimizing sport-specific measures of physiologic functional capacity and exercise performance. The following equation computes a goal body weight based on a desired percentage body fat level:

Goal body weight $=$ fat-free body mass

$$
\div(1.00-\text { desired } \% \text { fat })
$$

Suppose a $91-\mathrm{kg}$ (200-lb) man, currently with $20 \%$ body fat, wants to know how much fat weight to lose to attain a body fat composition of $15 \%$. The computations progress as follows:

$$
\begin{aligned}
\text { Fat mass } & =91 \mathrm{~kg} \times 0.20 \\
& =18.2 \mathrm{~kg} \\
\text { Fat-free body mass } & =91 \mathrm{~kg}-18.2 \mathrm{~kg} \\
& =72.8 \mathrm{~kg} \\
\text { Goal body weight } & =72.8 \mathrm{~kg}(1.00-0.10) \\
& =72.8 \mathrm{~kg} 0.90 \\
& =80.9 \mathrm{~kg}(178 \mathrm{lb})
\end{aligned}
$$

Goal fat loss $=$ Current body weight - Goal body weight

$$
\begin{aligned}
& =91 \mathrm{~kg}-80.9 \mathrm{~kg} \\
& =10.1 \mathrm{~kg}(22.2 \mathrm{lb})
\end{aligned}
$$

If this athlete lost 10.1 kg of body fat, his new body weight of 80.9 kg would contain fat equal to $10 \%$ of body mass. These calculations assume no change in FFM during weight loss. Moderate caloric restriction plus increased daily energy expenditure through exercise induce fat loss and conserve the FFM. Chapter 30 discusses prudent yet effective approaches to fat loss.

## Summary

1. Standard height-weight tables reveal little about body composition. Studies of athletes clearly show that overweight does not necessarily coincide with excessive body fat.
2. BMI relates more closely to body fat and health risk than simply body mass and stature. BMI still fails to consider the bodys proportional composition.
3. Total body fat consists of essential fat and storage fat. Essential fat contains fat present in bone marrow, nerve tissue, and organs; it is an important component for normal biologic function. Storage fat represents the energy reserve that accumulates as adipose tissue beneath the skin and visceral depots.
4. Storage fat averages $12 \%$ of body mass for men and $15 \%$ for women. Essential fat averages $3 \%$ of body mass for men and $12 \%$ for women. The greater essential fat in females relates to childbearing and hormonal functions.
5. A person probably cannot reduce body fat below the essential fat level and still maintain optimal health.
6. Menstrual dysfunction occurs in athletes who train hard and maintain low body fat levels. This effect relates to the interaction between the physiologic and psychologic stress of regular training, hormonal balance, energy and nutrient intake, and body fat.
7. Delayed onset of menarche in chronically active young females may confer health benefits because such individuals show a lower lifetime occurrence of reproductive organ and other cancers.
8. Popular indirect methods of body composition assessment include hydrostatic weighing and prediction methods that incorporate skinfold and girth measurements.
9. Hydrostatic weighing determines body density with subsequent estimation of percentage body fat. The computation assumes a constant density for the bodys fat and fat-free tissue compartments.
10. The air displacement method of BOD POD provides a reasonable alternative to hydrostatic weighing for body volume determination and subsequent body composition assessment.
11. The error inherent in predicting body fat from wholebody density lies in assumptions concerning the densities of the fat and fat-free components. These densities, especially fat-free body mass, differ from assumed constants because of race, age, and athletic experience.
12. Body composition assessments that use skinfolds and girths show population specificity; they are most accurate with subjects similar to those who participated in the equations original derivation.
13. Hydrated fat-free body tissues and extracellular water facilitate electrical flow compared with fat tissue because of the greater electrolyte content of the fat-free component. Impedance to electric current flow in BIA analysis relates to the bodys fat quantity.
14. Near-infrared interactance should be used with caution to assess body composition in the exercise sciences; this methodology currently lacks verification of adequate validity.
15. Ultrasound, CT, MRI, and DXA indirectly assess body composition. Each has a unique application and special limitations for expanding knowledge of the compositional components of the live human body.
16. Average males possess a body fat content of approximately $15 \%$ and women, $25 \%$. These values from healthy individuals often provide a frame of reference to evaluate body fat of individual athletes and specific athletic groups.
17. Goal body weight computes as fat-free body mass: 1.00 - desired \%fat.

1, References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

Invent Now: Hall of Fame Inventor Profile:
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## Physique, Performance, and Physical Activity

## CHAPTER 29

## CHAPTER OBJECTIVES

- Compare body composition characteristics of average young men and women with elite competitors in endurance running, wrestling, triathlon, professional golf, and weightlifting and bodybuilding
- Give examples of gender differences in world record performances for track and field, weightlifting, cycling, speed skating, and swimming
- Contrast body fat values for male and female competitive swimmers with runners and give possible reasons for the differences
- Summarize body composition characteristics, including body mass index, of early American professional football players and modern-day
counterparts; compare modern professionals with current collegiate players
- Contrast body composition characteristics of elite high school wrestlers and less successful counterparts
> Contrast body composition, girths, and excess muscle mass of male and female bodybuilders
> Compare ratios of fat-free body mass (FFM) to fat mass of female bodybuilders with other elite female athletes
> Discuss the upper limit of FFM in large-sized athletes

Body composition evaluation partitions gross size into two major structural componentsbedy fat and fat-free body mass (FFM). In Chapter 28, we characterized the major physique differences between adult men and women. Pronounced physique differences also exist among participants of the same gender in diverse high skill sports.

Different anthropometric methodologies have quantified physique status. Visual appraisal often describes individuals as small, medium, and large or as thin (ectomorphic), muscular (mesomorphic), or fat (endomorphic). This older approach, termed somatotyping and proposed by psychologist/ physician William H. Sheldon (1898 1977), describes body shape by placing a person into a category such as thin or muscular. Visual appraisal quantifies neither body dimensions (e.g., size of the abdomen or hips) nor how biceps development compares with thigh or calf development. Somatotyping serves as an adjunct method to analyze physique status of world-class athletes ${ }^{4} 6,9$ and familial heritabilities, ${ }^{32,45}$ but in this chapter we focus on the objectively determined body fat and FFM components of body composition. This chapter takes a closer look at the physiques of champion athletes in
different sport and competition categories. Our review quantifies aspects of physique for Olympic competitors, endurance runners, collegiate and professional American football players, triathletes, high school wrestlers, champion male and female bodybuilders, collegiate gymnasts, professional golfers, and NBA professional basketball players. Although some data from the earlier studies on body composition and performance are dated, relatively few newer studies exist. Thus, it remains instructive to cite these data to illustrate basic differences among highly skilled male and female competitors in different sport categories.

## PHYSIQUES OF CHAMPION ATHLETES

Early studies of Olympic competitors linked physique to a high level of sports achievement. ${ }^{9,34}$ Tables 29.1 and 29.2 list the anthropometric characteristics of male and female competitors in the 1964 Tokyo and 1968 Mexico City Olympics. ${ }^{10,21}$ Bone diameters and stature provided estimates of lean body mass and percentage body fat. TABLE 29.3 lists anthropometric data for body mass, stature, and eight skinfolds

TABLE 29.1 Age, Body Size, and Body Composition of Male Athletes Who Competed in Selected Events in the Tokyo and Mexico City Olympics

| Specialty | Event | Olympics | $N$ | Age (y) | Stature (cm) | Mass (kg) | $\mathrm{LBM}^{a}(\mathrm{~kg})$ | Body Fat ${ }^{\text {b }}$ (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Sprint | $\begin{aligned} & 100,200 \mathrm{~m} ; \\ & 4 \times 100 \mathrm{~m} ; \\ & 110-\mathrm{m} \text { hurdles } \end{aligned}$ | Tokyo | 172 | 24.9 | 178.4 | 72.2 | 64.9 | 10.1 |
|  |  | Mexico City | 79 | 23.9 | 175.4 | 68.4 | 62.8 | 8.2 |
| Long-distance running | $\begin{array}{r} 3000,5000 \\ 10,000 \mathrm{~m} \end{array}$ | Tokyo | 99 | 27.3 | 173.6 | 62.4 | 61.5 | 1.4 |
|  |  | Mexico City | 34 | 25.3 | 171.9 | 59.8 | 60.1 | $-0.5^{\text {c }}$ |
| Marathon | 42.2 km | Tokyo | 74 | 28.3 | 170.3 | 60.8 | 59.2 | 2.7 |
|  |  | Mexico City | 20 | 26.4 | 168.7 | 56.6 | 58.1 | 2.7 |
| Decathlon |  | Tokyo | 26 | 26.3 | 183.2 | 83.5 | 68.5 | 18.0 |
|  |  | Mexico City | 8 | 25.1 | 181.3 | 77.5 | 67.1 | 13.4 |
| Jump | High, long, triple jump | Tokyo | 89 | 25.3 | 181.5 | 73.2 | 67.2 | 8.2 |
|  |  | Mexico City | 14 | 23.5 | 182.8 | 73.2 | 68.2 | 6.0 |
| Weight throwing | Shot, discus, hammer | Tokyo | 79 | 27.6 | 187.3 | 101.4 | 71.6 | 29.4 |
|  |  | Mexico City | 9 | 27.3 | 186.1 | 102.3 | 70.7 | 30.9 |
| Swimming | Free, breast, back, butterfly medley | Tokyo | 450 | 20.4 | 178.7 | 74.1 | 65.1 | 12.1 |
|  |  | Mexico City | 66 | 19.2 | 179.3 | 72.1 | 65.6 | 9.0 |
| Basketball | All events | Tokyo | 186 | 25.3 | 189.4 | 84.3 | 73.2 | 13.2 |
|  |  | Mexico City | 63 | 24.0 | 189.1 | 79.7 | 73.0 | 8.4 |
| Gymnastics |  | Tokyo | 122 | 26.0 | 167.2 | 63.3 | 57.0 | 9.9 |
|  |  | Mexico City | 28 | 23.6 | 167.4 | 61.5 | 57.2 | 7.0 |
| Wrestling | Bantam and featherweight | Tokyo | 29 | 27.3 | 163.3 | 62.3 | 54.4 | 12.7 |
|  |  | Mexico City | 32 | 22.5 | 166.1 | 57.0 | 56.3 | 1.2 |
| Rowing | Single and double skulls; pairs, fours, eights | Tokyo | 357 | 25.0 | 186.0 | 82.2 | 70.6 | 14.1 |
|  |  | Mexico City | 85 | 24.3 | 185.1 | 82.6 | 69.9 | 15.4 |

[^51]TABLE 29.2 Age, Body Size, and Body Composition of Female Athletes Who Competed in Selected Events in the Tokyo and Mexico City Olympics

| Specialty | Event | Olympics | $N$ | Age (y) | Stature (cm) | Mass (kg) | $\mathrm{LBM}^{a}(\mathrm{~kg})$ | Body Fat ${ }^{\text {b }}$ (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Sprint | $\begin{aligned} & \text { 100, } 200 \mathrm{~m} ; \\ & 100-\mathrm{m} \text { hurdles } \end{aligned}$ | Tokyo | 85 | 22.7 | 166.0 | 56.6 | 49.6 | 12.4 |
|  |  | Mexico City | 28 | 20.7 | 165.0 | 56.8 | 49.0 | 13.7 |
| Jump | High, long, triple jump | Tokyo | 56 | 23.6 | 169.5 | 60.2 | 51.7 | 14.1 |
|  |  | Mexico City | 12 | 21.5 | 169.4 | 56.4 | 51.7 | 8.4 |
| Weight throwing | Shot, discus, hammer | Tokyo | 37 | 26.2 | 170.4 | 79.0 | 52.3 | 33.8 |
|  |  | Mexico City | 9 | 19.9 | 170.9 | 73.5 | 52.6 | 28.5 |
| Swimming | Free, breast, back, butterfly, medley | Tokyo | 272 | 18.6 | 166.3 | 59.7 | 49.8 | 16.6 |
|  |  | Mexico City | 28 | 16.3 | 164.4 | 56.9 | 48.6 | 14.5 |
| Diving | Spring, high | Tokyo | 65 | 18.5 | 160.9 | 54.1 | 46.6 | 13.9 |
|  |  | Mexico City | 7 | 21.1 | 160.4 | 52.3 | 46.3 | 11.5 |
| Gymnastics | All events | Tokyo | $102$ | $22.7$ | $157.0$ | $52.0$ | $44.4$ | $14.7$ |
|  |  | Mexico City | $21$ | $17.8$ | $156.9$ | $49.8$ | $44.3$ | $11.0$ |

Adapted from De Garay, et al. Genetic and anthropological studies of Olympic athletes. New York: Academic Press, 1974; and Hirata K. Physique and age of Tokyo Olympic champions. J Sports Med Phys Fitness 1966;6:207.
${ }^{a}$ Calculated by Behnkes method: LBM (lean body mass) $=\mathrm{h}^{2} \times 18$, where $\mathrm{h}=$ stature, dm (see reference 2 ).
${ }^{b}$ Body fat $(\%)=($ Body mass - LBM $) /$ Body mass $\times 100$.

TABLE 29.3 Comparison of Body Mass, Stature, and Eight Skinfolds in Male and Female Swimmers, Divers, and Water Polo Athletes at the Sixth World Championships Held in Perth, Australia, 1992

|  | Mass (kg) | Stature (cm) | Tri $^{\boldsymbol{a}}$ | Scap | Supra | Abd | Thi | Calf | Bic | Iliac |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | ---: | ---: | ---: |
| Males |  |  |  |  |  |  |  |  |  |  |
| $\quad$ Swimming | 78.4 | 183.8 | 7.0 | 7.9 | 6.3 | 9.4 | 9.6 | 6.5 | 3.7 | 9.2 |
| Diving | 66.7 | 170.9 | 6.8 | 7.9 | 6.0 | 9.6 | 9.6 | 6.0 | 3.8 | 8.5 |
| Water polo | 86.1 | 186.5 | 9.2 | 9.9 | 8.2 | 14.9 | 12.6 | 7.9 | 4.3 | 13.4 |
| Females |  |  |  |  |  |  |  |  |  |  |
| Swimming | 63.1 | 171.5 | 12.1 | 8.8 | 7.3 | 12.1 | 19.1 | 11.4 | 5.9 | 9.8 |
| Diving | 53.7 | 16.2 | 11.4 | 8.5 | 6.8 | 11.1 | 18.2 | 9.7 | 4.9 | 7.9 |
| Water polo | 64.8 | 171.3 | 15.3 | 10.5 | 9.6 | 17.6 | 23.4 | 13.5 | 7.1 | 12.1 |

Modified from Mazza JC, et al. Absolute body size. In: Carter JE, Ackland TR, eds. Kinanthropometry in aquatic sports. A study of world class athletes. Human Kinetics Sport Science Monograph Series, vol 5. Champaign, IL: Human Kinetics, 1994.
${ }^{a}$ Abbreviations for skinfolds (mm): Tri, triceps; Scap, subscapular; Supra, supraspinale; Abd, abdomen; Calf, midcalf; Bic, biceps; Iliac, iliac crest.
for male and female swimmers, divers, and water polo athletes at the sixth World Championships in Perth, Australia, 1992. Also of interest are the body size differences among different groups of athletes within a particular sport. Figure 29.1 (top) compares the body mass, stature, chest girth, upper- and lower-limb girths, and leg length for 12 male swimmers rated best in the 200- and 400-m free-style with less successful counterparts. The bottom figure also compares selected body size variables between the 12 best $50-100-$, and $200-\mathrm{m}$ female breaststroke swimmers with other competitors. The best male swimmers are heavier and taller and have larger chest, upper-arm, and thigh girths and upper- and lower-limb lengths than counterparts not ranking among the top 12 . The
best female breaststroke swimmers, also taller and heavier, possessed larger arm span, foot and arm lengths, and hand and wrist breadths than less successful competitors.

## Michael PhelpsWorld Champion Swimmer Anomaly

An apparent anomaly in body proportions seems apparent in champion swimmer Michael Phelps, winner of 8 gold medals in the 2008 Beijing Olympics. Phelpss arm span measures 203 $\mathrm{cm}, 10 \mathrm{~cm}$ more than his stature. This exceeds the nearly perfect arm to leg to torso ratios of da Vincis Vitruvian Man (see p. xxvii). This, coupled with his size 14 feet that reportedly



Figure 29.1 Top. Comparison of the body mass, stature, chest and limb girths, and leg length of the best (top 12 ranks) 200and $400-\mathrm{m}$ freestyle male swimmers with the remaining competitors (others). Bottom. Comparison of differences in body size variables including arm span (actual values divided by 4) between the best 50-, 100-, and 200-m female breaststroke swimmers (top 12 ranks) and the rest of the competitors (others). The $y$ axis is in centimeters for all variables except body mass, which is in kilograms. (Modified from Mazza JC, et al. Absolute body size. In: Carter JE, Ackland TR, eds. Kinanthropometry in aquatic sports. A study of world-class athletes. Human Kinetics Sport Science Monograph Series, vol 5. Champaign, IL: Human Kinetics, 1994.)


Michael Phelpseight times Olympic gold champion.
bend 15 degrees farther at the ankle than other swimmers, turn his feet into virtual dolphin-like flippers. The added flexibility apparently applies to his knees and elbows, which should theoretically increase the efficiency of the propulsive characteristics of each stroke. Phelps larger upper body compared to his relatively smaller-proportioned lower body helps to explain his superior thrust through the water at about 4.7 mph , the speed of a brisk walk but not faster than a small goldfish when adjusted for body length (Table 29.4). Even if one accounts for Beijings Water Cube as one of the worlds fastest pools (the 3-m depth is the deepest allowable, and the 10 lanes apparently reduce speed-robbing turbulence), it is difficult to argue that the pools characteristics (or the new

| TABLE 29.4 | Comparison of Swimming <br> Speed in Goldfish and Michael <br> Phelps (10-m Butterfly Time <br> of 50.77 s) |  |
| :--- | :---: | :---: |
| Absolute Speed | Goldfish | Phelps |
| mph | 0.85 | 4.4 |
| $\mathrm{~km} \cdot \mathrm{~h}^{-1}$ | 1.37 | 7.1 |
| Relative Speed, <br> body lengths $\cdot \mathrm{s}^{-1}$ | 4.5 | 1.0 |

Speedo LZR Racer suit worn by the competitors) could explain how Phelps so convincingly demolished existing world records. A cogent argument against the suit providing the edge in these records is that Phelps wore the full-length LZR suit in only three of his eight racesthe $200-\mathrm{m}$ freestyle, the $4 \times 100-\mathrm{m}$, and $4 \times 200-\mathrm{m}$ freestyle relayshe swam without the suit in his five butterfly and individual medley contests. Phelps unique physical dimensions coupled with the most important factorineomparable stroke mechanics honed after many thousands of hours of carefully supervised workouts, obviously played key roles in his extraordinary achievements.

## Gender

Table 29.1 indicates that for the men, basketball players, rowers, and weight throwers were tallest and heaviest; they also possessed the largest FFM and percentage body fat. For example, weight throwers in both Olympiads averaged 30\% body fat, whereas 94 marathon and 133 long-distance runners averaged an exceptionally low $1.6 \%$ body fat. The largest body composition discrepancy within a sports category emerged in comparisons of the Tokyo wrestlers ( $12.7 \%$ body fat) and wrestlers in Mexico City ( $1.2 \%$ body fat). Age, stature, and FFM were similar in both groups, making this difference even more remarkable.

For female Olympians, a relatively low body fat percentage provides the most striking physique characteristic. Except for weight throwers ( $31 \%$ body fat), competitors in the other sports groups approximated the $13.1 \%$ average body fat for all 676 female participants in both Olympiads.

For aquatic athletes (Table 29.3), skinfolds at most sites were larger in females than in males. As noted in Chapter 10, a swimmers morphology alters the horizontal components of lift and drag. Selected anthropometric variables influence the magnitude of propulsive and resistive forces that affect the swimmers forward movement. ${ }^{7,8}$ In well-trained freestyle swimmers, arm length, leg length, and hand and foot sizefactors governed largely by geneticsinfluence stroke length and stroke frequency. ${ }^{18}$

## Fat Free-to-Fat Ratio

Figure 29.2 compares the ratio of FFM to fat mass (FM), derived from the world literature for the specific sport among male and female competitors. The inset tables present data for
average body mass, percentage body fat, and FFM. Male marathon runners and gymnasts have the largest FFM:FM; American football offensive and defensive linemen and shot putters show the smallest ratios. Among females, bodybuilders have the largest FFM:FM values (equal of males), while the smallest FFM:FMs emerge for field-event participants. Surprisingly, female gymnasts and ballet dancers rank intermediate compared with other female sport participants.

## Racial Differences

Racial differences in physique may affect athletic performance. ${ }^{11,55}$ Black sprinters and high jumpers, for example, have longer limbs and narrower hips than white counterparts. From a mechanical perspective, a black sprinter with leg and arm size identical to a white sprinter has a lighter, shorter, and slimmer body to propel. This might confer a more favorable power-to-body mass ratio at any given body size. Greater power output provides an advantage in jumping and sprint running events where generating rapid energy for short durations remains crucial to success. The advantage diminishes somewhat in the throwing events. Compared with whites and blacks, Asian athletes have short legs relative to upper torso components, a dimensional characteristic beneficial in short and longer distance races and in weightlifting. Successful weightlifters of all races compared with other athletic groups have relatively short arms and legs for their stature.

## Percentage Body Fat of Elite Athletes

Considerable literature describes body fat levels of male and female competitive athletes in diverse sports.

## By Category

Figure 29.3 presents six classifications of sports activities based on common characteristics and performance requirements, with percentage body fat rankings within each category for male and female competitors (where applicable). This compendium provides an overview of percentage body fat of athletes within a broad grouping of relatively similar sports.

## Field Event Athletes

Figure 29.4 shows body composition obtained by hydrostatic weighing and anthropometrypercentage body fat, fat weight, FFM, and lean-to-fat ratiofor the 10 top American athletes in the discus, shot put, javelin, and hammer throw 2 years before the 1980 Moscow Olympics. Comparative data describe international elite middle- and long-distance runners (average treadmill $\dot{\mathrm{V}}_{2 \text { max }} 76.9 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \min ^{-1}$ ) and Behnkes reference man. Table 29.5 lists the corresponding data for girth and skinfold anthropometry. Shot putters clearly possessed the largest overall body size (body mass and girths) followed by athletes in the discus, hammer, and javelin throw.

## Female Endurance Athletes

Table 29.6 presents body mass, stature, and body composition of 11 female long-distance runners of national and


Figure 29.2 Comparison of the lean fat ratio among male and female competitors in diverse sports. Values are based on the average body mass and percentage body fat for each sport from various studies in the literature. The lean fat ratio is FFM (kg) $\div$ fat mass ( kg ). Values in the inset tables represent averages for body composition if the literature contained two or more citations about a specific sport. The equation of Siri (Chapter 28) converted body density to percentage body fat.


Figure 29.3 Percentage body fat in athletes grouped by sport category. The value for males is displayed within the bar (in red) when a corresponding value exists for females (yellow). The values for percentage body fat (from body density by the Siri equation) represent averages from the literature.


Figure 29.4 Body composition determined by hydrostatic weighing of the top 10 American male athletes in the discus, shot put, javelin, and hammer throw. Data collected by two of the authors (FK and VK) at a 1978 U.S. Olympic minicamp at the University of Houston, Houston, TX. Athletes include former gold medalist Wilkins (discus) and world record holder Powell (discus). (Data for the international elite middle- and long-distance runners from Pollock ML, et al. Body composition of elite class distance runners. Ann NY Acad Sci 1977;301:361. Reference man (Ref man) data from Behnkes model in Chapter 28.)

TABLE 29.5 Skinfold and Girth Anthropometry of the Top 10 American Athletes in the Discus, Shot Put, Javelin, and Hammer Throw

| Measurement ${ }^{\text {a }}$ | Discus | Shot Put | Javelin | Hammer | Runners | Ref Man |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Body mass, kg | 108.2 | 112.3 | 90.6 | 104.2 | 63.1 | 70.0 |
| Stature, cm | 191.7 | 187.0 | 186.0 | 187.3 | 177.0 | 174.0 |
| Skinfolds, mm |  |  |  |  |  |  |
| Triceps | 13.0 | 15.0 | 11.9 | 12.7 | 5.0 | - |
| Scapular | 18.0 | 23.8 | 12.5 | 21.5 | 6.4 | - |
| Iliac | 24.5 | 29.6 | 17.0 | 27.4 | 4.6 | - |
| Abdomen | 25.6 | 31.4 | 18.4 | 29.1 | 7.1 | - |
| Thigh | 16.4 | 15.7 | 13.3 | 17.3 | 6.1 | - |
| Girths, cm |  |  |  |  |  |  |
| Shoulders | 129.8 | 133.3 | 121.5 | 127.4 | 106.1 | 110.8 |
| Chest | 113.5 | 118.5 | 104.6 | 111.3 | 91.1 | 91.8 |
| Waist | 94.1 | 99.1 | 86.6 | 94.8 | 74.6 | 77.0 |
| Abdomen | 97.5 | 101.5 | 87.8 | 98.0 | 74.2 | 79.8 |
| Hips | 110.4 | 112.3 | 102.0 | 108.7 | 87.8 | 93.4 |
| Thighs | 66.3 | 69.4 | 61.5 | 67.3 | 51.9 | 54.8 |
| Knees | 41.5 | 42.9 | 40.0 | 41.0 | $36.2{ }^{\text {b }}$ | 36.6 |
| Calves | 42.6 | 43.6 | 39.5 | 41.5 | 35.4 | 35.8 |
| Ankles | 25.4 | 24.9 | 24.1 | 24.3 | 21.0 | 22.5 |
| Biceps | 41.8 | 42.2 | 37.7 | 39.9 | 28.2 | 31.7 |
| Forearms | 33.1 | 33.7 | 30.8 | 32.4 | 26.4 | 26.4 |
| Wrists | 18.7 | 18.9 | 18.2 | 18.4 | 16.0 | 17.3 |
| Diameters, cm |  |  |  |  |  |  |
| Biacromial | 44.5 | 43.8 | 43.2 | 44.8 | 39.5 | 40.6 |
| Chest | 33.1 | 33.7 | 30.8 | 32.6 | 31.3 | 30.0 |
| Bi-iliac | 31.3 | 31.2 | 29.6 | 30.4 | 28.0 | 28.6 |
| Bitrochanter | 35.5 | 34.9 | 33.7 | 34.8 | 32.2 | 32.8 |
| Knee | 10.2 | 10.5 | 10.0 | 10.2 | 9.5 | 9.3 |
| Wrist | 6.3 | 6.2 | 6.0 | 6.2 | 5.6 | 5.6 |
| Ankle | 7.6 | 7.6 | 7.5 | 7.4 | - | 7.0 |
| Elbow | 7.6 | 7.6 | 7.6 | 7.2 | - | 7.0 |

${ }^{a}$ Details about measurement procedures from Katch FI, Katch VL. The body composition profile: techniques of measurement and applications. Clin Sports
Med 1984;3:31. Data correspond to the athletic groups presented in Fig. 29.4.
${ }^{b}$ Not measured; value computed from the ratio for the reference man calf to knee.
international caliber. ${ }^{59}$ The runners averaged $15.2 \%$ body fat (hydrostatic weighing), similar to reported data for high school cross-country runners ${ }^{2}$ but considerably lower than the $26 \%$ body fat for sedentary females of the same age, stature, and body mass. ${ }^{28}$ Compared with other athletic groups, the runners have relatively less fat than collegiate basketball players ( $20.9 \%$ ), ${ }^{48}$ gymnasts ( $15.5 \%$ ), ${ }^{49}$ younger distance runners $(18 \%),{ }^{34}$ swimmers $(20.1 \%),{ }^{30}$ tennis players ( $22.8 \%$ ), ${ }^{30}$ or triathletes. ${ }^{22}$

Interestingly, the runners average body fat equaled the $15 \%$ value generally reported for nonathletic males. The 6 to $9 \%$ body fat levels of several apparently healthy runners in Table 29.6 falls within the range for topflight male endurance athletes. The leanest women in the population, based on Behnkes reference standards, have essential fat equal to 12 to $14 \%$ of body
mass. This apparent discrepancy between estimated fat content of distance runners and the theoretical lower limit for body fat in women requires further study. Note the relatively high body fat (35.4\%) for one of the best runners suggests that, at least for this runner, other factors override the dead weight and the regulatory limitations to distance running imposed by excess fat.

## Male Endurance Athletes

Table 29.7 presents body composition data for 11 male elite middle- and long-distance runners and 8 elite marathoners. The group included Steve Prefontaine, former American record holder in the 800- and 1500-m runs, and Frank Shorter, the 1976 Olympic gold medalist in the marathon. A representative sample of 95 untrained college-aged men provides comparison data.

TABLE 29.6 Body Composition of Female Endurance Runners

| Subject | Age <br> (y) | Stature (cm) | Mass (kg) | FFM <br> (kg) | Body Fat |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  | (kg) | (\%) |
| $1{ }^{a}$ | 24 | 172.7 | 52.6 | 49.5 | 3.1 | 5.9 |
| $2^{\text {b }}$ | 26 | 159.8 | 71.5 | 46.2 | 25.3 | 35.4 |
| $3{ }^{\text {c }}$ | 28 | 162.6 | 50.7 | 47.6 | 3.1 | 6.1 |
| 4 | 31 | 171.5 | 52.0 | 47.3 | 4.7 | 9.0 |
| 5 | 33 | 176.5 | 61.2 | 50.8 | 10.4 | 17.0 |
| 6 | 34 | 166.4 | 52.9 | 44.8 | 8.1 | 15.2 |
| 7 | 35 | 168.4 | 55.0 | 48.7 | 6.3 | 11.6 |
| 8 | 36 | 164.5 | 53.1 | 44.3 | 8.8 | 16.6 |
| 9 | 36 | 182.9 | 61.5 | 50.4 | 11.1 | 18.1 |
| 10 | 36 | 182.9 | 65.4 | 55.7 | 9.7 | 14.8 |
| 11 | 37 | 154.9 | 53.6 | 44.0 | 9.6 | 18.0 |
| $\overline{\text { Average }}$ | 32.4 | 169.4 | $\overline{57.2}$ | 48.1 | 9.1 | $\underline{15.2}$ |

From Wilmore JH, Brown CH. Physiological profiles of women distance runners. Med Sci Sports 1974;6:178.
${ }^{a}$ Worlds best time in marathon (2:49:40) as of 1974
${ }^{b}$ Worlds best time in 50-mile run (7:04:31); established 18 months after the body composition evaluation.
${ }^{c}$ Noted U.S. distance runner. Five consecutive national and international cross-country championships.

TABLE 29.7 Body Composition Characteristics of Elite Male Middle- and Long-Distance Runners and Elite Marathoners

| Group | Stature (cm) | Mass (kg) | $\begin{aligned} & \text { Density } \\ & \left(\mathrm{g} \cdot \mathrm{~cm}^{-3}\right) \end{aligned}$ | Body Fat (\%) | FFM <br> (kg) | Fat Mass (kg) | $\begin{gathered} \text { Sum } 7 \\ \text { Skinfolds (mm) } \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Distance runners |  |  |  |  |  |  |  |
| Brown | 187.3 | 72.10 | 1.07428 | 10.8 | 64.31 | 7.79 | 53.0 |
| Castaneda | 178.6 | 63.34 | 1.09102 | 3.7 | 61.00 | 2.34 | 32.5 |
| Crawford | 171.8 | 58.01 | 1.09702 | 1.2 | 57.31 | 0.70 | 32.5 |
| Geis | 179.1 | 66.28 | 1.07551 | 10.2 | 59.52 | 6.76 | 49.0 |
| Johnson | 174.6 | 61.79 | 1.08963 | 4.3 | 59.13 | 2.66 | 35.5 |
| Manley | 177.8 | 69.10 | 1.09642 | 1.5 | 68.06 | 1.04 | 32.0 |
| Ndoo | 169.3 | 53.97 | 1.08379 | 6.7 | 50.35 | 3.62 | 33.5 |
| Prefontaine | 174.2 | 68.00 | 1.08842 | 4.8 | 64.74 | 3.26 | 38.0 |
| Rose | 175.6 | 59.15 | 1.08248 | 7.3 | 54.83 | 4.32 | 31.5 |
| Tuttle | 176.8 | 61.44 | 1.09960 | 0.2 | 61.32 | 0.12 | 31.5 |
| Mean | 170.5 | 60.92 | 1.08916 | 4.5 | 58.18 | 2.74 | 34.5 |
| Marathon runners |  |  |  |  |  |  |  |
| Cusack | 174.6 | 64.19 | 1.08096 | 7.9 | 59.12 | 5.07 | 45.5 |
| Galloway | 180.9 | 65.76 | 1.08419 | 6.6 | 61.42 | 4.34 | 43.0 |
| Kennedy | 167.0 | 56.52 | 1.09348 | 2.7 | 54.99 | 1.53 | 37.0 |
| Moore | 184.1 | 64.24 | 1.09193 | 3.3 | 62.12 | 2.12 | 37.0 |
| Pate | 179.6 | 57.28 | 1.09676 | 1.3 | 56.54 | 0.74 | 32.5 |
| Shorter | 178.4 | 61.17 | 1.09475 | 2.2 | 59.82 | 1.35 | 45.0 |
| Wayne | 172.1 | 61.61 | 1.07859 | 8.9 | 56.13 | 5.48 | 42.5 |
| Williams | 177.2 | 66.07 | 1.09569 | 1.8 | 64.88 | 1.19 | 41.5 |
| Mean | 176.8 | 62.11 | 1.08954 | 4.3 | 59.38 | 2.73 | 40.5 |

Data from Pollock ML, et al. Body composition of elite class distance runners. Ann NY Acad Sci 1977;301:361.

Both groups of runners have extremely low body fat values considering that essential fat theoretically constitutes about $3 \%$ of body mass. Clearly, these competitors represent the lower end of the lean-to-fat continuum for topflight endurance athletes. This physique characteristic most likely influences success in distance running. This makes sense for several reasons. First, effective heat dissipation during running maintains thermal balanceexcess fat thwarts heat dissipation. Second, excess body fat provides dead weight; it adds directly to exercise energy cost without contributing propulsive energy.

For body dimensions and structure, male distance runners generally have smaller girths and bone diameters than untrained males. ${ }^{9}$ Structural differences, particularly bone diameters, reflect a genetic influence similar to the distinct anthropometric characteristics of aquatic athletes (see Fig. 29.1). The best long-distance runners inherit a slight build with well-proportioned skeletal dimensions. The prime ingredients for a champion include a genetically optimal physique profile blended with a lean body composition, highly developed aerobic system, optimal distribution of muscle fiber architecture, and proper psychologic mind-set for protracted intense training. Interestingly, the body size and composition (length of lower limbs, skinfold thicknesses, circumference of extremities, skeletal muscle mass, BMI, and percentage body fat) and training volume (weekly training hours, running years, the number of finished marathons) of male Caucasiam ultraendurance runners is not as important as their personal best marathon time in predicting performance in a 24 -hour endurance race. ${ }^{33}$

## INTEGRATIVE QUESTION

Discuss the physiologic and anthropometric characteristics necessary for successful endurance running performance.

Triathletes. The triathlon combines continuous endurance performance in swimming, bicycling, and running. The extreme triathlon, the ultraendurance Ironman competition, requires competitors to swim $3.9 \mathrm{~km}(2.4 \mathrm{mi})$, bicycle $180.2 \mathrm{~km}(112 \mathrm{mi})$, and run a standard $42.2-\mathrm{km}(26.2-\mathrm{mi})$ marathon. The course records for the Ironman triathlon in Kailua-Kona, Hawaii, stand at 8:15:34 for men (Chris McCormack, 2007) and 9:6:23 for women (Chrissie Wellington, 2008). The serious triathletes training averages nearly 4 hours daily, covering a total of 280 miles per week by swimming 7.2 miles ( $30: 00 \mathrm{~min}$ per mi pace), bicycling 227 miles ( 18.6 mph ), and running 45 miles ( $7: 42$ min per mi pace). ${ }^{42}$ Percentage body fat of six male and three female participants in the 1982 Ironman triathlon ranged between 5.0 and $11.3 \%$ for men and 7.4 and $17.2 \%$ for women. Body fat averaged $7.1 \%$ for the top 15 male finishers, with corresponding $\dot{\mathrm{V}}_{2 \text { max }}$ of $72.0 \mathrm{~mL} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$. Triathletes body fat content and aerobic capacity is comparable to other
athletes in single endurance sports, ${ }^{44}$ with an overall physique most closely resembling that of elite cyclists ${ }^{43}$ or swimmers ${ }^{37}$ rather than runners. Aerobic capacity of these athletes during swimming consistently averages below values during treadmill running or stationary cycling. ${ }^{35}$ Significant reductions occurred in percentage body fat and skeletal muscle mass following one ultraendurance event where athletes swam 11.6 km , cycled 540 km , and ran 126.6 km within 58 hours. ${ }^{1}$

A longitudinal study evaluated the effects of a triathlon season on bone dynamics and hormonal status in seven male competitive triathletes at the beginning of training and 32 weeks later. ${ }^{39}$ Total and regional bone mineral density (BMD) was determined by dual-energy X-ray absorptiometry, and specific biochemical markers assessed bone turnover. The triathlon season had a small but favorable effect on BMD at the lumbar spine and skull, but no effect on total body or proximal femur BMD. No changes occurred in hormonal levels.

## Swimmers Versus Runners

Male and female competitive swimmers generally have higher body fat levels than distance runners, despite swim trainings considerable energy requirement. The cool water of the training environment generally produces lower core temperatures than equivalent land exercise. A lower core temperature may prevent the depressed appetite that often accompanies intense training on land.

Limited evidence indicates similar daily energy intake for male collegiate swimmers ( 3380 kCal ) and distance runners ( 3460 kCal ), which balances training energy expenditure. In contrast, female swimmers averaged a higher daily energy intake of 2490 kCal compared with 2040 kCal for running counterparts. ${ }^{27}$ Swimmers had higher estimated daily energy expenditure than runners. The swimmers energy expenditure surpassed energy intake, placing them in a slightly negative energy balance. Thus, a positive energy balance (intake greater than output) cannot explain typically higher body fat levels in male (12\%) and female (20\%) swimmers than in male ( $7 \%$ ) and female ( $15 \%$ ) runners. Subsequent research from the same laboratory evaluated energy expenditure and fuel use for swimmers and runners during each form of training ( 45 min at 75 to $80 \% \dot{\mathrm{~V}} \mathrm{O}_{2 \max }$ ) and 2 hours recovery. ${ }^{14}$ The hypothesis assumed that differences in hormonal response and substrate catabolism between the two exercise modes accounted for body fat differences between groups. The results indicated that the small between-group differences in energy expenditure, substrate use, and hormone levels could not account for body fat differences.

Future research must determine whether real differences in physiologic response to land and water training account for body composition differences between swimmers and runners. An alternative explanation suggests that self-selection causes those individuals with higher body fat levels to compete in swimming. Excess body fat presents a liability to

## FOCUS ON RESEARCH

## Body Composition Analysis by Dissection

Clarys JP, et al. Gross tissue weights in the human body by cadaver dissection. Hum Biol 1984;56:459.
$>$ Chemical and anatomic dissection procedures provide two direct methods to study human body composition. The chemical method quantifies body water, lipid, protein, and various mineral elements in different tissues and the whole body. Anatomic dissection partitions the body into components including skin, muscle, adipose tissue, bone, and whole organs. Since 1940, the body composition literature reveals only eight complete analyses of adult humans, with only three done by chemical methods.

Until the research of Clarys and colleagues, no comparisons existed between indirect (body density assessment) and direct dissection assessment of body composition. These researchers used anthropometry, radiography, photogrammetry, densitometry, and complete anatomic dissection of 25 cadavers to determine the gross tissue mass of skin, adipose tissue, muscle, bone, and vital organs (see figure). The cadavers ranged in age from 55 to 94 years and included 12 embalmed ( 6 male, 6 female) and 13 nonembalmed ( 6 male, 7 female) whites. For each cadaver, analysis included removing skeletal muscle and other major organs (brain, heart, lungs, liver, kidneys, and spleen). Bones were then separated at their articulations and scraped to leave surfaces free of muscle and adipose tissue. Muscle included the ligaments, and bone retained the cartilage of any articular surface. Airtight plastic buckets stored all dissected tissues including scrapings. The tissues were weighed to within 0.1 g and their densities determined. Complete cadaver dissection took approximately 15 hours and required a team of 10 to 12 anatomists and kinesiologists.

The figure shows an average adipose tissue mass of $40.5 \%$ of total body mass in females and $28.1 \%$ in males. The researchers introduced the concept of adipose tissue-free weight (ATFW)the whole-body mass minus the mass of all dissectible adipose tissue (adipose tissue contains about $83 \%$ pure fat). Muscle accounted for $52 \%$ of the ATFW in males and $48.1 \%$ in females, while bone constituted $19.9 \%$ of ATFW in males and $21.3 \%$ in females. Combining the data for males and females, the average proportion of the ATFW included $8.5 \%$ skin, $50.0 \%$ muscle, and $20.6 \%$ bone.

Densitometry to estimate the fat and fat-free mass (FFM) assumes a constant density for the FFM. This in turn requires that the proportions of the FFM compo-nentsfat-free muscle, fat-free adipose tissue, fat-free bone, and other fat-free tissuesremain unchanged from one person to another, including the densities for each tissue. Although Clarys research did not include measures of whole-body fat, considerable variation existed in the ATFW. The extent of the variation challenges the important assumption of a constant density for the bodys FFM when using hydrostatic weighing to assess body fat.


Various tissues in the adult body expressed as a percentage of total body mass. Body mass in kg .

TABLE 29.8 Body Compositions of Collegiate and Professional Football Players Grouped by Position

| Position ${ }^{\text {a }}$ | Level | N | Stature (cm) | Mass (kg) | Body Fat (\%) | FFM (kg) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Defensive backs | St. Cloud ${ }^{\text {b }}$ | 15 | 178.3 | 77.3 | 11.5 | 68.4 |
|  | U Mass ${ }^{\text {c }}$ | 12 | 179.9 | 83.1 | 8.8 | 76.8 |
|  | USC ${ }^{d}$ | 15 | 183.0 | 83.7 | 9.6 | 75.7 |
|  | Gettysburg ${ }^{e}$ | 16 | 175.9 | 79.8 | 13.6 | 68.9 |
|  | Pro, modern ${ }^{f}$ | 26 | 182.5 | 84.8 | 9.6 | 76.7 |
|  | Pro, older ${ }^{\text {g }}$ | 25 | 183.0 | 91.2 | 10.7 | 81.4 |
| Offensive backs and receivers | St. Cloud | 15 | 179.7 | 79.8 | 12.4 | 69.6 |
|  | U Mass | 29 | 181.8 | 84.1 | 9.5 | 76.4 |
|  | USC | 18 | 185.6 | 86.1 | 9.9 | 77.6 |
|  | Gettysburg | 18 | 176.0 | 78.3 | 12.9 | 68.2 |
|  | Pro, modern | 40 | 183.8 | 90.7 | 9.4 | 81.9 |
|  | Pro, older | 25 | 183.0 | 91.7 | 10.0 | 87.5 |
| Linebackers | St. Cloud | 7 | 180.1 | 87.2 | 13.4 | 75.4 |
|  | U Mass | 17 | 186.1 | 97.1 | 13.1 | 84.2 |
|  | USC | 17 | 185.6 | 98.8 | 13.2 | 85.8 |
|  | Gettysburg |  | - | - | - - |  |
|  | Pro, modern | 28 | 188.6 | 102.2 | 14.0 | 87.6 |
| Offensive linemen and tight ends | St. Cloud | 13 | 186.0 | 99.2 | 19.1 | 79.8 |
|  | U Mass | 23 | 187.5 | 107.6 | 19.5 | 86.6 |
|  | Gettysburg | 15 | 182.6 | 110.4 | 26.2 | 81.0 |
|  | USC | 25 | 191.1 | 106.5 | 15.3 | 90.3 |
|  | Pro, modern | 38 | 193.0 | 112.6 | 15.6 | 94.7 |
| Defensive linemen | St. Cloud | 15 | 186.6 | 97.8 | 18.5 | 79.3 |
|  | U Mass | 8 | 188.8 | 114.3 | 19.5 | 91.9 |
|  | USC | 13 | 191.1 | 109.3 | 14.7 | 93.2 |
|  | Gettysburg | 11 | 178.0 | 99.4 | 21.9 | 77.6 |
|  | Pro, modern | 32 | 192.4 | 117.1 | 18.2 | 95.8 |
|  | Pro, older | 25 | 185.7 | 97.1 | 14.0 | 83.5 |
| All positions | St. Cloud | 65 | 182.5 | 88.0 | 15.0 | 74.2 |
|  | U Mass | 91 | 184.9 | 97.3 | 13.9 | 83.2 |
|  | USC | 88 | 186.6 | 96.6 | 11.4 | 84.6 |
|  | Gettysburg | 60 | 178.0 | 90.6 | 18.1 | 73.3 |
|  | Pro, modern | 164 | 188.1 | 101.5 | 13.4 | 87.3 |
|  | Pro, older | 25 | 183.1 | 91.2 | 10.4 | 81.3 |
|  | Dallas-Jets ${ }^{h}$ | 107 | 188.2 | 100.4 | 12.6 | 87.7 |

[^52]energy cost and thermoregulation during weight-bearing exercise on land, yet contributes importantly to buoyancy and perhaps to hydrodynamic economy in swimming from reduced drag forces.

## American Football Players

The first detailed body composition analyses of American professional football players in the early 1940s
demonstrated the inadequacy of determining a persons optimal body mass from height weight standards (see Focus on Research, Chapter 28). ${ }^{57}$ The body fat content of the players averaged only $10.4 \%$ of body mass, while FFM averaged 81.3 kg . Certainly these men were heavy but not fat. The heaviest lineman weighed $118 \mathrm{~kg}(17.4 \%$ body fat; 97.7 kg FFM), whereas the lineman with the most body fat (23.2\%) weighed 115.4 kg . Body mass of a defensive back with the least fat ( $3.3 \%$ ) was 82.3 kg with an FFM of 79.6 kg .

Table 29.8 presents a clearer picture of average values for body mass, stature, percentage body fat, and FFM of college and professional football players grouped by position. ${ }^{58,60}$ The Pro, older group consists of 25 players from the 1942 Washington Redskins, the first professional players measured for body composition by hydrostatic weighing. The Pro, modern group consists of 164 players from 14 teams in the National Football League (NFL; 69\% veterans, $31 \%$ rookies). Some 107 members of the 1976 to 1978 Dallas Cowboys and New York Jets make up the third group. Four groups of collegiate players include candidates for spring practice at St. Cloud State College in Minnesota, the University of Massachusetts (U Mass), and Division III Gettysburg College, and teams from the University of Southern California (USC), 1973 to 1977, national champions and participants in two Rose Bowls. Body composition measurements for this data set featured the criterion hydrostatic weighing with correction for measured residual lung volume.

One would generally expect modern-day professional players to have a larger body size at each position than a representative collegiate group. This occurred for comparisons with St. Cloud and U Mass players, but the USC players generally maintained a physique similar to modern professionals. With the exception of defensive linemen, the USC players at each position showed nearly the same body fat content as current professionals but they weighed less. For FFM, the USC players weighed no more than 4.4 kg less than professionals at each position. The average defensive lineman in the NFL outweighed his USC counterpart in FFM by only 1.8 kg . Total body mass of the professional linemen, however, exceeded USC counterparts, primarily because the professionals possessed $18.2 \%$ body fat versus the collegians $14.7 \%$. These data suggest that elite college and professional players maintain similar body size and body composition.

As a group, professional players of almost 75 years ago were lower in body fat ( $10.4 \%$ ), shorter, and had lower total body mass and FFM than professionals of 30 years ago. The exceptions, defensive and offensive backs and receivers, were almost identical to current players in body size and composition. The biggest differences in physique emerged for the defensive linemen; modern players were 6.7 cm taller, 20 kg heavier, fatter by 4.2 percentage points of body fat, and had 12.3 kg more FFM. Obviously, bigness was not an important factor in line play during the 1940 s. To illustrate this point, Figure 29.5A shows the average body mass for all roster players in the NFL ( $N=51,333$ ) over a 76-year period. ${ }^{29}$ From 1920 to 1985,
offensive linemen were the heaviest players; this changed beginning with the 1990 season, when defensive linemen achieved the same body mass as offensive linemen and then surpassed them. Although the body mass for offensive linemen appeared to have leveled off at nearly 280 pounds, defensive linemen continued to increase in body weight, particularly from 1990 to 1996, when they averaged 16 pounds more (double the weight gain for offensive linemen for the comparable period). On average, offensive linemen were 1.3 pounds per year heavier from 1920 to 1995. At this rate of increase, they should have attained 300 plus pounds by the year 2007 (with an average height of 6 ft 8 in .)! At this size, BMI would be 35.2 , classifying them as high for disease risk (see Fig. 28.1). Not surprisingly, the data for the height weight statistics for the 2007 (and 2008) Super Bowl offensive and defensive lines exceeded these predictions, where average body mass exceeded 300 pounds. This comparison clearly placed the team BMI values of 37.0 and 37.5 in the obese category ( TABLE 29.9).

The BMI data for 2168 NFL players based on 2004 team rosters were consistent with the data presented in Figure 29.5 and Table 29.9almost all of the players had a BMI that exceeded 25 ( $97 \%$ ), $56 \%$ had BMIs greater than $30,26 \%$ had BMIs greater than 35 , and $3 \%$ had BMIs greater than $40 .{ }^{19}$ Compared to 20- to 39 -year-old men in a 19992002 national survey, the percentage of NFL players within the same age range with a BMI of 30 or greater was twice that of the national sample ( $56 \%$ vs. $23 \%$ ). The percentage of players with a BMI of 40 or greater was similar to that among 20- to 39 -year-old men in a 19992002 survey ( $3.0 \%$ vs. $3.7 \%$ ). Compared to the NIH classification categories of obesity (Chapter 30), 564 players ( $36 \%$ of the sample) qualified as obesity class 2 , with 65 players in obesity class 3 . The authors concluded, as have we based on the most recent BMI data for NFL players, that the high prevalence of obesity (overweight based on BMI) in this group of large men warrants further investigation to determine the long-term health consequences of excessive weight compared to stature. The roster data for each of the 2007 and 2008 NFL teams make this very point-large-sized athletes, in the short term, are at higher-thannormal risk for a variety of diseases based on their body size. It also may be of interest to note that the top 50 NFL running backs of all time from 1970 to 2007 (based on total yards rushed), had an average BMI of 29.6 (range 35.125 .8 ); it was only slightly higher at 29.7 for the top ten rushers (www.pro-football-reference.com/blog/?p=489). The relationship between total yards rushed and BMI for these 50 exceptional running backs was $r=0.14$, indicating that a players BMI is not related to on-field achievements. This low correlation is due in part to the relatively low variance in BMI among these athletes.

A Worrisome Trend Even Among Less Skilled and Younger Players. Exceptionally high BMIs also occur at less elite levels of collegiate competition. The average BMI of 33.1 for the Division III 1999 Gettysburg offensive line $(N=15)$ ( 29.9 for 2000 offensive line, $N=13$ ), ${ }^{50}$ and the BMI of 31.7 for other NCAA Division III American football



Figure 29.5 A. Average body weight by position for all roster players in the NFL between 1920 and 1995. B. Average body weight of all roster offensive and defensive linemen in the NFL in 1994. Team rankings progress from the heaviest to lightest body weight for the teams offensive linemen. (From active team rosters for 28 NFL teams as of the first regular-season weekend, September 4 5, 1994). The comparison body weight data for the pro offensive and defensive line (1977) shown in the inset box are combined data for the New York Jets and Dallas Cowboys football teams (collected by textbook authors FK and VK). The 1942 data were provided by Dr. Albert Behnke from his studies of the Washington Redskins. (Data courtesy of the National Football League public relations department.)

TABLE 29.9 Average Body Mass and Stature for the 2007 NFL Super Bowl Offensive and Defensive Linemen

| Variable | Colts | Bears |
| :--- | :--- | :--- |
| Body mass | $301.3 \mathrm{lbs}(136.6 \mathrm{~kg})$ | $302.2 \mathrm{lbs}(137.5 \mathrm{~kg})$ |
| Stature | $75.1 \mathrm{in} .(190.8 \mathrm{~cm} ;$ | $75.9 \mathrm{in} .(192.8 \mathrm{~cm} ;$ |
|  | $1.908 \mathrm{~m})$ | $1.928 \mathrm{~m})$ |
| BMI, $\mathrm{kg} \cdot \mathrm{m}^{-2}$ | 37.5 | 37.0 |
| BMI classification | Obese | Obese |

Source: 2006 team rosters; obese $=\mathrm{BMI}>30.0$;
normal weight $=$ BMI 22.025 .9
linemen ( $N=26$; 1994 1995) raises similar concern about potential health risks (e.g., high blood pressure, insulin resistance, and type 2 diabetes) for such large young men (stature: 1.84 m ; body mass: 107.2 kg ) and long-term outlooks remain undetermined but certainly are not encouraging. ${ }^{46}$ At the high school level, the BMI of Parade magazines All-American football teams increased dramatically beginning
in the early 1970s through 1989 and then further increased in rate of gain to the year 2004. ${ }^{56}$ The plot in Figure 29.6 shows a clear shift at 1972 in the slope of the regression line (yellow line) relating BMI to year of competition compared with age-matched individuals from large-scale epidemiologic normative data (red line). This shift toward a higher BMI coincided with either improved nutrition and training and/or the emerging prevalence among high school athletes of performance-enhancing drugs (chiefly anabolic steroids). ${ }^{3}$ Particularly disturbing are the most recent 2008 data for high school offensive and defensive linemen, for which the BMI averaged 34, almost the same as the average 2004 BMI value. For the last data point for the Parade magazine 2008 high school football players, the BMI has in just 8 years increased dramatically to now exceed the average values for the 2007 Bowl Championship Series (BCS) National Champion collegiate linemen and both 2007 Super Bowl teams!

## Division I Big Ten Collegiate Football Players 20042005

A unique data set exists for Division I Big Ten collegiate football players from 2004 2005. Forty-three percent


High school football players $\quad \square$ Nonathletic peers
Figure 29.6 BMIs of high school football players over time compared with nonathlete counterparts.

## IN A PRACTICAL SENSE

## Predicting Body Fat from Skinfolds, Girths, and BIA Measurements for Different Athletic Groups

Appropriate assessment of body composition allows determination of optimal body weight for competition, comparisons between athletes within the same sport, and monitoring changes in the bodys lean and fat components resulting from dietary modification and/or exercise training. A valid appraisal of body composition also provides an important first step in identifying potential eating disorders and formulating nutritional counseling. In the absence of body fat appraisal by hydrostatic weighing, predictions using skin-
folds and/or girth measurements and bioelectric impedance analysis (BIA) have been used for diverse athletic groups.

The bodys fat-free component can vary, making multicomponent models most effective to convert whole-body density to percentage body fat. The accompanying table presents populationspecific skinfold, anthropometric (girth), and BIA equations for body composition assessment of athletes in general and in specific sport categories.
${ }^{\text {a }}$ Use the following formulas to convert body density (Db) to \% body fat (BF): Men \%BF = [(4.95/Db) - 4.50] X 100; Women \%BF = [(5.01/Db) - 4.57] X 100;
Boys $(7-12 y) \% B F=[(5.30 / D b)-4.89] \times 100$; Boys $(13-16 y) \% B F=[(5.07 / D b)-4.64] \times 100$; Boys $(17-19 y) \% B F=[(4.99 / D b)-4.55] \times 100$.
${ }^{\mathrm{b}} 4$ SKF $(\mathrm{mm})=$ sum of four skinfolds: triceps + anterior suprailiac + abdomen + thigh. ${ }^{\mathrm{C}} 7 \mathrm{SKF}(\mathrm{mm})=$ sum of seven skinfolds: chest + midaxillary + triceps

+ subscapular + abdomen + anterior suprailiac + thigh. ${ }^{\text {d }} 7 \mathrm{SKF}(\mathrm{mm})=$ subscapular + triceps + chest + midaxillary + suprailiac + abdominal + thigh;
gender $=0$ for female, 1 for male; race $=0$ for white, 1 for black. ${ }^{\mathrm{e}} \mathrm{HT}=$ height ( cm ); $\mathrm{R}=$ resistance $(\Omega)$; Xc = reactance ( $\Omega$ ); $\mathrm{BW}=$ body weight (kg);
$C=$ circumference $(\mathrm{cm})$; thigh $(\mathrm{cm})$ at the gluteal fold; $A B(\mathrm{~cm})$ : average abdominal circumference $=\left[\left(A B_{1}+A B_{2}\right) / 2\right]$, where $A B_{1}(\mathrm{~cm})=$ abdominal circumference anteriorly midway between the xyphoid process of the sternum and umbilicus, and laterally between the lower end of the rib cage and iliac crests, and $\mathrm{AB}_{2}(\mathrm{~cm})=$ abdominal circumference at the umbilicus level; $\mathrm{NR}=$ age not reported; $\mathrm{HS}=$ high school.


## IN A PRACTICAL SENSE

## EXAMPLE CALCULATIONS <br> Boy Athlete (18 y)

Data: Subscapular (SS) skinfold: 10 mm ; abdominal (AB) skinfold:
18 mm ; triceps (TRI) skinfold: 10 mm ; midaxillary (MA) skinfold: 8 mm
$\mathrm{Db}=1.10647-\left(0.00162 \times \mathrm{SS}_{\mathrm{SKF}}\right)-(0.00144$
$\left.\times \mathrm{AB}_{\text {SKF }}\right)-\left(0.00077 \times\right.$ TRI $\left._{\text {SKF }}\right)+(0.00071$
$\times \mathrm{MA}_{\text {SKF }}$ )
$=1.10647-(0.00162 \times 10)-(0.00144 \times 18)$
$-(0.00077 \times 10)+(0.00071 \times 8)$
$=1.10647-0.0162-0.02592-0.0077+0.00568$
$=1.06233$
$\% \mathrm{BF}=[(499 \div \mathrm{Db})-455] \times 100$
$=[(499 \div 1.06233)-455] \times 100$
$=14.7 \%$

Continued

## Female Ballet Dancer (20 y)

Data: Body weight: 55.0 kg

$$
\begin{aligned}
\text { FFM }(\mathrm{kg}) & =(0.73 \times \mathrm{BW})+3.0 \\
& =43.15 \mathrm{~kg} \\
\% \mathrm{BF} & =[(\mathrm{BW}-\mathrm{FFM}) \div \mathrm{BW}] \times 100 \\
& =[(55-43.15) \div 55] \times 100 \\
& =21.5 \%
\end{aligned}
$$

## Male Football Player (20 y)

Data: Body weight: 105.0 kg; stature: 188 cm

$$
\begin{aligned}
\% \mathrm{BF} & =55.2+(0.481 \times \mathrm{BW})-(0.468 \times \mathrm{HT}) \\
& =55.2+(0.481 \times 105)-(0.468 \times 188) \\
& =55.2+50.51-87.98 \\
& =17.7 \%
\end{aligned}
$$

of 1124 football players had BMIs that exceeded 30. An additional 14 percent had BMIs above 35 . The study pointed out that bigger size did not correlate with more victories. The Iowa team was the lightest team in the Big Ten, with an average BMI of 28.5 , but won a share of the conference championship. In contrast, Indiana had the highest average team BMI with 30.9, followed by Penn State (30.3), and Michigan (30.2). Wisconsins offensive lines average BMI was 38.3, and the Badgers boasted a conference-high 11 linemen who exceeded 300 pounds. Table 29.10 lists the team rank for BMI from high to low. This surely represents a situation where achieving the lowest rank of 10 is cherished instead of were number 1 !

The implications of such huge body mass for these and other large athletes in terms of health risk and long-term outlook remain undetermined but certainly are worrisome. One of the underreported but important health risks concerns disordered breathing problems during sleep prevalent among large-sized Canadian professional football players. ${ }^{17}$ The average neck girth ( 45.2 cm ; 17.7 in .) and elevated BMI (31.5) predicted risk for sleep-disordered breathing and apnea (and accompanying snoring). Certainly the large-sized high school players (and top collegiate and NFL large players) are likely to exhibit sleep-associated disorders that could affect field performance and future health. As we emphasize in Chapter 27, use of BMI to classify individuals as overfat can be misleading as confirmed in a study of 85 collegiate American football players. ${ }^{40}$ The BMI overestimated the prevalence of overweight and obesity in $51 \%$ of the players, with only 14 players qualified as obese using bioimpedance to assess body composition. Nonetheless, the offensive linemen exceeded the at-risk criteria for BMI ( $>30$ ), waist girth $(>102 \mathrm{~cm})$, and $\% \mathrm{BF}(>25 \%)$. It probably is fair to state that large collegiate football players will still meet multiple criteria for obesity (a worrisome finding), in addition to their BMI.

## TABLE 29.10 Average BMI of Division I Big Ten Collegiate American Football Offensive and Defensive Linemen

| Team Rank | Average BMI of <br> Linemen (kg $\cdot \mathbf{m}{ }^{\mathbf{2}}$ ) |
| :--- | :---: |
| 1. Indiana | 30.9 |
| 2. Penn State | 30.3 |
| 3. Michigan | 30.2 |
| 4. Michigan State | 30.1 |
| 5. Ohio State | 30.0 |
| 6. Illinois | 29.8 |
| 7. Northwestern | 29.6 |
| 8. Wisconsin | 29.5 |
| 9. Minnesota | 29.4 |
| 10. Iowa | 28.5 |
| 11. Purdue | 28.5 |

Data for 20042005 reported from the Daily Iowan. 2007, www.dailyiowan.com

## INTEGRATIVE QUESTION

A football coach wishes to field a team whose players are not overly fat. He selects the frequently used BMI to screen out players with excessive body fat. What are the possible outcomes of his decision for football performance?

Other Longitudinal Trends in Body Size for Professional Basketball and Baseball Players. To expand upon longitudinal trends for body size among elite athletes, we determined stature and body mass for two groups of


Figure 29.7 BMI, body mass, and stature of professional NBA players (1970 1993) and BMI of major league baseball players (1986 1995). (Data for NBA players from team rosters, compiled by F. Katch; major league baseball data from team rosters courtesy of Major League Baseball.)
professional athletes: (1) all National Basketball Association (NBA) players from 1970 to 1993 ( $N$ ranged from 156 to 400 yearly) and (2) professional major league baseball players from 28 teams during the 1986, 1988, 1990, 1992, and 1995 seasons ( $N=5031$ roster players).

For the NBA players (Fig. 29.7), average body mass increased by 3.8 pounds ( 1.7 kg ) or $1.8 \%$ during the 23 -year interval. Stature increased more slowly; it changed by only 1 inch or less than $1 \%$ over the same interval. The NBA players BMI during this time remained within a narrow range of 0.8 BMI units, from 23.6 to 24.4. Major League Baseball players (shown in red in the same figure) show slightly higher mean values than do the basketball players. Compared with American professional and collegiate football players, baseball and basketball athletes have maintained BMIs within guidelines considered relatively healthful for minimizing mortality and disease risk.

## integrative question

Explain if a singular prototype for body composition (\%fat, FFM) consistently emerges when one analyzes the body composition of elite athletes in different sports.

Professional Golfers. Limited data exist on the body composition of professional golfers, although height and weight for male tour PGA $(\mathrm{N}=33)$ and Champions Tour players $(\mathrm{N}=18)$ are available from popular golf magazines. The accompanying Table 29.11 lists the height, weight, and BMI for 2005 PGA tour players, Champions Tour Champions, and 257 golfers stratified by proficiency levels based on handicap index. ${ }^{47}$ Data for Behnkes reference man (refer to Chapter 28, p. 735) are

TABLE 29.11 Comparison of Height, Body Weight, and BMI for 2005 Champions Tour, PGA Gold Tour Champions, and Highly Proficient Golfers

| Group | Height (cm) | Weight (kg) | BMI (kg $\cdot \mathrm{m}{ }^{\mathbf{2}}$ ) |
| :---: | :---: | :---: | :---: |
| PGA Tour ${ }^{a}(\mathrm{~N}=33)$ | 182.0 | 84.1 | 25.4 |
| Champions Tour ${ }^{a}(\mathrm{~N}=18)$ | 181.0 | 85.8 | 26.2 |
| Highly proficient golfers ${ }^{b}$ $(\mathrm{N}=257)$ | 180.6 | 87.9 | 26.9 |
| Behnke Reference Man | 174.0 | 70.0 | 23.1 |
| ${ }^{a}$ Data from the Official Annual 2006 PGA Tour and the Official Annual 2006 Champions Tour. New York: Boston Hannah International Publishers, 2006. <br> ${ }^{b}$ Data from Reference 47. |  |  |  |

included for comparison. Interestingly, little difference if any exists in the height, weight, and BMI for the two groups of professional players with other tour golfers. The mortality ratio for these highly skilled golf athletes based on BMI would rate as very low (refer to Fig. 28.1). The most recent study of Swedish Golf Federations membership registry and the nationwide Mortality Registry corroborates this classification for health status based on standardized mortality ratios for 300,818 Swedish golfers ( 203,778 males and 97,040 females) with stratification for age, sex, and socioeconomic status. ${ }^{13}$ Swedish golfers had mortality rates about $60 \%$ of those in the general population for both sexes and in all age groups after adjustment for socioeconomic status. In a comparison study of 257 golfers stratified by proficiency levels based on handicap index, their average BMI index was only marginally higher than the two pro groups. All three golf groups were still taller, heavier, and had a larger BMI than Behnkes reference man.

## Weightlifters and Bodybuilders

Men. Resistance-trained bodybuilders, Olympic weightlifters, and power weightlifters exhibit remarkable muscular development and FFM combined with a relatively lean physique. ${ }^{31}$ Percentage body fat (underwater weighing) averaged $9.3 \%$ in bodybuilders, $9.1 \%$ in power weightlifters, and $10.8 \%$ in Olympic weightlifters. Considerable leanness exists for each group of athletes, even though height weight tables classify up to $19 \%$ of these men as overweight. The groups did not differ in skeletal frame size, FFM, skinfolds, and bone diameters. The only differences occurred for shoulders, chest, biceps, and forearm girths; bodybuilders were larger at each site. The bodybuilders exhibited nearly 16 kg more muscle than predicted for their size; power weightlifters, 15 kg ; and Olympic weightlifters, 13 kg . The three- or four compartment model for body composition prediction is useful for assessing body composition changes in male bodybuilders during training. ${ }^{53}$

Women. Bodybuilding gained widespread popularity among women in the United States during the late 1970s. As women aggressively undertook the vigorous demands of
resistance training, competition became more intense and achievement level increased. Bodybuilding success depends upon a lean appearance complemented by a well-defined yet enlarged musculature, raising interesting questions about the womens body composition. How lean do the competitors become, and does a relatively large muscle mass accompany low body fat levels?

Body composition assessment of 10 competitive female bodybuilders averaged $13.2 \%$ body fat (range, 8.0 to $18.3 \%$ ) and 46.6 kg FFM. ${ }^{16}$ Except for champion gymnasts, who also average about $13 \%$ body fat, bodybuilders were 3 to $4 \%$ shorter, 4 to $5 \%$ lighter, and had 7 to $10 \%$ lower total body fat mass than other top female athletes. The bodybuilders most striking compositional characteristic, a dramatically large FFM FM ratio of 7:1, nearly doubles the 4.3:1 ratio for other female athletic groups. This difference presumably occurred without steroid use. Interestingly, 8 of the 10 bodybuilders reported normal menstrual function with concurrent relatively low body fat. When female bodybuilders train for competition during a 12-week preparation period, the major portion of the total weight lost ( -5.8 kg ; from $18.3 \%$ to $12.7 \%$ body fat) occurred primarily from reduced fat mass and not fat-free mass $\left(-1.4 \mathrm{~kg}\right.$ decline). ${ }^{54} \mathrm{~A} 25.5-\mathrm{mm}$ decline in the sum of triceps, subscapular, biceps, iliac crest, supraspinale, abdominal, front thigh, and medial calf skinfolds accompanied the body composition changes. This experiment reveals that healthy females at the lower end of the body fat continuum can still reduce fat mass over a 3-month training duration to a level that approaches the theoretical boundary for storage fat without apparent deleterious, acute health effects.

Men Versus Women. Table 29.12 compares body composition, girths, and excess body mass of male and female bodybuilders. Excess mass represents the difference between actual body mass and body mass-for-stature from the Metropolitan Life Insurance tables. Overweight for the men corresponded to a $14.8-\mathrm{kg}(18 \%)$ excess; and for the women, a $1.2-\mathrm{kg}(12 \%)$ excess. Obviously, excess body mass in these lean athletes primarily reflected FFM as increased skeletal muscle mass.

## TABLE 29.12 Body Composition and Anthropometric Girths of Male and Female Bodybuilders

| Sex | Age (y) | Mass (kg) | Stature (cm) | Fat (\%) | FFM (kg) | Excess Mass ${ }^{\text {a }}$ (kg) |
| :--- | :--- | :--- | :--- | :--- | ---: | ---: |
| Male $^{b}(\mathrm{~N}=18)$ | 27.0 | 82.4 | 177.1 | 9.3 | 74.6 | 14.8 |
| Female $^{c}(\mathrm{~N}=10)$ | 27.0 | 53.8 | 160.8 | 13.2 | 46.6 | 1.2 |

${ }^{a}$ Body mass minus body mass estimated from height weight tables.
${ }^{b}$ Katch VL, et al. Muscular development and lean body weight in bodybuilders and weightlifters. Med Sci Sports 1980;12:340.
${ }^{c}$ Freedson PS, et al. Physique, body composition, and psychological characteristics of competitive female bodybuilders. Phys Sportsmed 1983;11:85.
${ }^{d}$ Calculated as Gi $/ \sqrt{\text { mass }(\mathrm{kg}) / \text { stature }(\mathrm{dm})^{0.7}}$, where Gi equals any one of the girths. The term (mass/stature ${ }^{0.7}$ ) is a frame structure estimate of perimetric (girth) size. The adjusted values are the perimetric equivalent adjusted girths due to sex differences, because they are corrected for whatever differences may exist as a result of differences in body size.

Contrasts of the girth data allow comparison of individuals (or groups) who differ in body size. The analysis shows that gender differences in girths when scaled to body size (referred to as adjusted in the table) do not differ as much as the uncorrected absolute girth values. Relative to body size, females exceed the male bodybuilders in 7 of 12 body areas. Women probably can alter muscle size to almost the same relative extent as men, at least when scaled to body size. The larger hip size in women probably reflects greater fat stores in this location.

INTEGRATIVE QUESTION
Do established gender differences in body composition justify sex-specific normative standards to evaluate different components of physical fitness and motor performance?

## UPPER LIMIT FOR FAT-FREE BODY MASS

The FFM for Japanese elite sumo wrestlers (seki-tori) averages $109 \mathrm{~kg} .{ }^{36}$ These athletes share the distinction of being the worlds largest with some American professional football players who weigh $159 \mathrm{~kg}(350 \mathrm{lb})$. It seems unlikely that athletes in this weight range would possess less than $15 \%$ body
fat; the FFMs of the largest football players at $15 \%$ body fat theoretically correspond to 135 kg . In reality, a football player with a body mass of 159 kg would more likely have 20 to $25 \%$ body fat. At $20 \%$ body fat, the FFM would be about 127 kg , certainly the highest value ever measured hydrostatically. But this value remains hypothetical in the absence of reliable data. Even for an exceptionally large professional basketball player (body mass, 138.3 kg [ 305 lb ]; stature, 210.8 cm [83 in.]), percentage body fat is unlikely to be less than $10 \%$ of body mass. Thus, fat mass equals 13.8 kg and FFM equals 114.2 kgperhaps an upper limit FFM value for an athlete of such dimensions.

To gain additional insight into the question of an upper limit in FFM among athletes, we reviewed more than 35 years of body composition data from our laboratories to determine the largest FFM values calculated densitometrically. Thirtyfive athletes exceeded an FFM of 100 kg ; the top five values were $114.3,109.7,108.4,107.6$, and 105.6. The three top values were larger than the two values of 106.5 kg reported for defensive football linemen from 19691971 data $^{3}$ and for other resistance-trained athletes. ${ }^{12}$

The body composition of an exceptionally large professional football player (NFL Oakland Raiders; unpublished data, Dr. Robert Girandola, Department of Kinesiology, University of Southern California) determined by repeated trials of underwater weighing exceeds values for FFM presented in research literature. The player, with a
body fat content of $11.3 \%$. (body mass: 141.4 kg ; stature: 193 cm ; BMI: 38.4), had a FFM of 125.4 kg , the uppermost value ever reported. With the continuing increase in the body size of pro football offensive and defensive players, this players large FFM determined in 1997 before he turned professional will probably not remain the peak value for FFM as body composition data on other large athletes become available. In the absence of additional data, we assume that 125.4 kg represents the current upper limit of FFM in elite athletes.

## Summary

1. Athletes generally have physique characteristics unique to their specific sport. Field-event athletes have a relatively large FFM and a high percentage body fat; distance runners possess the least amount of lean tissue and fat mass.
2. Champion performance blends unique physique characteristics and highly developed physiologic support systems.
3. Male and female triathletes possess a body composition and aerobic capacity most similar to elite bicyclists.
4. Body composition analyses of American football players reveal they are among the heaviest of all athletes, yet maintain a relatively lean body composition. At the highest levels of competition, Division I collegiate and professional football players show remarkable similarity in body size and composition.
5. Top-rated high school football linemen (2008) exceed the stature and body mass (and BMI) of

20072008 NFL Super Bowl participants and 2007
NCAA Division I champion offensive and defensive linemen American football players.
6. Professional golfers and those of high skill level have normal BMI ratios compared to other groups of athletes.
7. Competitive male and female swimmers generally have higher body fat levels than distance runners. The difference probably results from self-selection related to economically exercising in the different environments rather than real metabolic effects caused by the environments.
8. Female bodybuilders alter muscle size to the same relative extent as male bodybuilders.
9. The FFM FM ratio of competitive female bodybuilders exceeds the FFM FM ratio of other elite female athletes.
10. A value of 125.4 kg represents the current upper limit of FFM of elite athletes.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

Pro Football Reference.com: Running Backs and BMI www.pro-football-reference.com/blog/?p=489
Average BMI of Division I Big Ten Collegiate American Football Offensive and Defensive Linemen www.dailyiowan.com

## CHAPTER 30



## Overweight, Obesity, and Weight Control

## CHAPTER OBJECTIVES

- Discuss the worldwide impact of overfatness and obesity in the United States and worldwide
> Evaluate the contribution of inherited factors to development of excess body fat
- List 10 key health risks of excessive body fat
- Describe how excess body weight in childhood and adolescence relates to adult risk for obesity and poor health
> Discuss each of the following criteria for excessive body fat: (1) percentage body fat, (2) regional fat distribution, and (3) fat cell size and number
- Compare fat cell size and number in individuals with average body fat and the massively obese
- Discuss how genetic factors create white and brown fat cells, and what impact molecular biology can have on increased energy expenditure in obesity
> Describe general effects of weight gain and loss on adult fat cell size and number
> Outline three approaches to unbalance the energy balance equation to trigger weight loss
> Describe characteristics of individuals who successfully maintain prolonged weight loss
- Summarize proposed advantages and disadvantages of ketogenic diets, high-protein diets, and very low-calorie diets (VLCD) to reduce body fat
- Present the rationale for including regular physical activity in a prudent weight-loss program
- Review how moderate increases in physical activity for a previously sedentary, overly fat person affect (1) daily food intake and (2) energy expenditure on a short- and long-term basis
> Outline why combining regular physical activity with moderate food restriction achieves successful weight loss
> Summarize how different exercise modes affect body composition during weight loss
> Explain whether specific (target) exercises induce localized fat loss
> Give specific diet and exercise advice to gain body weight to improve appearance or enhance sports performance


## Part 1 OBESITY

## HISTORICAL PERSPECTIVE

Throughout history, biblical scholars have preached against the ills of excessive food intake and sedentary living. For example, the 12th-century Jewish sage, Rabbi Moses ben Maimon (also known as Maimonides; 1138 1204), quotes the incomparable Greek physician Galen (AD 129 201; refer to Roots and Historical Perspectives in the Introduction of this text) in one of his many essays on health, that excess fat is harmful to the body and makes it sluggish, disturbs its functions, and hinders its movements. Maimonides also taught, indeed prophetically, that everyone who practices a sedentary lifestyle and does not exercise will live his or her life a painful one. He posited that excessive eating is like a deadly poison to the body and a principal cause of all illness.

Hippocrates (b. 460377 BC), the ancient Greek physician regarded as the Father of Medicine, opined that obesity is a health risk and considered it a cause of disease that led to death. The Hippocratic texts conveyed the overarching belief that obesity deviated from the norm or ideal so essential for maintaining a healthy balance to all aspects of life. Galen and others wrote essays that extolled the virtues of walking, running, wrestling, rope climbing, and vigorous, physically active pursuits in addition to baths, massage, rest, and an appropriate lifestyle as antidotes to rebalance ones health.
Interestingly, Hippocrates believed that one viable strategy for reducing weight was for obese individuals to undertake exercise before eating and to eat while still breathing hard. The practice of modulating food intake for dietary control of disease conditions was promoted in the first half of the 9th century by an ancient Assyrian physician, Yuhanna ibn Masawayh (known in the Western world as Jean Mesue; AD 777 857). This prolific medical writer practiced medicine in Baghdad and served as personal physician to four caliphs. Known for his medical aphorisms, Mesue produced the first known treatise concerning dietetics, incorporating ideas from the earlier writings of Galen. He was one of the first ancient medical nutritionists to describe the properties of 140 foodstuffs from the plant and animal kingdoms and their effects on the human body.

For the past 20 centuries, medical practitioners (and writers, philosophers, scientists, and theologians) throughout the world have advocated a sensible approach to healthy living, but apparently without much success. The following quote provides a succinct summary of the historical development of scientific and cultural ideas about obesity gleaned from the ancients to the present: ${ }^{18}$

[^53]weakness on the part of the overweight individual. Cases of massive obesity were identified in stone-age carvings and have been described frequently since the time of Galen and the Roman Empire. More specific types of obesity began to be identified in the 19th century. Following the identification of the cell as the basic building block of animals and plants, fat cells were described and the possibility that obesity was due to too many fat cells was suggested. After the introduction of the calorimeter by Lavoisier, the suggestion that obesity might represent a metabolic derangement has been suggested and tested. Standards for measuring body weight appeared in the 19th century. The possibility that familial factors might also be involved was clearly identified in the 18th and 19th centuries. Most of the concepts that are currently the basis for research in the field of obesity had their origin in the 19th century and often earlier.

## OBESITY REMAINS A WORLDWIDE EPIDEMIC

In our modern scientific era, no clear answer exists to a seemingly simple question: Why have so many people become too fat, and what can be done to reduce the problem? Overfatness results from a complex interaction of genetic, environmental, metabolic, physiologic, behavioral, social, and perhaps racial influences. ${ }^{26,78,141}$ Individual differences in specific factors that predispose humans to excessive weight gain include eating patterns and eating environment; food packaging; body image; variations related to resting metabolic rate; dietinduced thermogenesis; level of spontaneous activity, or fidgeting; basal body temperature; susceptibility to specific viral infections, levels of cellular adenosine triphosphatase, lipoprotein lipase, and other enzymes; and metabolically active brown adipose tissue.

A random-digit telephone survey of nearly 110,000 adults in the United States found that large numbers struggle to lose weight or just maintain body weight. ${ }^{196}$ Only one-fifth of Americans attempting to lose weight use the recommended combination of eating fewer calories and engaging in at least 150 minutes of weekly leisure-time physical activity. Those attempting weight loss often rely on potentially harmful dietary practices and drugs while ignoring sensible weight-loss programs. Notwithstanding the upswing in attempts to lose weight, people throughout the industrialized nations are considerably more overweight than people were a generation ago. Obesity is an equal opportunity affliction; the obesity epidemic now afflicts all regions of the United States. ${ }^{152}$

Figure 30.1 compares data from National Health and Nutrition Examination Survey (NHANES; www.cdc.gov/ nchs/products/pubs/pubd/hestats/overweight/overwght_adult_ $03 . \mathrm{htm}$ ) of overweight and obesity prevalence among adults and children in the United States from the 1960s to 2002 for children and 2004 for adults. Current classification standards place the prevalence of overweight and obesity in adults at nearly 140 million Americans ( $66 \%$ of the population, including $35 \%$ of college students), ${ }^{142}$ an unprecedented increase from $56 \%$ in 1982. Overweight occurrence is particularly high among women and minority groups (Hispanic, African


Figure 30.1 The fattening of America. Prevalence of overweight and obesity among adults in the United States during the measurement periods 1960 to 2004. For adults, overweight including obese is defined as a $\mathrm{BMI} \geq 25$, overweight but not obese as a $\mathrm{BMI}>25$ but $<30$, and obese as a $\mathrm{BMI} \geq 30$. For children, no definition exists for obese; overweight refers to a BMI at or above the sex- and age- specific 95th percentile cut-points from the CDC Growth Charts: United States. National Center for Health Statistics. National Health and Nutrition Examination Survey. Other data sources cited by the NCHS include: Flegal KM, et al. Prevalence and trends in obesity among U.S. adults, 1999 2000. JAMA 2002;288:1723; Ogden CL, et al. Prevalence of overweight and obesity in the United States, 1999 2004. JAMA 2006;295:1549.

American, Pacific Islanders). The major increase results from a near doubling of the obesity component to one in four Americans over the past two decades. As of February 2006, about $34 \%$ of the adult population (nearly 60 million people) classify as obese, compared with only $14.5 \%$ in 1980. To give some perspective about the sheer size of the epidemic, 60 million obese people equals the entire population of either France, the United Kingdom, or Italy, or in the United States for the year 2007, the combined number of men, women, and children who reside in Michigan, New York, Florida, and Ohio (or Alabama, California, Kentucky, Massachusetts, Oregon, and Tennessee). To use a sports metaphor, if 60 million people wished to attend a Super Bowl Game, it would require 60 stadiums of 100,000 seats filled to capacity to accommodate them all. If this group only carried an excess of 20 pounds of fat, this would be the equivalent of approximately 4.2 trillion extra
kCal , the equivalent energy storage to power a walk around the earths equator about 1.7 million times!

Similar increases in obesity have occurred worldwide. ${ }^{68,133,238}$ Such alarming rates of increase contribute to the rising onslaught of diabetes and cardiovascular disease prompting the World Health Organization (www.who.int/en/) and the International Obesity Task Force (www.iotf.org/) to declare a global obesity epidemic. For example, Figure 30.2 shows estimates for 2009 from selected European countries for obesity assessed by BMI. Worldwide estimates indicate that 310 million people are obese and 775 million more are overweight. Obesity is now the second leading cause of preventable deaths in the United States (300,000 deaths yearly; smoking is first), with a total upper annual cost estimated at $\$ 140$ billion (www. obesity.org), or approximately $10 \%$ of the U.S. health care expenditures. ${ }^{2}$ Figure 30.3 depicts the powerful effect of excess


Figure 30.2 The obese condition expands across Europe. Adult levels of obesity ( BMI above $30 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ ) in 20 European countries during 2007 2009. Data from the International Obesity Taskforce (www.iotf.org/), a global network of expertise and research-led think tank and advocacy arm of the International Association for the Study of Obesity (www.iaso.org/).


Figure $\mathbf{3 0 . 3}$ Survival estimates for women and men categorized by body mass index (BMI). (From Peeters A, et al. Obesity in adulthood and its consequences for life expectancy. Ann Intern Med 2003;138:24.)
body weight in predicting death at an older age. Overweight, but not obese, nonsmoking men and women in their mid-30s to mid-40s die at least 3 years sooner than normal-weight counterparts, a risk just as damaging to life expectancy as cigarette smoking. Obese individuals can expect about a 7-year decrease
in longevity. Correctly, physicians tell us to eat less and increase the time spent exercising. In industrialized nations, economic factors operate to counter this advice: Food continues to become cheaper and more fat laden, while most occupations have not changed or decreased their exertional demands.

A milestone in American governmental action regarding obesity took place on December 1, 2003. The United States Preventive Services Task Force (www.ahrq.gov/clinic/uspstfix. htm ), a government advisory group composed of medical experts, urged physicians to weigh and measure all patients and recommend counseling and behavior therapy for those found to be obese. Specifically, the group recommended that doctors prescribe intensive behavior therapy at least twice monthly (in individual or group sessions) for up to 3 months under the supervision of a health-professional team of psychologists, registered dietitians, and exercise specialists. These guidelines, which usually become the standard of care for medical practice, represent a major shift in how the health care system treats obesity, hopefully prompting health plans and insurers to pay for obesity treatment. Apparently, this plea had some effect. After a quarter century of increases, obesity prevalence has not measurably increased from 2005 to 2009, even though levels still remain far too high $34 \%$ of U.S. adults ages 20 and over.

Children experience an equally depressing situation because the prevalence of overweight in children (BMI $>$ 95th percentile for age and sex) has attained grim proportions. ${ }^{161,162,218}$ A comprehensive report released by the National Academies of the Institutes of Medicine (www.iom.edu/) on the causes and solutions for childhood obesity in the United States indicates that in the last 30 years childhood obesity has tripled among children ages 6 to 11 (particularly in rural America), to more than $15 \%$. The rates have doubled for those ages 2 to $5(>10 \%)$ and from 12 to 19 , to more than $15 \%$. Pediatric obesity represents childhoods most common chronic disorder, particularly prevalent among poor and minority children. ${ }^{61,231}$ Part of this rise in body weight relates to the nearly $300 \%$ increase between 1977 and 1996 in the foods that children consume from restaurants and fast-food outlets. ${ }^{217}$ Soft drink consumption in young consumers accounts for an additional 188 kCal per day above energy intakes of children who do not consume these beverages. ${ }^{215}$ Excessive fatness in youth represents an even greater adult health risk than obesity begun in adulthood. Overweight children and adolescents, regardless of final body weight as adults, exhibit higher risk of a broad range of illnesses as adults than adolescents of normal weight.

## A PROGRESSIVE LONG-TERM PROCESS

Excess accumulation of body fat (i.e., overfatness) represents a heterogeneous disorder in which energy intake chronically exceeds energy expenditure. Disruption in energy balance often begins in childhood, and if this occurs (particularly among older children at the upper decile for body fat), the chance for adult obesity increases considerably. For example, obese children at ages 6 to 9 have a $55 \%$ chance of becoming obese as adultsa risk 10 times that of children of normal weight. Simply stated, a child generally does not outgrow an overly fat condition.

Ages 25 to 44 are the dangerous years when adults develop excessive fatness. ${ }^{36}$ Middle-aged men and women invariably weigh more than college-aged counterparts of the


## Childhood Obesity Rates

The stunning 3-decade rise in childhood obesity that began in the 1970s has appeared to have plateaued, at least temporarily. An analysis of inperson measurements of height and weight from more than 8000 children shows that the percentage of obese youngsters has stabilized since 1999 in every age and racial group surveyed. Overall, $32 \%$ were overweight or obese, $16 \%$ were obese, and $11 \%$ classified as extremely obese. The researchers from the Centers for Disease Control and Prevention suggest that educational and regulatory campaigns to get children to exercise more and eat less junk food may have begun to pay off.


1970
Ogden C, et al. High body mass index for age among US children and adolescents, 2003 2006. JAMA 2008; 299:2401.
same stature. Between ages 20 and 40, Americans gain about 2 pounds a year for a 40 -pound gain in body weight. Women tend to gain the most weight; about $14 \%$ add more than 30 pounds between ages 25 and 34 . The degree to which this creeping overfatness in adulthood reflects a normal biologic pattern remains unclear.

## Four Reasons for Classifying Overweight and Obesity

1. Provides meaningful comparisons of body weight status within and between populations
2. Identifies individuals and groups at increased risk of morbidity and mortality
3. Identifies priorities for intervention at individual and community levels
4. Establishes a firm basis for evaluating diverse intervention strategies

## Source: World Health Organization

## The Reasons Remain Elusive

Substantial alterations in the populations gene pool (requiring millions of years of evolutionary change) cannot explain the dramatic nationwide obesity increase since 1980. Researchers maintain that if the progression of obesity continues at the current rate, the entire population will be overweight within a few generations. By $2025,75 \%$ of the American population will classify as overweight, with about one-third classified obese. More than likely, a sedentary lifestyle and ready availability of tasty, lipid- and calorie-rich foods served in increasingly larger portions remain prime culprits for expressing unhealthy patterns of preexisting susceptible genes in the fattening of Western civilization, as depicted in the figure below. ${ }^{15,30}$


## Male $\square$ Female

## Generally a Nation of the Overfed

A general increase in energy intake has occurred over a 30 -year period among adult Americans (Fig. 30.4). Adult women now eat 335 more kCal per day than they did in 1970, while the daily intake for men has increased by 168 calories. In 2000, this translated to an average increase of 278 pounds of food, compared with 1497 pounds per capita intake in 1970. The disparity is even larger for the comparison with 2009. On the surface, some of this increase seems desirable because it includes increased vegetable intake. Nevertheless,

$\square$ Fruits (fresh and processed)
$\square$ Grains (barley, corn, and oat products; rice, rye, wheat flour)
$\square$ Vegetables (fresh and processed)
$\square$ Sugars (candy, beet, and cane sugars, corn sweeteners, honey, syrup)
$\square$ Fats and oils (cooking and salad oils, shortening, table spreads)
$\square$ Proteins (dairy, eggs, fish, meat, nuts, poultry)

Figure 30.4 Eating more of just about everything: a 30year comparison. (Source: USDA Economic Research Service; www.ers.usda.gov/)

## FOCUS ON RESEARCH

## Genetic Tendency to Gain Weight

## Bouchard C, et al. The response to long-term feeding in identical twins. N Engl J Med 1990;322:1477.

$>$ Bouchard and colleagues studied differences in body fat acquisition and its distribution from overfeeding (84,000 extra kCal ) in 12 pairs of male monozygotic twins for 100 days. Their results provide some of the most persuasive support for an inherited tendency toward obesity.

The twin pairs (average age: 21 y ; range: 1927 y ) lived in a dormitory under 24-hour supervision for 120 consecutive days. This period included 14 days of baseline testing, 3 days of testing before overfeeding, 100 days of overfeeding, and 3 days of posttesting. Subjects ate normally during baseline testing, with each meal analyzed for nutrient composition and energy content. Body mass remained stable during this time. Subjects were tested during the pre- and postoverfeeding periods for resting metabolic rate body fat, by hydrostatic weighing; adipose tissue fat composition, by analysis of needle biopsy specimens from the abdominal (umbilicus-level) and femoral (mid-thigh level) areas; trunk-fat mass, by computed tomographic (CT) scans of abdominal and abdominal visceral areas; and anthropometric assessment that included five trunk and five limb skinfolds and waist and hip circumferences.

After baseline testing, the twins consumed a diet for 6 days a week containing 1000 kCal per day in excess of baseline energy requirement. Daily meal composition was $50 \%$ carbohydrate, $35 \%$ lipid, and $15 \%$ protein. On day 7 , subjects consumed their baseline number of calories. The men ate three meals plus an evening snack, and daily activities included reading, playing cards and video games, watching television, and walking outdoors for 30 minutes. Measurements during overfeeding included body mass (daily), skinfolds (every 5 days), and waist and hip girths (every 25 days).

The top figure displays average percentage changes from before to after overfeeding. Body mass increased significantly (average $8.1-\mathrm{kg}$ gain), as did fat mass and FFM. However, the $111 \%$ average gain in adipose cell mass dramatically exceeded the 5\% FFM increase. The sum of skinfold thickness (used to reflect change in subcutaneous fat) increased $70 \%$, from 76 to 129 mm . Skinfold thickness increased more on the trunk ( $87 \%$ ) than on the limbs ( $50 \%$ ). Waist and hip girth also increased significantly. The ratio of waist girth to hip girth increased, indicating greater fat accretion at the waist than hip. Overfeeding increased adipose tissue fat mass in all subcutaneous and visceral sections estimated from CT scans.

Importantly, considerable individual differences existed for changes in body mass and body composition with overfeeding, with greater variation between twin pairs than within pairs. The bottom figure displays within-pair differences for the changes in body mass with equivalent excess energy intake. Each colored point represents one twin pair (A and B). The closer the points fall to the diagonal line, the more similar the twins are. The large differences


Top. Effects of 100 days of $84,000-\mathrm{kCal}$ overfeeding in 12 pairs of male monozygotic twins. Values are percentage change from before to after overfeeding. Bottom, Similarity within twin pairs of changes in body mass in response to overfeeding.

## FOCUS ON RESEARCH <br> Continued

between twin pairs for changes in body mass exceeded the differences within twin pairs.

A threefold difference emerged for changes in body mass, body composition, trunk fat, and visceral fat between the high and low weight gainers. This clearly indicated that surplus energy intake (with other factors controlled) did not produce similar changes in the outcome variables among twin pairs. Also, neither body mass nor body fat increases predicted visceral fat accumulation. Of
clinical significance was the observation that some persons store fat more readily than others on the trunk, in the abdominal cavity, or at both areasa fat deposition pattern with increased health risk. Bouchard hypothesized that a persons genotype determines adaptations to a sustained energy surplus. More than likely, a yet-undetermined genetic characteristic produces large individual differences in the tendency toward obesity in general and the patterning of fat on the body in particular.
nearly one-third of these vegetables comprised iceberg lettuce, French fries, and potato chips. The grain component of this increase consists of processed flour-based pasta, tortillas, and hamburger buns not fiber-rich whole grain breads and cereals. Highly processed, low-fiber carbohydrates have the equivalent nutritional value of table sugar.

## GENETICS INFLUENCES BODY FAT ACCUMULATION

The notable interaction between genetics and environment makes it difficult to quantify the role of each in obesity development. Research with twins, adopted children, and specific segments of the population attributes up to $80 \%$ of the risk of becoming obese to genetic factors. For example, newborns with large body weights become fat adolescents only when the father or particularly the mother is overweight. ${ }^{70}$ Little risk exists for an overweight toddler to grow into an obese adult if both parents are of normal weight. But if a child under age 10 , regardless of current weight, has one or both obese parents, the child has more than twice the normal risk of becoming an obese adult. ${ }^{229,247}$ Even for normal-weight prepubertal girls, body composition and regional fat distribution relate to the body composition characteristics of both parents. ${ }^{228}$

Ones genetic makeup does not necessarily cause obesity, but instead lowers the threshold for its development because of the impact of susceptibility genes. ${ }^{176}$ Researchers have identified key genes and specific DNA sequence variants that relate to the molecular causes of appetite and satiety that predispose a person to obesity. A more complete understanding of the genetic role in body fat accretion requires identification of the key genes and their mutations (including the relevant proteins) that contribute to chronic energy imbalance. Dr. Claude Bouchard, a research scientist at the Pennington Biomedical Research Center (www.pbrc.edu/) and one of the individuals we profile (see p. 722), continues to play a key role in the search for and identification of obesity genes.

Inherited factors contribute to variability in weight gain among individuals fed an identical daily caloric excess and
can contribute to the tendency to regain lost weight (see Focus on Research, p. 786). ${ }^{16,62}$ Studies of individuals who represent nine different kinds of relatives indicate that genetic factors that affect metabolism and appetite determine about $25 \%$ of the variation among persons in percentage body fat and total fat mass. A larger percentage variation in body fat status relates to a transmissible (cultural) effect (unhealthy expression patterns of preexisting genes; Fig. 30.5). In an obesity-producing environmentsedentary and stressful, with ready access to inexpensive, large-portion, high-calorie, good-tasting foodthe genetically susceptible (obesityprone) individual gains weight and possibly lots of it. Athletes


Figure 30.5 Total transmissible variance for body fat. Total body fat and percentage body fat were determined by hydrostatic weighing. (From Bouchard C, et al. Inheritance of the amount and distribution of human body fat. Int J Obes 1988; 12:205.)
in weight-related sports with a genetic propensity for obesity must constantly battle to maintain optimal body weight and composition for competitive performance.

## A Mutant Gene and Leptin

Researchers now link human obesity to a mutant gene. ${ }^{180,210}$ Studies at the University of Cambridge in England identified a specific defect in two genes that control body weight. ${ }^{100,154}$ Two cousins from a Pakistani family in England inherited a defect in the gene that synthesizes leptin (derived from the Greek root leptos, meaning thin), a crucial hormonal body weight-regulating substance, produced by fat and released into the bloodstream, that acts on the hypothalamus. Congenital absence of leptin produced continual hunger and marked obesity in these children. The second genetic defect observed in an English patient affected the bodys response to leptins signal. This triggering signal largely determines how much one eats, how much energy one expends, and ultimately how much one weighs.

The model in Figure 30.6 proposes that the $o b$ gene normally becomes activated in adipose tissue (and perhaps muscle tissue), where it encodes and stimulates production of a body fat signaling, hormone-like protein (ob protein or leptin), which then enters the bloodstream. This satiety signal molecule travels to the arcuate nucleus, a collection of specialized neurons in the mediobasal hypothalamus that controls appetite and metabolism and develops soon after birth. Normally, leptin blunts the urge to eat when caloric intake maintains ideal fat stores. Leptin may affect certain neurons in the hypothalamic region that stimulate the production of chemicals that suppress appetite and/or reduce the levels of neurochemicals that stimulate appetite. ${ }^{86,128}$ Such mechanisms would explain how body fat remains intimately connected via a physiologic pathway to the brain to regulate energy balance. In a way, the adipocyte serves an endocrine-like function. With a gene defective for either adipocyte leptin production and/or hypothalamic leptin sensitivity (as probably exists in humans), the brain inadequately assesses the bodys adipose tissue status. This would enable the continuation for the urge to eat. In essence, leptin availability (or its lack) affects the neurochemistry of appetite and the brains dynamic wiring to possibly impact appetite and obesity in adulthood.

The hormone hypothalamic biologic control mechanism helps to explain the extreme difficulty obese persons have in sustaining fat loss. In children and adults, when energy balance remains in steady state, plasma leptin circulates in direct proportion to adipose tissue mass, with four times more leptin in obese compared to lean individuals. Consequently, human obesity resembles a relative state of leptin resistance similar to obesity-related insulin resistance. ${ }^{80}$ High blood leptin concentrations associate strongly with the combination of upperbody obesity, glucose intolerance, hypertriglyceridemia, and hypertensioneore metabolic disturbances in the insulin-
resistant metabolic syndrome (see Chapter 20). This unique metabolic disturbance ultimately acts as a conduit to trigger


Figure 30.6 A genetic model for obesity. A malfunction of the satiety gene markedly affects production of the satiety hormone leptin. This disrupts events that occur in the hypothalamus, the center responsible for adjusting the bodys fat level.
higher incidence for heart disease, stroke, and type 2 diabetes. ${ }^{18,140,219}$ Weight loss reduces serum leptin concentration, while weight gain increases serum leptin. ${ }^{121,239}$ Gender, hormones, pharmacologic agents, and the bodys current energy requirements also affect leptin production. ${ }^{34}$ Neither short- nor long-term exercise meaningfully affects leptin, independent of the effects of exercise on total adipose tissue mass. ${ }^{48,91,164}$ Subcutaneous recombinant leptin injections produced dose response effect with body weight and body fat loss in lean and obese men and women with elevated endogenous serum leptin concentrations. ${ }^{90}$ This suggests a potential role for leptin and related hormones in treating obesity. ${ }^{178}$

The linkage of genetic and molecular abnormalities to obesity allows researchers to view overfatness as a disease rather than a psychologic flaw. Early identification of ones genetic predisposition toward obesity makes it possible to begin diet and exercise interventions before obesity sets in and fat loss becomes exceedingly difficult if not almost impossible.

Leptin alone does not determine obesity or explain why some people eat whatever they want and gain little weight, while others become overfat with the same caloric intake. Besides defective leptin production, defective receptor action increases resistance to endogenous satiety chemicals. A specific gene, the uncoupling protein-2 gene $U C P 2$ (www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601693), adds another piece to the obesity puzzle. High activity of this gene activates a protein that burns excess calories as heat energy without coupling to other energy-consuming processes. This futile metabolism blunts excess fat storage. Individual differences in gene activation and alterations in metabolic activity lend credence to the common claim Every little bit of excess I eat turns to fat. A drug that turns on the $U C P 2$ gene to synthesize more of the heat-generating protein could provide a pharmacologic windfall to shed excess body fat. Other newly discovered molecules that control eating include AGRP (agouti-related protein), a protein controlled by leptin that may affect hypothalamic cells to increase caloric intake. The brain also synthesizes melanin-concentrating hormone when leptin levels increase. ${ }^{146}$ An excess of this protein molecule increases an animals appetite, causing it to eat and gain weight. Drugs that inhibit or destabilize the action of the brain chemicals that control eating may ultimately provide the long-term cure for the overfat condition.

## Influence on Racial Factors

Racial differences in food and exercise habits and cultural attitudes toward body weight help to explain the greater prevalence of obesity among black women (nearly $50 \%$ ) than white women (33\%). Research with obese women shows that small differences in resting energy expenditure (REE), related to racial differences in lean body mass, ${ }^{22}$ contribute to the racial differences in obesity. ${ }^{65,92,102}$ This racial effect, which also exists among children and adolescents, ${ }^{221,227}$ predisposes a black female to gain weight and regain it after weight loss. On average, black women burn nearly 100 fewer kCal each day during rest than white counterparts. The slower rate of caloric expenditure persists even after adjusting for differences in body mass and body composition. A $100-\mathrm{kCal}$ reduction in daily metabolism translates to nearly 1 pound of body fat gained each month. Total daily energy expenditure of black women averages $10 \%$ lower than whites, owing to a 5\% lower REE and $19 \%$ lower physical activity energy expenditure. ${ }^{26}$ Additionally, obese black women showed greater decreases in REE than white women following energy restriction and weight loss. ${ }^{66}$ The combination of a lower initial REE and more profound depression of REE with weight loss suggests that black women (including athletes) experience
greater difficulty achieving and maintaining goal body weight than overweight white women.

## A Word of Caution

When evaluating purported racial differences in body composition characteristics and their implications on health (and physical performance), one must carefully evaluate methods to explore such differences. ${ }^{37,237}$ For example, interethnic and interracial differences in body size, structure, and body fat distribution can mask true differences in body fat at a given BMI. A single generalized BMI health risk model obscures the potential to document chronic disease risks among different population groups. ${ }^{72,208}$ As discussed in Chapter 28, the nature and magnitude of the relationship between body mass or BMI and health risk may vary among racial and ethnic groups.

## PHYSICAL INACTIVITY: A CRUCIAL COMPONENT IN EXCESSIVE FAT ACCUMULATION

Regular physical activity, through either recreation or occupation, effectively impedes weight gain and adverse changes in body composition. This effect thwarts the tendency to regain lost weight and counters a common genetic variation that makes people more likely to gain excess weight. ${ }^{95,101,176,214,249}$ Individuals who maintain weight loss over time show greater muscle strength and engage in more physical activity than counterparts who regained lost weight. ${ }^{241}$ Variations in physical activity alone accounted for more than $75 \%$ of regained body weight. Such findings point up the need to identify and promote strategies that increase regular exercise. Current national guidelines by the Surgeon General and Institute of Medicine recommend a minimum of 30 to 60 minutes of moderate physical activity daily. We endorse an increase to 80 to 90 minutes of exercise, six to seven days a week (preferably seven) over and above regular routines, to combat the obesity epidemic in the U.S. population.

Physically active lifestyles lessen the normal pattern of fat gain in adulthood. For young and middle-aged men who exercise regularly, time spent in physical activity relates inversely to body fat level. ${ }^{148}$ Middle-aged long-distance runners remain leaner than sedentary counterparts. Surprisingly, no relationship emerges between the runners body fat level and caloric intake. Perhaps the relatively greater body fat among middle-aged runners results from less-vigorous training, not greater food intake.

From age 3 months to 1 year, the total energy expenditure of infants who later became overweight averaged $21 \%$ lower than infants with normal weight gain. ${ }^{181}$ For children ages 6 to 9 years, percentage body fat inversely related to physical activity level in boys but not girls. ${ }^{8}$ Obese preadolescent and adolescent children generally spend less time in physical activity or engage in lower intensity physical activity than normal-weight peers. ${ }^{41,135,235}$ By the time young girls attain adolescence, many
do not engage in leisure-time physical activity. For girls, the decline in time spent in physical activity averaged nearly $100 \%$ among blacks and $64 \%$ among whites between ages 9 or 10 and 15 or $16 .{ }^{115}$ By age $16,56 \%$ of the black girls and $31 \%$ of the white girls reported no leisure-time physical activity.

## Benefits of Increased Energy Output with Aging

Maintaining a lifestyle that includes a regular and constant level of endurance exercise attenuates but does not fully forestall the tendency to add weight through middle age. Sedentary men and women who begin an exercise regimen lose weight and body fat compared with those who remain sedentary; those who stop exercising gain body weight relative to those who remain active. Moreover, the amount of weight change is proportional to the change in exercise dose. ${ }^{251,252}$ Figure 30.7 displays the inverse association among


Figure 30.7 Relationship among average body mass index (top) and waist circumference (bottom) and age for men who maintained constant weekly running for varying distances ( $<16$ to $>64 \mathrm{~km} \cdot \mathrm{wk}^{-1}$ ). Men who annually increase their running distance by 1.39 miles ( 2.24 km ) per week compensate for the anticipated weight gain during middle age. (From Williams PT. Evidence for the incompatibility of ageneutral overweight and age-neutral physical activity standards from runners. Am J Clin Nutr 1997;65:1391.)
distance run and BMI and waist circumference in all age categories. Active men typically remained leaner than sedentary counterparts for each age group; men who ran longer distances each week weighed less than those who ran shorter distances. The typical man who maintained a constant weekly running distance through middle age gained 3.3 pounds, and waist size increased about three-quarters of an inch regardless of distance run. Such findings suggest that by age 50, a physically active man can expect to weigh about 10 pounds more (with a $2-\mathrm{in}$. larger waist) than he weighed at age 20 despite maintaining a constant level of increased physical activity. This proclivity to gain weight and girth may relate to reduced levels of testosterone and growth hormone that induce age-related changes in physique and increase abdominal and visceral fat. To counter weight gain in middle age, one should gradually increase the amount of weekly exercise the equivalent of running 1.4 miles for each year of age starting at about age 30 .

## INTEGRATIVE QUESTION

What evidence documents that body fat accumulation among children and adults does not necessarily result from excessive food intake?

## HEALTH RISKS OF EXCESSIVE BODY FAT

Obesity represents an important cause of preventable death in America. The combined effects of poor diet and physical inactivity caused approximately 400,000 deaths in the year 2000, a $33 \%$ jump over 1990. If the body weight of Americans continues to increase at its current rate, by 2020 one in five health care dollars spent on middle-aged Americans will result from obesity. Impaired glucose tolerance and overall diminished quality of life emerge even among obese children and adolescents. ${ }^{28,39,193,203}$ Hypertension, elevated blood sugar, postmenopausal breast cancer, and elevated total cholesterol and low high-density lipoprotein-cholesterol heighten an overweight individuals risks of poor health at any given level of excess weight. Increased loads on the major joints can lead to pain and discomfort, complications from osteoarthritis, inefficient body mechanics, and reduced mobility. ${ }^{93}$ The prevalence of obesity has counteracted the decline over previous years in coronary disease among middle-aged women. ${ }^{97}$ Obese and overweight individuals with two or more heart disease risk factors should reduce weight, while overweight persons without any other risk factors should at least maintain current body weight. Even a modest weight reduction improves insulin sensitivity and blood lipid profile, and prevents or delays diabetes onset in high-risk individuals. ${ }^{45,76}$

## Physical Fitness is Good Medicine

Improved physical fitness interacts with the overfat condition to lower disease risk. ${ }^{188}$ Men ages 30 to 83 years who are overweight but physically fit suffered fewer deaths from all
causes than unfit but normal-weight men. ${ }^{136}$ Unfit, lean men also show a higher risk of all-cause mortality than overfat, fit men. Such findings support the strategy of increasing physical activity to improve cardiovascular fitness of overweight men and women rather than relying solely on diet to improve the health risk profile.

Despite the current obesity epidemic, weight control remains low on the list of national public health priorities; it receives far less funding from the NIH than other widely prevalent diseases. Current direct and indirect total healthcare costs of obesity have risen to nearly $\$ 117$ billion, or about $10 \%$ of the more than $\$ 1$ trillion dollar cost of remaining ill! Use of health-care resources also increases proportionately with excess body fat. Clearly, maintaining a lean body composition throughout life reduces multiple disease risk. Whether weight loss by an already overweight or obese adult reduces health risk to the level of individuals who never gained weight in the first place remains unclear.

## Excessive Fatness in Childhood and Adolescence Predicts Adverse Health Effects in Adulthood

The origin of adult obesity and its adverse health consequences often begins in childhood. Children who gain more weight than peers tend to become overweight adults with increased risk for hypertension, elevated insulin, hypercholesterolemia, and heart disease. ${ }^{46,202}$ Being overweight during adolescence links to adverse health effects 55 years later. The Harvard Growth Study from 1922 to 1935 evaluated 3000 school children annually on a variety of health variables, including triplicate measures of body mass and stature at the same time each year until they left or graduated high school. ${ }^{40}$ Of the initial group, the researchers studied 1857 subjects for
an additional 8 years. Subjects were designated either lean (in the 25th to 50th percentile for BMI) or overweight (exceeding 75th percentile for BMI ). Compared with leaner subjects, overweight children as adults showed a greater risk of mortality from all causes and a twofold higher coronary heart disease risk. Women overweight in adolescence were eight times more likely to report problems with personal care and routine living tasks (walking, stair climbing, lifting) and a 1.6 -fold increase in arthritis than women rated lean in adolescence.

The alarming rise in obesity during childhood and adolescence requires immediate interventions to prevent subsequent risk for disease as these children become adults. Figure 30.8 shows the percentile cutoffs for a two-level procedure recommended by the American Academy of Pediatrics to identify either overweight children (BMI $>95$ th percentile; requires in-depth medical assessment) and those at risk of becoming overweight (BMI 85th 95th percentile; requires second-level screening including family history and risk factor assessment).

## Defined Health Risks

Considerable information exists regarding increasing levels of body fat and defined health risks in children, adolescents, and adults. Excessive body fat relates closely to the alarming increase in type 2 diabetes among children. For adult diabetics, $70 \%$ classify as overweight and nearly $35 \%$ are obese. A moderate 4 to $10 \%$ increase in body weight after age 20 associates with 1.5 greater risk of death from coronary artery disease and nonfatal myocardial infarction. ${ }^{183}$ Even maintaining body weight at the high end of the normal range increases heart disease risk. An 8 -year study of nearly 116,000 female nurses observed that all but the thinnest women showed increased risk for heart attack and chest pains. ${ }^{143}$ Nurses of average body weight experienced $30 \%$ more heart attacks than the thinnest counterparts, while the risk for a moderately overweight nurse


Figure 30.8 Two-level procedure using BMI to identify overweight adolescents and adolescents at risk of becoming overweight. (From Green M, ed. Bright futures: guidelines for health supervision of infants, children and adolescents. Arlington, VA: National Center for Education in Maternal and Child Health, 1994; www. mchlibrary.info/pubs/default.html)
averaged $80 \%$ higher. This means that a woman who gains 9 kg from her late teens to middle age doubles her heart attack risk. Epidemiologic evidence indicates excess body weight as an independent and powerful risk for congestive heart failure. ${ }^{113}$

## fyi <br> Regular Exercise Fights Heart Disease Regardless of Body Weight

Regular physical activity combats heart disease, even in the overweight or obese. Data from nearly 40,000 women, initially free from heart disease, in the Womans Health Study were followed for 10.9 years. Obese women who burned fewer than 1000 kCal weekly through exercise were 2.53 times more likely to develop heart disease than active nor-mal-weight women. But obese women who expended 1000 kCal or more in weekly exercise reduced that relative risk to 1.87 times. Regardless of body weight, women who exercised regularly showed an $18 \%$ reduced heart disease risk compared to sedentary women. The authors speculated that exercise may reduce or combat the ill effects of factors released by fat cells that promote the formation of abnormal blood clots.

Weinstein A, et al. The joint effects of physical activity and body mass index on coronary heart disease risk in women. Arch Intern Med 2008;168:884.

Weight gain also increases risk for cancers of the breast, colon, esophagus, prostate, kidney, and uterus (FIG. 30.9). ${ }^{23,220,256}$ Maintaining a BMI below 25 could prevent one of every six cancer deaths in the United States, or about 90,000 deaths yearly. ${ }^{23}$ One-half of cardiovascular deaths and one-third of colon, endometrial, and breast cancer deaths linked to the overweight condition.

Researchers followed a cohort of 82,000 female nurses ages 30 to 55 years every 2 years from 1976 to determine whether initial BMI modifies the relation between long-term weight gain or weight loss and hypertension risk. Figure 30.10 depicts the relative risk for hypertension, adjusted for multiple factors linked to hypertension in three groups stratified for BMI at age 18 . For women in the first and second BMI tertiles at age 18 (BMI <22.0), weight loss in later years did not reduce hypertension risk. Weight gain after age 18 markedly increased hypertension risk over that of women who maintained a stable body weight. For women whose BMI exceeded 22.0, subsequent weight loss dramatically decreased risk (relative risk of 0.72 for weight loss of 5.09 .9 kg and 0.57 for a loss of 10 kg or more). Weight gain increased hypertension risk in a manner similar to that of the lighter group of women. Obesity now ranks with high cholesterol, hypertension, cigarette smoking, and sedentary lifestyle as a major heart attack risk factor in contrast to its former status as a contributing risk factor.


Figure 30.9 Extra weight and the risk of cancer in women and men. (From Calle EE, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625.)


Figure $\mathbf{3 0 . 1 0}$ Multivariate relative risk for hypertension according to weight change after age 18 years within strata of BMI at age 18. Risk adjusted for: age, BMI at age 18, stature, family history of myocardial infarction, parity, oral contraceptive use, menopausal status, postmenopausal use of hormones, and smoking status. Horizontal pink line indicates normal risk. (From Huang Z, et al. Body weight, weight change, and risk for hypertension in women. Ann Intern Med 1998;128:81.)

## fyi

## Specific Health Risks of Excessive Body Fat

Impaired cardiac function from increased mechanical work and autonomic and leftventricular dysfunction
Hypertension, stroke, and deep-vein thrombosis Increased insulin resistance in children and adults and type 2 diabetes ( $80 \%$ of these patients are overweight)
Renal disease
Sleep apnea, mechanical ventilatory constraints (particularly in exercise), and pulmonary disease from impaired function because of added effort to move the chest

> wall

Problems receiving anesthetics during surgery
Osteoarthritis, degenerative joint disease, and gout
Endometrial, breast, prostate, and colon cancers
Abnormal plasma lipid and lipoprotein levels
Menstrual irregularities
Gallbladder disease
Enormous psychologic burden and social stigmatization and discrimination

## CRITERIA FOR EXCESSIVE BODY FAT: HOW FAT IS TOO FAT?

In Chapter 28, we discussed limitations of the height weight tables and BMI to assess body composition. Three approaches more appropriate for measuring a persons fat content are:

1. Percentage of body mass composed of fat
2. Distribution or patterning of fat at different anatomic regions
3. Size and number of individual fat cells

## fyi

## Obesity Is More Harmful to the Heart Than Smoking

More bad news for obese peopleheart attacks attack them more than a decade sooner than those of normal weight with a lower BMI. The leading theory in cardiology is that fat tissue produces harmful factors that precipitate heart attacks. The cholesterol build up in the coronary arteries and inflammatory or other chemicals produced by fat cells presumably trigger arterial plaque in the coronaries to suddenly rupture, causing a blood clot to form to unleash a heart attack. Data analyzed from a nationwide U.S. registry of people hospitalized for heart attack and unstable angina (chest pain) from 2001 to 2007 showed clearly that the higher the persons BMI, the younger the age of a first heart attack. The most obese people (BMI of 40 or more and average weight of 127 kg ) had their heart attacks on average at age 59 compared to age 75 for the lightest group (average weight 47 kg or underweight). All patients, regardless of body size, had about the same level of LDL cholesterol thought to be a major risk factor for heart attacks. Rates of smoking were equal across the BMI groups. Patients at the highest BMI ( $>40.0$ ) experienced a heart attack 12 years earlier than an individual at the low end of the BMI range. The second most important factor was cigarette smoking, where smokers had their first heart attack 10 years earlier than nonsmokers. This study was the first to show that BMI exerted a more powerful effect than smoking on early occurrence of myocardial infarction.

## BMI

$25.1 \quad 30.0 \quad 30.1 \quad 35.0 \quad 35.1 \quad 40.0>40.0$

| Years <br> heart attack <br> occurred <br> earlier than <br> normal | 3.5 | 6.8 | 9.4 | 12 |
| :--- | :--- | :--- | :--- | :--- |

Madala MC, et al. Obesity and age of first non-ST-segment elevation myocardial infarction. J Am Coll Cardiol 2008 16;52:979.

## Percentage of Body Fat

What determines the demarcation between a normal level of body fat and an excess? In Chapter 28, we suggested the following serve as the normal body fat range for adult men and womenthe average percentage body fat value $\pm 1$ standard deviation. For men and women ages 17 to 50 years, this variation equals 5\% body fat units. Using this statistical boundary, overfatness then corresponds to a body fat level that exceeds the average value plus $5 \%$ body fat. For example, in young men whose body fat averages $15 \%$ of body mass, the borderline for obesity becomes $20 \%$ body fat. For older men whose fat averages $25 \%$, obesity would include body fat in excess of $30 \%$. For young women, obesity corresponds to body fat content above $30 \%$; for older women, borderline obesity corresponds to about $37 \%$ body fat. We emphasize that just because the average value for percentage body fat increases with age, this does not dictate that people should become fatter as they age. In our opinion, one criterion for determining too fat emerges from data for younger men and womenabove $20 \%$ for men and above $30 \%$ for women. With this single gender-specific standard, average age-related population values do not become the reference standard and thus the acceptable criterion. We also recognize that this classification standard based on an average for young adults becomes extremely rigorous when applied to the entire population. It probably places more than $50 \%$ of adults in the overly fat category, a value below the $66 \%$ value for overweight and obese Americans presented in Figure 30.1. It also closely corresponds to proposed gender-based body fat standards computed for young adults from the relationship between BMI and four component estimates of percentage body fat for African Americans and whites. ${ }^{71}$


## Standard for Overfatness

Menabove 20\%; Womenabove 30\%

We consider that obesity exists along a continuum from the upper limit of normal ( $20 \%$ body fat for men and $30 \%$ for women) to as high as $50 \%$ and a theoretical maximum of nearly $70 \%$ of body mass in the massively obese. This latter groups weight ranges from 170 to 250 kg or higher. This can create a life-threatening situation in such extreme cases because the bodys total fat content exceeds lean body mass!

## Regional Fat Distribution

The patterning of the bodys adipose tissue, independent of total body fat, alters health risks in children, adolescents, and adults. ${ }^{38,58,69,230,257,259}$ Figure 30.11 shows two types of regional fat distribution. Increased health risk from fat deposition in the abdominal area (central or android-type obesity), particularly internal visceral deposits, may result from this tissues active lipolysis with catecholamine stimulation. Fat stored in this region shows greater metabolic responsiveness than fat in the gluteal and femoral regions (peripheral or
gynoid-type obesity). Increases in central fat more readily support processes that cause heart disease. ${ }^{206}$ In men, the amount of fat located inside the abdominal cavity (intraabdominal, or visceral, adipose tissue) is twice as large compared to that of women. ${ }^{13}$ For men, the percentage of visceral fat increases progressively with age, whereas this fat deposition in women begins to increase at menopause onset. ${ }^{123}$

Central fat deposition, independent of fat storage in other anatomic areas, reflects an altered metabolic profile that increases at least eight of the following:

1. Hyperinsulinemia (insulin resistance)
2. Glucose intolerance
3. Type 2 diabetes
4. Endometrial cancer
5. Hypertriglyceridemia
6. Hypercholesterolemia and negatively altered lipoprotein profile
7. Hypertension
8. Atherosclerosis


Figure 30.11 Male (android pattern) and female (gynoid pattern) fat patterning, including waist-to-hip girth ratio threshold for significant health risk.

As a general guideline, waist-to-hip girth ratios that exceed 0.80 for women and 0.95 for men increase risk of death even after adjusting for BMI. ${ }^{43,179,250}$ One limitation of the ratio is that it poorly captures the specific effects of each girth measure. Waist and hip circumferences reflect different aspects of body composition and fat distribution. Each has an independent and often opposite effect on cardiovascular disease risk. An increased waist girth is the so-called malignant form of obesity characterized by central fat deposition. This region of fat deposition provides a reasonable indication of the accumulation of intraabdominal (visceral) adipose tissue. This makes waist girth the trunk measure of clinical choice as a practical measure to evaluate the metabolic and health risks and accelerated mortality with obesity. ${ }^{109,156,195,216}$ Over a broad range of BMI values, men and women with high waist circumference values possess greater relative risk for cardiovascular disease, type 2 diabetes, cancer, dementia, and cataracts (the leading cause of blindness worldwide) than individuals with small waist circumference or peripheral obesity. ${ }^{105,190,248}$ Excess weight distribution in the abdominal area (and correspondingly high blood insulin levels)
also increases colorectal cancer risk. ${ }^{94,111}$ A waist girth that exceeds 91 cm ( 36 in .) in men and 82 cm ( 32 in .) in women nearly doubles the risk of this cancer. ${ }^{191}$ The unnumbered figure in the following FYI shows how to apply three BMI categories and waist girth measurements (above and below 40 inches for men and 34.6 inches for women) to assess a persons risk of health problems ranked from least risk to very high risk.

## Abdominal Adiposity Associated With Risk of Death

Researchers have examined the association of BMI (measured without wearing shoes), waist girth (narrowest torso girth), and waist-to-hip ratio with the risk of death among 359,387 participants (without prior history of cancer, heart disease, or stroke at baseline) from nine countries in the European Prospective Investigation into Cancer and Nutrition (EPIC; http://epic.iarc.fr/). The mean

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Relative risk of death among men and women according to waist girth and waist-to-hip ratio after adjustment for BMI (top panel for men and lower panel for women). Solid lines (orange) indicate relative risks, and red lines indicate $95 \%$ confidence intervals. The reference points for waist girth and waist-to-hip ratio are the sex-specific medians. (From Pischon T, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008 13;359:2105.)
age at baseline was $51.5 \pm 10.4$ years; $65.4 \%$ of the participants were women. After 9.7 years, 14,723 participants had died (4\%). The lowest risks of death related to BMI occurred at a BMI of 25.3 for men and 24.3 for women. By definition, underweight BMI $=<18.5$ ), normal weight $=18.5$ to $<25.0$, overweight $=25.0$ to $<30.0$, and obesity $=$ $>30.0$. After adjustment for BMI, waist girth and waist-to-hip ratio strongly associated with the risk
of death. The correlations for BMI with waist girth and waist-to-hip ratio were $\mathrm{r}=0.85$ and 0.55 (men), and $\mathrm{r}=0.84$ and 0.38 (women). BMI remained significantly associated with the risk of death when the statistical analysis included either waist circumference or waist-to-hip ratio. The authors advocate the use of waist girth or waist-tohip ratio in addition to BMI to assess death risk, particularly among persons with a relatively low BMI.

| BMI category |  |  |  |
| :---: | :---: | :---: | :---: |
| Waist girth | $\begin{gathered} \text { Normal } \\ 18.5-24.9 \mathrm{~kg} \cdot \mathrm{~m}^{-2} \end{gathered}$ | Overweight $25-29.9 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ | Obese class I $30-34.9 \mathrm{~kg} \cdot \mathrm{~m}^{-2}$ |
| $\begin{aligned} & \text { Men: < } 102 \mathrm{~cm} \\ & \text { Women: < } 88 \mathrm{~cm} \end{aligned}$ | Least risk | lnereased risk | High risk |
| Men: $\geq 102 \mathrm{~cm}$ <br> Women: $\geq 88 \mathrm{~cm}$ | lnceased risk | High risk | Very high risk |

Applying BMI and waist girth measurements in adult men and women from least risk to very high risk for health and medical problems. For men, $102 \mathrm{~cm}=40$ inches; for women, $88 \mathrm{~cm}=34.6$ inches. (Data from the world literature, including Douketis, JD. Body weight classification. CMAJ 2005;172:995.)

## Adipocyte Size and Number: Hypertrophy Versus Hyperplasia

Adipocyte size and number provide another way to assess and classify obesity. Adipose tissue mass increases in two ways:

1. Fat cell hypertrophy: Existing adipocytes enlarge or fill with fat
2. Fat cell hyperplasia: Total adipocyte number increases

One technique for studying adipose cellularity involves sucking small fragments of subcutaneous tissue (usually from the triceps, subscapular, buttocks, and/or lower abdomen) into a syringe through a needle inserted directly into the fat depot. Chemical treatment of the tissue sample isolates the individual adipocytes for counting. Dividing fat mass in the sample by adipocyte number determines the average quantity of fat per cell. One can estimate total adipocyte number by determining total body fat by a criterion method such as hydrostatic weighing. For example, an individual who weighs 88 kg with $13 \%$ body fat has a total fat mass of $11.4 \mathrm{~kg}(0.13 \times 88 \mathrm{~kg})$. Dividing 11.4 kg by the average fat content per cell estimates total adipocyte number. If the average adipocyte contains $0.60 \mu \mathrm{~g}$ of fat, then this persons body contains 19 billion adipocytes ( $11.4 \mathrm{~kg} \div 0.60 \mu \mathrm{~g}$ ).

Total adipocyte number $=$ Mass of body fat $\div$ Fat content per cell

In one of our laboratories, needle biopsy and photomicrographic techniques extracted fat and measured the average fat content of adipocytes at three anatomic sites. Figure 30.12 shows adipocytes from the upper buttocks of one of this textbooks authors whose total fat mass at the time equaled 17.02 kg (body mass: $89.1 \mathrm{~kg} ; 19.1 \%$ body fat) with $0.73 \mu \mathrm{~g}$ of fat per cell; the estimated total adipocyte number was 23.3 billion ( $17.02 \mathrm{~kg} \div 0.73 \mu \mathrm{~g}$ ). Over the next 20 years, a weight gain of 3.2 kg presumably was accounted for by an increase in total fat mass (without increasing FFM; more than likely a decline in FFM with aging). The additional fat accretion can probably be explained by increases in the size of individual fat cells without fat cell proliferation.

## Fat Cell Development and Adipocytes

Pioneering research in the early 1980s began to search for a molecular trigger to explain the link between newly developing fat cells (preadipocytes or precursors to fat cells) and subsequent obesity. Researches studied cellular differentiation to determine why some fat cells became excessively large and abundant and others remained normal in size without increasing their number. It had been determined that either the conservation of energy or the expenditure of energy differed in the development of adult white adipose tissue and infant brown adipose tissue. Specific genes were identified that first were expressed in preadipocytes compared to mature fat cells.


Figure 30.12 (Upper panel) Needle biopsy to extract adipocytes from the upper buttocks region. A small area is sterilized and anesthetized, and the biopsy needle placed beneath the skin surface to extract minute samples of fluid and tissue that is further analyzed to isolate a representative sample of fat cells. Photomicrographs of the adipocytes from the buttocks of a physically active professor before (center) and after (right) 6 months of marathon training. Adipocyte diameter averaged $8.6 \%$ smaller after training. The average volume of fat in each cell decreased by $18.2 \%$. The large spherical structures in the background are lipid droplets. Bottom panel. Cross section of human adipocytes $\times 440$. (From Geneser F. Color atlas of histology. Philadelphia: Lea \& Febiger, 1985. Top panel two photomicrographs courtesy of P. M. Clarkson, Muscle Biochemistry Laboratory, Department of Kinesiology, University of Massachusetts, Amherst, MA.)

Once identified, attention focused on what transcription factors and enhancers turned on those genes. From hundreds of turned on genes during fat cell differentiation, the aP2 gene became a good candidate as an appropriate model to study differentiation between brown fat cell versus white fat cell growth and development. ${ }^{77}$ Research in the 1990s originally identified the peroxisome proliferation-activated receptor gamma (PPAR $\gamma$ ) as the master gene of white fat cell development. Subsequent research has demonstrated that this human gene also serves the following three functions: (1) serves as a receptor for antidiabetic drugs (TZD drug class or thiazolidinediones); (2) triggers cellular metabolic effects to decrease adiposity; ${ }^{60,197}$ and (3) functions in the control of cell proliferation, atherosclerosis, macrophage function, and immunity. ${ }^{226}$

The brown fat present in infants (but presumably not in adults) has one main functionto generate enough heat for the babys survival. Heat production occurs metabolically by leaking hydrogen ions across the mitochondrions inner membrane, generating heat (futile metabolism) instead of converting it into ATP for other metabolic processes in white lipid droplets. Figure 30.13 shows a schematic diagram of these basic metabolic differences between how brown fat uses its mitochondria to convert food into heat rather than what occurs in white fat to produce ATP to power cellular functions.

## Molecular Biology to the Rescue

In 2004, researchers discovered a protein molecule PGC-lalpha that binds to the important PPAR $\gamma$ molecule and activates genes important to brown fat specific differentiation. ${ }^{57,194,209}$ The gene for PGC-1alpha expressed in white fat cells impacted an uncoupling protein (UCP1) that caused mitochondria to produce heat (thermogenesis or uncoupled mitochondrial respiration). Interestingly, this same gene also causes muscles with aerobic exercise training to switch their fiber-type to more oxidative fibers (type II to type I). ${ }^{83}$

The gene PRDM16 serves as one of the master regulators of brown fat differentiation. It stimulates brown adipogenesis by binding to PPAR $\gamma$ and activating its transcriptional function. This gene activates the PGC-1alpha gene and accelerates the expression of nine other brown fat specific genes, and with some molecular tinkering, makes the energy-wasting brown fat cells behave more like the energy-conserving white fat cells.

The bottom line of research with preadipocyte cells and PRDM16 and PGC-1alpha relates to their possible roles in regulating mitochondrial function.

This approach in obesity research shifts focus to the molecular basis of energy expenditure. Researchers are hopeful that the discovery of a new drug (or combination of drugs) included with these molecular gene manipulations, even if they only have a 1 to $2 \%$ internal metabolic effect for augmenting caloric expenditure in obese individuals, could over time with other management methods positively impact the obese condition. ${ }^{35,244}$

## Cellularity Differences Between Nonobese and Obese Persons

Figure 30.14 compares body mass, total fat, and adipose tissue cellularity in 25 subjects, 20 of whom classified as clinically obese (BMI $\sim 40.0$ ). The body mass of the obese averaged more than twice that of the nonobese, and they had nearly three times more body fat. In cellularity, adipocytes in the obese averaged $50 \%$ larger with nearly three times more cells ( 75 vs. 27 billion). Cell number represents the major


Figure 30.13 A unique set of molecular switches governs fat cell differentiation. Two master regulator genes, PPARgamma with RXR (a cofactor retinoic acid receptor) initiates white fat development; when PRDM16 switches on, the preadipocyte activates PGC- $1 \alpha$ (plays a central role in regulating cellular energy metabolism) along with other genes, which define the brown fat phenotype. The evidence is now abundantly clear that fat cells are not simply inert globs of lipid. Instead, they are dynamic and influential in exchanging chemical signals with the brain and reproductive and immune systems. Existing fat cells grow and shrink, and absorb and release energy-rich lipids as needed depending on substrate availability and utilization. When overloaded with surplus calories, fat cells can initiate cell division to absorb the oversupply; once they hypertrophy as they fill with excess fat, they remain in a state of flux until a shift occurs in the energy balance equation. Molecular remodeling of fat cells has the potential to shift the balance in favor of expenditure rather than storage. If the mechanism for brown fat production could be determined and turned on in obese adults (as both cell types originate from the same precursor cells), and if metabolic pathways i obese individuals could utilize the heat-producing mechanisms from brown fat, the extra heat energy from these cells might compete with the energy storage function of white fat cells and shift the energy balance equation in the direction of fat loss.


Figure 30.14 Comparison of body mass, total fat mass, and adipocyte size and number in obese and nonobese subjects. (Modified from Hirsch J, Knittle J. Cellularity of obese and non-obese human adipose tissue. Fed Proc 1970;29:1518.)
structural difference in adipose tissue mass between the severely obese and nonobese persons.

Relating total body fat content to cell size and cell number further demonstrates the contribution of adipocyte number to obesity. As body fat increases, adipocytes eventually reach a biologic upper limit. Once this occurs, cell number becomes the key factor determining any further obesity. Even doubling adipocyte size does not explain the large difference in total fat mass between obese and average persons. For comparison, an average-sized person has between 25 and 30 billion adipocytes, whereas the clinically severe obese may have more than three to five times this number, particularly when obesity occurs in childhood or adolescence. Differences also exist in the composition of the fatty acid structures in different adipose tissue regions (perivisceral, omental, subcutaneous fat) among overweight/obese males and females. ${ }^{73}$

## Effects of Weight Loss

Figure 30.15 shows a classic study of weight loss effects on adipose tissue characteristics of 19 obese adults during two stages of weight loss. During the first stage, subjects reduced body mass by 46 kg ( 149 to 103 kg ). Adipocyte number before weight reduction averaged 75 billion; this remained unchanged even after the $46-\mathrm{kg}$ reduction. In contrast, adipocyte size decreased by $33 \%$ from 0.9 to $0.6 \mu \mathrm{~g}$ of lipid per cell. When subjects attained normal body mass of 75 kg by losing an additional 28 kg , cell number still remained unchanged but cell size continued to shrink to about one-third that in a nonobese comparison group. When the patients achieved a normal body mass and body fat level, adipocytes had become considerably smaller than the nonobese. In adults, the major change in adipose cellularity in weight loss is shrinkage of adipocytes with no change in cell number. These findings suggest that weight loss in obese persons does not really cure their obesity, at least for total adipocyte number.

## Effects of Weight Gain

An interesting series of studies in the late 1960s and early 1970s evaluated the dynamics of weight gain on adipose tissue cellularity. In one study, adult male volunteers with an initial average body fat content of $15 \%$ deliberately increased daily caloric intake by three times normal to about 7000 kCal for 40 weeks. ${ }^{204}$ For a typical subject, body mass increased $25 \%$ and percentage body fat nearly doubled from 14.6 to $28.2 \%$. Fat deposition represented 10.5 kg of the 12.7 kg of weight gained during the overfeeding period. In a similar experiment with subjects with no personal or family history of obesity, voluntary overeating increased body mass by $16.4 \mathrm{~kg} .{ }^{186}$ In both experiments, adipocytes increased substantially in size with no change in cell number. When caloric intake decreased and subjects attained normal weight, total body fat declined and the adipocytes reverted to their original size. In general, moderate weight gain from overeating in adults enlarges existing adipocytes rather than stimulating new adipocyte development.

Possibility that New Adipocytes Form. Extreme accumulation of body fat in adults stimulates increased adipose cellularity because adipocyte size reaches an upper limit of about $1.0 \mu \mathrm{~g}$ fat, beyond which no further hypertrophy occurs. At extremes of obesity, almost all adipocytes attain their hypertrophic limit. In this situation, the preadipocyte pool provides additional adipocytes to increase cell number, with a concomitant increase in the quantity of fat stored within the liver and between muscle fibers. In maturity-onset severe obesity, in which the already obese adult gains even more body fat, hypercellularity may accompany the increasing size of existing adipocytes. The increased number of cells at this point constitutes a failure of adipocyte regulation that unfortunately leads to further fat accumulation.


Figure 30.15 Changes in adipose cellularity with weight reduction in obese subjects. (Data from Hirsch J. Adipose cellularity in relation to human obesity. In: Stollerman GH, ed. Advances in internal medicine, vol 17. Chicago: Year-Book, 1971.)

## Summary

1. Obesity or excess accumulation of body fat is a heterogeneous disorder with a final common pathway where energy intake chronically exceeds energy expenditure.
2. Over the past 30 years, the average body weight of adult Americans has increased considerably. Currently, $34 \%$ of adults ( $60+$ million) classify as obese ( $\mathrm{BMI} \geq 30$ ); $65 \%$ ( 130 million adults) are either overweight or obese ( $\mathrm{BMI} \geq 25$ ).
3. Fifteen to $20 \%$ of American children and $12 \%$ of adolescents (up from $7.6 \%$ in 1976 1980) classify as overweight. Excessive body fatness, childhoods most common chronic disorder, is most prevalent among poor and minority children.
4. Genetic factors account for 25 to $30 \%$ of excessive body fat accumulation. Genetic predisposition does not necessarily cause obesity, but in the right environment, the genetically susceptible individual gains body fat.
5. Substantial alterations in the populations gene pool do not explain the dramatic worldwide obesity epidemic.
6. A defective gene for adipocyte leptin production and/or hypothalamic leptin insensitivity (plus defects in production and/or sensitivity to other
chemicals) causes the brain to assess adipose tissue status improperly. Excessive food intake creates a chronic positive energy balance.
7. Excessive body fat is a leading cause of preventable death in the United States. Comorbid hypertension, elevated blood sugar level, postmenopausal breast cancer, and elevated total cholesterol and low HDL cholesterol levels increase an overweight persons risk of poor health at any level of excess weight.
8. The overfatness threshold for adult men and women should more closely reflect percentage body fat levels of younger adultsmen above $20 \%$; women above $30 \%$.
9. Body fat patterning affects health risks independent of total body fat. Fat distributed in the abdominal region (central, or android-type, obesity) poses a greater risk than fat deposited at the thighs and buttocks (peripheral, or gynoid-type, obesity).
10. Body fat increases in two ways before adulthood: (1) enlargement of individual adipocytes ( fat cell hypertrophy) and (2) increase in total cell number ( fat cell hyperplasia).
11. Modest weight gain and weight loss in adults changes adipocyte size with little change in cell number. In extreme weight gain, adipocyte number increases once cell size reaches a hypertrophic limit.

## Part 2 PRINCIPLES OF WEIGHT CONTROL: DIET AND EXERCISE

For many adults, body weight fluctuates only slightly during the year, even though annual food intake averages more than 800 kg . This represents an impressive constancy considering that slight increases in daily food intake translate to substantial weight gain over time if unaccompanied by compensatory increases in energy expenditure. The human body functions in accord with the laws of thermodynamics. If total food calories exceed daily energy expenditure, excess calories accumulate and store as fat in adipose tissue.

## ENERGY BALANCE: INPUT VERSUS OUTPUT

The first law of thermodynamics (often called the law of conservation of energy) posits that energy can be transferred from one system to another in many forms but cannot be created or destroyed. In human terms, this means that the energy balance equation dictates that body mass remains constant when caloric intake equals caloric expenditure. Figure 30.16 shows
that any chronic imbalance on the energy output or input side of the equation changes body weight.

Three ways unbalance the energy balance equation to produce weight loss:

1. Reducing caloric intake below daily energy requirements
2. Maintaining caloric intake and increasing energy expenditure through additional physical activity above daily energy requirements
3. Decreasing daily caloric intake and increasing daily energy expenditure

When considering the sensitivity of the energy balance equation, if caloric intake exceeds output by only 100 kCal per day, the surplus calories consumed in a year equal $36,500 \mathrm{kCal}$ ( 365 days $\times 100 \mathrm{kCal}$ ). Because $0.45 \mathrm{~kg}(1.0 \mathrm{lb})$ of body fat contains 3500 kCal (each 1 lb [ 454 g ] of adipose tissue contains about $86 \%$ fat, or $390 \mathrm{~g} \times 9 \mathrm{kCal} \cdot \mathrm{g}^{-1}=3514 \mathrm{kCal}$ per lb ), this caloric excess causes a yearly gain of about 4.7 kg $(10.3 \mathrm{lb})$ of body fat. In contrast, if daily food intake decreases by just 100 kCal and energy expenditure increases by 100 kCal (e.g., by walking or jogging one extra mile each day), then the yearly deficit equals the energy in $9.5 \mathrm{~kg}(21 \mathrm{lb})$ of body fat.


Figure 30.16 The energy balance equation plus intervention strategies and specific targets to alter energy balance in the direction of weight loss. Pro, protein; $T E F$, thermic effect of food.

## A Prudent Recommendation

The objective of weight-loss programs has changed dramatically over the past decade. The previous approach assigned a goal body weight that coincided with an ideal weight based on body mass and stature. Achievement of goal body weight heralded the weight-loss programs success. Currently, the World Health Organization (www.who.int/en), the Institute of Medicine of the National Academy of Sciences (www.iom.edu/), and the National Heart, Lung and Blood Institute (www.nhlbi.nih.gov/) recommend that an obese person reduce initial body weight by 5 to $15 \%$. This more realistic weight loss diminishes weight-related comorbidities and complications from hypertension, type 2 diabetes, and abnormal blood lipids and often exerts a positive effect on socialpsychological complications. Setting the initial weight loss goal beyond the 5 to $15 \%$ recommendation often gives patients an unrealistic and potentially unattainable target in light of current treatment methods.

## DIETING FOR WEIGHT CONTROL

The first law of thermodynamics affirms that weight loss occurs whenever energy output exceeds energy intake, regardless of the diets macronutrient mixture. Advantages of relatively high percentages of unrefined complex carbohydrates in the re-duced-calorie diet lie in their moderate-to-low glycemic index; high vitamin, mineral, and phytochemical content; low energy density; and low saturated fatty acid levels. A prudent dietary approach to weight loss unbalances the energy balance equation by reducing energy intake by 500 to 1000 kCal below daily energy expenditure. Moderately reduced food intake produces greater fat loss relative to the energy deficit than more severe energy restriction. Individuals who create larger daily deficits to lose weight more rapidly tend to regain the weight compared to those who lose weight at a slower rate.

Suppose an overfat woman who normally consumes 2800 kCal daily and maintains a body mass of 79.4 kg wishes to lose weight by caloric restriction (dieting). She maintains regular physical activity but reduces food intake to 1800 kCal to create a $1000-\mathrm{kCal}$ daily deficit. In 7 days, the accumulated deficit equals 7000 kCal , or the energy equivalent of 0.9 kg of body fat. Actually, she would lose considerably more than 0.9 kg during the first week because initially the bodys glycogen stores make up a large portion of the energy deficit. Stored glycogen contains fewer calories per gram and considerably more water than stored fat. For this reason, short periods of caloric restriction often encourage the dieter but produce a large percentage of water and carbohydrate loss per unit weight loss with only a small decrease in body fat. As weight loss continues, a larger proportion of body fat supports the energy deficit created by food restriction (see Fig. 30.23). To reduce body fat by an additional 1.4 kg , the dieter must maintain the reduced caloric intake of 1800 kCal for another 10.5 days; at this point, body fat theoretically decreases at a rate of 0.45 kg every 3.5 days.

## Long-Term Success

The potential for successful long-term weight loss maintenance generally varies inversely with the initial degree of fatness
(Fig. 30.17). For most individuals, initial success in weight loss relates poorly to long-term success. Participants in supervised weight-loss programs (pharmacologic or behavioral interventions) generally lose about 8 to $12 \%$ of their original body mass. Unfortunately, typically one- to two-thirds of the lost weight returns within a year, and almost all of it within 5 years. ${ }^{106,114,150,158}$ Figure 30.18 illustrates clearly that over a 7.3-year follow-up of 121 patients, return to original weight occurred in $50 \%$ of the dieters within 2 to 3 years, and only seven patients remained at their reduced body weights. These discouraging but typical statistics highlight the extreme difficulty of long-term maintenance of a low-calorie diet; it becomes particularly difficult in the relaxed atmosphere of ones home with ready access to food and often little emotional support.

## National Weight Control Registry: Clues to Success

Success stories exist despite difficulties usually encountered with sustaining weight loss. ${ }^{89,117}$ Among lifetime members of a commercial weight-loss organization that promotes


Figure 30.17 Likelihood of success in long-term maintenance of weight loss inversely relates to the level of obesity at the start of intervention.


Figure 30.18 General trend for percentage of patients remaining at reduced weights at various time intervals following accomplished weight loss.
prudent caloric restriction, behavior modification, group support, and moderate physical activity, more than half maintained their original weight loss goal after 2 years, and more than a third had done so after 5 years. ${ }^{151}$ Behavior modification, a common intervention in weight loss programs, provides a set of principles and techniques to alter exercise and eating habits. The therapy increases skills for replacing existing habits with new habits associated with more-healthful behaviors. Behavior therapy characteristics include eating well-balanced meals with reduced portion size, restricting daily caloric intake by 500 to 700 kCal , keeping meticulous records of food intake and physical activity, and increasing daily physical activity by 200 to 300 kCal .

A project recruited 784 individuals (629 women; 155 men) in the National Weight Control Registry (NWCR; www.nwcr.ws/), the largest database of individuals who successfully achieved prolonged weight loss. Criteria for NWCR membership included being age 18 years or older and maintaining weight loss of at least 30 pounds $(13.6 \mathrm{~kg})$ for 1 year or longer. Participants averaged 66 pounds ( 30 kg ) of weight
loss, and $14 \%$ lost more than 100 pounds ( 45.4 kg ). Members maintained the required minimum 30-pound weight loss for a 5.5-year average, and $16 \%$ maintained the loss for 10 years or longer. Most participants had been overweight since childhood; nearly half had one overweight parent, and more than $25 \%$ had both parents overweight. Genetic background may have predisposed these persons to obesity, but an impressive weight loss and its maintenance proves that heredity alone need not predestine a person to the obese condition.

About $55 \%$ of the NWCR members used either a formal program or professional assistance to lose weight; the rest succeeded on their own. Regarding weight-loss methods, $89 \%$ modified food intake and maintained relatively high levels of physical activity ( 2800 kCal weekly on average) to achieve goal weight loss. Only $10 \%$ relied solely on diet, and $1 \%$ used exercise exclusively. The diet strategy of nearly $90 \%$ of participants restricted intake of certain types and/or amounts of foods$44 \%$ counted calories, $33 \%$ limited lipid intake, and $25 \%$ restricted grams of lipid. Forty-four percent ate the same foods they normally ate but in reduced amounts (Table 30.1).

## TABLE 30.1 Top. Dietary Strategies to Achieve Weight Loss of Participants of the NWCR. Bottom. Effects of Weight Loss on Various Dimensions of Life Reported by Participants

|  |  | Percentage |  |
| :--- | :---: | :---: | :---: |
| Strategy | Women | Men | Total |
| Restricted intake of certain types or classes of food | 87.8 | 86.7 | 87.6 |
| Ate all foods but limited the quantity | 47.2 | 32.0 | 44.2 |
| Counted calories | 44.8 | 39.3 | 43.7 |
| Limited \% lipid intake | 31.1 | 36.7 | 33.1 |
| Counted lipid grams | 25.7 | 21.3 | 25.2 |
| Followed exchange diet | 25.2 | 11.3 | 22.5 |
| Used liquid formula | 19.1 | 26.0 | 20.4 |
| Ate only 1 or 2 food types | 5.1 | 6.7 | 5.5 |


|  |  | Percentage |  |
| :--- | :---: | :---: | :---: |
| Area of Life | Improved | No Difference | Worsened |
| Quality of life | 95.3 | 4.3 | 0.4 |
| Level of energy | 92.4 | 0.7 | 0.9 |
| Mobility | 92.3 | 7.1 | 1.6 |
| General mood | 91.4 | 6.9 | 0.1 |
| Self-confidence | 90.9 | 9.0 | 1.3 |
| Physical health | 85.8 | 12.9 | 0.9 |
| Interactions with: |  |  | 0.4 |
| Opposite sex | 65.2 | 32.9 | 0.1 |
| Same sex | 5.0 | 46.8 | 0.6 |
| Strangers | 69.5 | 30.4 | 0.4 |
| Job performance | 54.5 | 45.0 | 5.9 |
| Hobbies | 49.1 | 36.7 | 37.3 |
| Spouse interactions | 56.3 |  | 0.9 |

[^54]The registry members belief in the importance of physical activity for weight maintenance represents a significant finding; nearly all of them exercised as part of their strategy. Many walked briskly for at least 1 hour daily. About 92\% exercised at home, and one-third exercised regularly with friends. Women primarily walked and did aerobic dancing, while men chose competitive sports and resistance training. The data in Table 30.1 also show that successful weight loss had far-reaching, positive effects on their lives. At least $85 \%$ improved general quality of life, level of energy, physical mobility, general mood, self-confidence, and physical health. Only 13 (1.6\%) worsened in any of these areas. Such observations reaffirm that weight loss through diet and exercise can thwart a genetic predisposition to obesity. Small weight regains were common despite the success of these individuals in maintaining a large percentage of their weight losses. Very few of these individuals were able to lose the weight again after any regain. ${ }^{166}$

A follow-up study in 2008 extended the results presented above, providing more details about the weekly energy expenditure patterns among the 887 men and 2796 women who enrolled in the NWCR between 1993 and 2004. ${ }^{29}$ Interestingly, NWCR participants expended an average of $2621 \mathrm{kCal} \cdot \mathrm{wk}^{-1}$ in physical activity, but the range of expenditure $\left(2,252 \mathrm{kCal} \cdot \mathrm{wk}^{-1}\right)$ was almost as large as the average. Approximately $25.3 \%$ reported $<1000 \mathrm{kCal} \cdot \mathrm{wk}^{-1}$ and $34.9 \%$ reported $>3000 \mathrm{kCal} \cdot \mathrm{wk}^{-1}$. Activity level on registry entry related to the magnitude but not the duration of weight loss. The amount of activity reported by men has decreased over time, while no significant change was observed in women. The large amount of individual variability in energy expenditure makes it extremely difficult to pinpoint what amount of activity would constitute the optimum to maintain weight loss.

## Weight Loss Improves Disease-Risk Biomarkers

Weight loss by the obese often exerts a profound effect on biologic factors related to disease risk. ${ }^{49,149}$ Figure 30.19 shows the percentage changes from initial body weight and the change in biomarkers of disease risk in obese patients over a 27-month period using two energy-restricting meal plans. In phase 1 during the first 3 months, group $\mathrm{A}(N=50)$ attempted to consume an energy-restricted diet ( 1200 to 1500 kCal daily) composed of conventional, self-selected meals prepared by the subjects; group $\mathrm{B}(N=50)$, assigned the same caloric intake, substituted two meals and two snack-replacement shakes, soups, hot chocolate, and snack bars (Slim-Fast) for selfselected foods. In phase 2 (months 4 to 27), all subjects consumed self-selected diets of equal caloric value with one meal and one shake replacement. Unequivocal results emerged from both study phases. Group Bs greater weight loss during the 3month phase 1 period was attributed to a larger caloric deficit created with this eating plan. Thereafter, both groups reduced on average an additional $0.07 \%$ of initial body weight each month ( 4.2 kg for group A and 3.0 kg for group B). The bottom figure shows absolute changes in eight disease biomarkers
during phases 1 and 2 . Both groups reduced systolic blood pressure and plasma insulin, glucose, and triacylglycerol concentrations over the 27-month weight-loss period. These findings support the notion that a modest but sustained weight loss produces long-term health benefits as reflected by improvement in documented risk factors.

## Setpoint Theory: A Case Against Dieting

One can crash off large amounts of weight in a relatively short time by simply not eating. Unfortunately, success is short-lived, and eventually the urge to eat wins out and the lost weight returns. Some argue that the reason for this failure lies in a genetically determined setpoint for body weight (or body fat) that differs from what the dieter would like. The proponents of a setpoint theory maintain that all persons (fat or thin) have a well-regulated internal control mechanism located deep within the lateral hypothalamus that maintains with relative ease a preset level of body weight and/or body fat within a tight range.

In a practical sense, this represents a persons body weight when not counting calories. Exercise and FDA-approved antiobesity drugs may lower a persons setpoint, whereas dieting exerts no effect. Each time body weight decreases below ones preestablished setpoint, internal adjustments that affect food intake and regulatory thermogenesis resist the change and conserve and/or replenish body fat. For example, resting metabolism slows and the individual becomes obsessed with food, unable to control the urge to eat. Even when persons overeat and gain body fat above their normal level, the body resists this change by increasing resting metabolism and causing the person to lose interest in food.

## Resting Metabolism Decreases

Resting metabolism often decreases when dieting progressively produces weight loss. ${ }^{153,246}$ Hypometabolism with caloric deficit often exceeds the decrease attributable to the loss of body mass or FFM independent of the persons weight status or prior dieting history. A depressed metabolism conserves energy, causing the diet to become progressively less effective despite a restricted caloric intake. This produces a weight-loss plateau. Further weight loss occurs at a slower pace than predicted from the mathematics of the restricted energy intake.

Figure 30.20A shows the close coupling between daily total energy expenditure (TEE) required to maintain a constant FFM in obese and nonobese subjects at their usual body weights. When body weight declined by $10 \%$ below the usual weight (Fig. 30.20B), TEE declined more than explained by the normal relation between energy expenditure and FFM. Both obese and normal-weight subjects became more energy efficient, requiring disproportionately lower energy intake to maintain the lower body weight. Conversely, increasing body weight by $10 \%$ above usual weight (Fig. 30.20C) produced a 15 to $20 \%$ unanticipated increase in energy expenditure that countered the gain in body fat.


Figure 30.19 A. Average percentage change from initial body weight of obese patients during 27 months of treatment with an energy-restricted diet containing 1200 to 1500 kCal . B. Absolute changes in biomarkers for groups A (energy-restricted, selfselected, self-prepared meals) and B (Slim-Fast replacement meals) from baseline (Phase 1) to 27 months of energy restriction (Phase 2). SBP, systolic blood pressure; DBP, diastolic blood pressure. (Modified from Detschuneit HH, et al. Metabolic and weight-loss effects of a long-term dietary intervention in obese patients. Am J Clin Nutr 1999;69:198.)

These data support the setpoint concept, or command signal that modulates metabolism to defend a specific level of body fat; unfortunately in the obese, regulation occurs at a higher body fat level.

Figure 30.21 shows further evidence of the bodys defense against deviations in body weight. This classic
research carefully monitored body mass, resting oxygen consumption (minimal energy requirement), and caloric intake of six obese men for 31 days. During the prediet period, body weight and resting oxygen consumption stabilized with a daily food intake of 3500 kCal . Thereafter, daily caloric intake decreased to 450 kCal . When the subjects switched to the


Figure 30.20 Relationship between daily total energy expenditure (TEE) and fat-free body mass (FFM) in obese and normal subjects (A) at their usual body weights, (B) after $10 \%$ weight reduction, and (C) after 10\% weight gain. (From Leibel RL, et al. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995;332:621.)


Figure 30.21 Results of a classic study of the effects of two levels of caloric intake on body mass and resting oxygen consumption. Failure of the actual weight loss to keep pace with that predicted on the basis of food restriction (dashed line) often leaves the dieter frustrated and discouraged. (Adapted from Bray G. Effect of caloric restriction on energy expenditure in obese subjects. Lancet 1969;2:397.)

## IN A PRACTICAL SENSE

## Recognizing Warning Signs of Disordered Eating

Disordered eating refers to a broad spectrum of complex behaviors, core attitudes, coping strategies, and conditions that share an emotionally based, inordinate, and often pathologic focus on body shape and weight.

## ANOREXIA ATHLETICA

A cluster of personality traits exists among some athletes that often shares a commonality with patients with clinical eating disorders. The same traits that help an athlete excel in sportscompulsive, driven, dichotomous thinker, perfectionist, competitive, compliant and eager to please (coachable), and self-motivatedincrease the risks for developing disordered eating patterns. This risk grows for individuals whose normal, genetically determined body size and shape deviate from the ideal imposed by the sport. The term
anorexia athletica describes the continuum of subclinical eating behaviors of athletes who fail to meet the criteria for a true eating disorder but who exhibit at least one unhealthy method of weight control, including fasting, vomiting, or use of diet pills, laxatives, or diuretics (water pills). Clinical observations indicate a prevalence of disordered eating behaviors of 15 to $60 \%$ among athletes, depending on the sport.

For many athletes, patterns of disordered eating coincide with the competitive season and abate when the season ends. For them, the preoccupation with body weight may not reflect a true underlying pathology but a desire to achieve optimum physiologic function and competitive performance. For a small number of athletes, the season never ends and they develop a full-blown eating disorder. Anorexia nervosa and bulimia nervosa are the two most common eating disorders. A third category, binge-eating disorder, does not include purging behavior.


The first published photo of an anorectic in an American medical journal. By the 1930s, there were three essential techniques in the management of anorexia nervosa: change of environment, forced feeding, and psychotherapy. Severe cases were generally treated in private psychiatric hospitals. (From Fasting girls. N Engl J Med 1932;207(5):Oct.)

## ANOREXIA NERVOSA

Originally described in ancient writings, anorexia nervosa is an unhealthy physical and mental state characterized by a crippling obsession with body size. A nervous loss of appetite reflects preoccupation with dieting and thinness and refusal to eat enough food to maintain normal body weight. The relentless pursuit of thinness (present in about 1 to $2 \%$ of the general population) includes an intense fear of weight gain and fatness (despite a low body weight) and failure to menstruate regularly (amenorrhea). Anorectic persons have a distorted body image; they actually perceive themselves as fat despite their emaciation.

Anorexia nervosa usually begins with a normal attempt to lose weight through dieting (Table 1). With prolonged dieting, the individual continues to eat less until practically no food is consumed. Eventually, food restriction becomes an obsession, and the anorectic person achieves no sense of satisfaction despite continued weight loss. Eventually, the anorectic person exhibits denial of the accompanying extreme emaciation.

## BULIMIA NERVOSA

The term bulimia, literally meaning ox hunger, refers to gorging or insatiable appetite. In bulimia nervosa, far more common than anorexia nervosa, purging and intense feelings of guilt and shame almost always follow the episodes of binge eating (Table 2). Approximately 2 to $4 \%$ of all adolescents and adults in the general population (almost exclusively female, including 5\% of college women) have bulimia nervosa. Unlike the continual semistarvation of anorexia nervosa, binge eating characterizes bulimia nervosa. The bulimic person consumes calorically dense food within several hours (often at night and out of sight), usually containing between 1000 and 10,000 calories. This is followed by fasting, self-induced vomiting, taking laxatives or diuretics, or compulsive exercising solely to avoid gaining weight.

## TABLE 1 Warning Signs of Anorexia Nervosa

Preoccupation with being too fat despite maintenance of normal body weight
Loss of menstrual cycle (amenorrhea)
Frequent commenting about body weight or shape
Significant loss of body weight
Weight too low for athletic performance
Ritualistic concern and preoccupation with dieting,
counting calories, cooking, and eating meals
Excessive concern about body weight, size, and shape, even after weight loss
Feeling of helplessness in the presence of food
Severe shifts in mood
Guilt about eating
Compulsive need for continuous, vigorous physical activity that exceeds training requirements for a specific sport
Maintenance of a skinny look (body weight less than 85\% of expected weight)
Prefers to eat in isolation
Wears baggy clothes to disguise thin-looking appearance Episodes of bingeing and purging

## IN A PRACTICAL SENSE

## TABLE 2 Warning Signs of Bulimia Nervosa

> Excessive concern about body weight, body size, and body composition
> Frequent gains and losses in body weight
> Visits to the bathroom following meals
> Fear of not being able to stop eating
> Eating when depressed
> Compulsive dieting after binge-eating episodes
> Severe shifts in mood (depression, loneliness)
> Secretive binge eating but never overeating in front of others
> More frequent criticism of own body size and shape Personal or family problems with alcohol or drugs Irregular menstrual cycle (oligomenorrhea)

## BINGE-EATING DISORDER

Episodes of bingeing, often without the subsequent purging behavior common to bulimia nervosa, characterize binge-eating disorder. Individuals eat more rapidly than normal until they can consume no additional food. Food intake greatly exceeds that determined by the physiologic hunger drive. Binge eating, done in private, occurs with feelings of guilt, depression, or self-disgust. These individuals

Continued
suffer greater self-anger, shame, lack of control, and frustration than nonbingeing overfat individuals. The diagnosis of bingeeating disorder requires that the individual experiences a lack of control over eating and marked psychologic distress when it occurs. The person must binge at least an average of 2 days a week for 6 months. Binge eating differs from the overfat condition because the same level of self-anger, shame, lack of control, and frustration about binge eating does not necessarily accompany obesity. Little factual information exists about the prevalence of binge-eating disorder; it may occur in approximately $2 \%$ of the U.S. population.

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low-calorie diet, body weight and resting metabolism decreased, but the percentage decline in metabolism exceeded the body weight decrease. The dashed line (upper figure) represents the expected weight loss for the $450-\mathrm{kCal}$ diet. The decline in resting metabolism (middle figure) conserved energy to make the diet progressively less effective. More than half of the total weight loss occurred over the first 8 days of dieting; the remaining weight loss occurred during the final 16 days. A plateau in the theoretical weight-loss curve often frustrates and discourages dieters, causing them to abandon the program.

## Biologic Feedback Mechanism

Further disconcerting news awaits those who desire permanent fat loss. When overfat people lose weight, adipocytes increase their level of the fat-storing enzyme LPL. ${ }^{114}$ This adaptation facilitates body fat synthesis, and the fatter the person before weight loss, the greater the LPL production with weight loss. In essence, the fatter one is at the start, the more vigorously the body attempts to regain the lost weight. This observation supports the existence of a biologic feedback mechanism between the brain and the bodys fat levels and helps to explain the difficulty overfat individuals have maintaining weight loss.

The setpoint theory delivers unwelcome news for those with a setpoint tuned too high; encouragingly, regular exercise may lower the setpoint level. Concurrently, regular exercise
conserves and even increases FFM, raises resting metabolism (if FFM increases), and induces metabolic changes that facilitate fat catabolism. These healthful adaptations all augment the weight-loss effort. On page 813, we discuss how food intake tends to decline initially, despite the increase in energy output, for overly fat men and women who begin to exercise regularly. As a physically active lifestyle continues and body fat decreases, caloric intake balances daily energy requirements to stabilize body mass at a new, lower level.

Challenge to the Setpoint Proponents. Some research challenges the argument that individuals who lose weight necessarily maintain the initial depressed metabolism that predisposes them to weight regain. ${ }^{240}$ Undoubtedly, energy restriction produces a transient state of hypometabolism if the dieter maintains the state of negative energy intake. This adaptive downregulation in resting metabolism does not persist when individuals lose weight but then reestablish balance where energy intake equals energy expenditure at their lower body weight. Consequently, research that fails to establish energy balance after weight loss gives the inaccurate impression that individuals who lose weight necessarily battle a prolonged overcompensating reduction in resting energy expenditure until they return to their original body weight. Replication of these findings will reinforce that downregulation of resting metabolism is not a necessary characteristic of weight loss or a primary component to explain the tendency for weight regain.

## Dieting Extremes

Professional organizations have voiced strong opposition to some dietary practices, particularly extremes of fasting and low-carbohydrate, high-fat, and high-protein diets. Dietary extremes raise concern about athletes and other adolescents and young adults who routinely engage in bizarre and often pathogenic weight-control behaviors (see In a Practical Sense, p. 807).

## Low Carbohydrate Ketogenic Diets

Ketogenic diets emphasize carbohydrate restriction while generally ignoring total calories and the diets cholesterol and saturated fat content. Billed as a diet revolution and championed by the late Dr. Robert C. Atkins, ${ }^{7}$ the diet was first promoted in the late 1800 s and has appeared in various forms since then. Long disparaged by the medical establishment, advocates maintain that restricting daily carbohydrate intake to 20 g or less for the initial 2 weeks, with some liberalization afterward, causes the body to mobilize considerable fat for energy. This generates excess plasma ketone bodiesbyproducts of incomplete fat breakdown from inadequate carbohydrate catabolism; ketones supposedly suppress appetite. Theoretically, the ketones lost in the urine represent unused energy that should further facilitate weight loss. Some advocates claim that urinary energy loss becomes so great that dieters can eat all they want as long as they restrict carbohydrates.

The singular focus of the low-carbohydrate diet craze may eventually reduce caloric intake, despite claims that dieters need not consider calorie intake as long as lipid represents the excess. Initial weight loss also may result largely from dehydration caused by an extra solute load on the kidneys that increases water excretion. Water loss does not reduce body fat. Low-carbohydrate intake also sets the stage for lean tissue loss because the body recruits amino acids from muscle to maintain blood glucose via gluconeogenesisan undesirable side effect for a diet designed to induce body fat loss.

Three clinical trials compared the Atkins-type, lowcarbohydrate diet with traditional low-fat diets for weight loss. ${ }^{67,187,258}$ The low-carbohydrate diet was more effective in achieving a modest weight loss for severely overweight persons. Some measures of heart health also improved as reflected by a more favorable lipid profile and glycemic control in those who followed the low-carbohydrate diet for up to 1 year. ${ }^{213}$ Such findings add a measure of credibility to low-carbohydrate diets and challenge conventional wisdom concerning the potential dangers from consuming a high-fat diet.

Importantly, Atkins-type, high-fat low-carbohydrate diets require systematic long-term evaluation (up to 5 years) for safety and effectiveness, particularly related to the blood lipid profile. The diet, which places no limit on the amount of meat, fat, eggs, and cheese a person consumes, poses nine potential health hazards:

1. Raises serum uric acid levels
2. Potentiates development of kidney stones

## Perhaps Not as Bad as Previously Believed

A two-year study of 322 overweight Israelis (average BMI of 31) reported a low-carbohydrate diet did better than a typically sanctioned low-fat diet to promote weight loss and boost blood levels of HDL-cholesterol. The Mediterranean diet, rich in olive oil, whole grains and fruits, with some wine, was more successful than the low-fat diet in controlling blood glucose levels. These findings may impact clinical medicine to consider the alternative low-carbohydrate and Mediterranean diets as safe and effective alternatives for patient treatment. This does not necessarily endorse the Atkins high-fat, low-carbohydrate diet because the lowcarbohydrate participants were encouraged to consume vegetable fats, in contrast to meat and cheese fats that Atkins dieters typically ingest. ${ }^{199}$
3. Alters electrolyte concentrations to initiate cardiac arrhythmias
4. Causes acidosis
5. Aggravates existing kidney problems from the extra solute burden in the renal filtrate
6. Depletes glycogen reserves, contributing to a fatigued state
7. Decreases calcium balance and increases risk for bone loss
8. Causes dehydration
9. Retards fetal development during pregnancy from inadequate carbohydrate intake

For high-performance endurance athletes who train at or above $70 \%$ of maximum effort, switching to a high-fat diet is ill advised because the body needs to maintain adequate blood glucose and glycogen packed in the active muscles and liver storage depots. Fatigue during intense exercise for more than 60 minutes duration occurs more rapidly when athletes consume high-fat meals than with carbohydrate-rich meals.

## High-Protein Diets

Low-carbohydrate, high-protein diets may shed pounds in the near term, but their long-term success remains questionable and may even pose health risks. ${ }^{56}$ These diets have been promoted to the obese as last-chance diets. Earlier versions consisted of protein in liquid form advertised as miracle liquid. Unknown to the consumer, the liquid protein mixture often contained a blend of ground-up animal hooves and horns, with pigskin mixed in a broth with enzymes and tenderizers to predigest it. Collagen-based blends produced from gelatin hydrolysis (supplemented with small amounts of essential amino acids) did not contain the highest quality amino acid mixture and lacked required vitamins and minerals (particularly copper). A negative copper balance coincides
with electrocardiographic abnormalities and rapid heart rate. ${ }^{59}$ Protein-rich foods often contain high levels of saturated fat, which increase the risk for heart disease and type 2 diabetes. Diets excessively high in animal protein increase urinary excretion of oxalate, a compound that combines primarily with calcium to form kidney stones. ${ }^{177}$ The diets safety improves if it contains high-quality protein with ample carbohydrate, essential fatty acids, and micronutrients. ${ }^{157}$

Some argue that an extremely high protein intake suppresses appetite through reliance on fat mobilization and subsequent ketone formation. The elevated thermic effect of dietary protein, with its relatively low coefficient of digestibility (particularly for plant protein), reduces the net calories available from ingested protein compared with a well-balanced meal of equivalent caloric value. This point has some validity, but one must consider other factors when formulating a sound weight-loss program, particularly for physically active individuals. A high-protein diet has the potential for these four deleterious outcomes:

1. Strain on liver and kidney function and accompanying dehydration
2. Electrolyte imbalance
3. Glycogen depletion
4. Lean-tissue loss

## Semistarvation Diets

A therapeutic fast or very low-calorie diet (VLCD) may benefit severe clinical obesity where body fat exceeds 40 to $50 \%$ of body mass. The diet provides between 400 and 800 kCal daily as high-quality protein foods or liquid meal replacements. Dietary prescriptions usually last up to 3 months but only as a last resort before undertaking more-extreme medical approaches for morbid obesity that include various surgical treatments (collectively called bariatric surgery). Surgical treatments that considerably reduce stomach size and reconfigure the small intestine induce a sustained weight loss, but they generally are prescribed for patients with a BMI of at least 40 , or a BMI of 35 when accompanied by other obesityrelated medical conditions.

Dieting with VLCD requires close supervision, usually in a hospital setting. Proponents maintain that severe food restriction breaks established dietary habits, which in turn improves the long-term prospects for success. These diets also may depress appetite to help compliance. Daily medications that accompany a VLCD include calcium carbonate for nausea, bicarbonate of soda and potassium chloride to maintain consistency of body fluids, mouthwash and sugar-free chewing gum for bad breath (from a high level of ketones from fatty acid catabolism), and bath oils for dry skin. For most individuals, semistarvation does not compose an ultimate diet or proper approach to weight control . Because a VLCD provides inadequate carbohydrate, the glycogen-storage depots in the liver and muscles deplete rapidly. This impairs physical tasks that require either intense aerobic effort or shorter-duration anaerobic power output. The continuous
nitrogen loss with fasting and weight loss reflects an exacerbated lean tissue loss, which may occur disproportionately from critical organs like the heart. The success rate remains poor for prolonged fasting.

Table 30.2 summarizes the principles and main advantages and disadvantages of popular dietary approaches to weight loss. Most diets produce weight loss during the first several weeks, although body water makes up much of the lost weight. In addition, lean tissue loss occurs with dieting alone, particularly in the early phase of a VLCD. An individual can certainly reduce weight through dieting alone, but few persons achieve long-term success in favorably altering body size and composition.

## FACTORS THAT AFFECT WEIGHT LOSS

Hydration level and duration of the energy deficit affect the amount and composition of weight lost.

## Early Weight Loss Largely Water

Figure 30.22 presents the general trend for the percentage composition of daily weight loss during 4 weeks of dieting. Approximately $70 \%$ of the weight lost over the first week of energy deficit consists of water loss. Thereafter, water loss progressively lessens, representing only about $20 \%$ of the weight lost in the second and third weeks; concurrently, body fat loss accelerates from 25 to $70 \%$. During the fourth week of dieting, reductions in body fat produce about $85 \%$ of the weight loss without further increase in water loss. Proteins contribution to weight loss increases from 5\% initially to about $15 \%$ after the fourth week. In practical terms, counseling efforts should emphasize that the weight lost during the initial attempts to reduce weight, when successful, consists chiefly of water and not fat; it takes approximately four weeks to establish the desired pattern of fat loss for each pound of weight loss.

## Hydration Level

Restricting water during the first several days of a caloric deficit increases the proportion of body water lost and decreases the proportion of fat lost. More total weight loss occurs with restricted daily water intake, but the additional weight lost comes solely from water as dehydration progresses. Dieters lose the same quantity of body fat regardless of fluid intake level.

## Longer-Term Deficit Promotes Fat Loss

Figure 30.23 reinforces the important concept that the caloric equivalent of the weight lost increases as duration of caloric restriction progresses. After 2 months on a diet, the caloric equivalent of weight loss exceeds twice that in the first week. This points out the importance of maintaining a caloric deficit for an extended duration. Shorter periods of caloric restriction

TABLE 30.2 Principles, Advantages, and Disadvantages of Some Popular Weight-Loss Methods

| Method | Principle | Advantages | Disadvantages | Comments |
| :---: | :---: | :---: | :---: | :---: |
| Surgical procedures | Alteration of gastrointestinal tract changes capacity or amount of absorptive surface | Caloric restriction less necessary | Risks of surgery and postsurgical complications include death ${ }^{a}$ | Radical procedures include stomach stapling and removal of section of small intestine (jejunoileal bypass) |
| Fasting | No energy input ensures negative energy balance | Rapid weight loss Reduced exposure to temptation | Ketogenic <br> Large portion of weight lost from lean body mass Nutrients lacking | Medical supervision mandatory and hospitalization recommended |
| Protein-sparing modified fast | Same as fasting except protein or protein with carbohydrate intake assumed to preserve lean body mass | Same as fasting | Ketogenic Nutrients lacking Some deaths reported, possibly from electrolyte depletion | Medical supervision mandatory <br> Example: The Last Chance Diet |
| One food centered diets | Low caloric intake favors negative energy balance | Easy to follow (initial psychologic appeal) | Too restrictive; nutrients lacking Repetitious nature causes boredom | No food or food combination burns off fat Examples: grapefruit diet and egg diet |
| Low- <br> carbohydrate/high- <br> fat diets | Increased ketone excretion removes energy from the body <br> Fat intake often voluntarily decreased; results in low caloric intake | Inclusion of rich foods has psychologic appeal Initial rapid water loss an incentive | Ketogenic High-fat intake contraindicated for heart and diabetes patients Nutrients lacking | Examples include Atkins diet and South Beach diet, and the Mayo, Drinking Mans and Air Force diets |
| Low-carbohydrate/ high-protein diets | Low caloric intake favors negative energy balance | Initial rapid water loss an incentive Increased thermic effect of protein | Expense and repetitious; difficult to sustain | If meat emphasized, the diet becomes high in fat |
| High-carbohydrate/ low-fat diets | Low caloric intake favors negative energy balance | Wise food selections can make the diet nutritionally sound | Initial water retention (from glycogen storage) may be discouraging | Examples include the Pennington diet and the Pritikin diet |

${ }^{a}$ Zigmond DS, et al. Hospitalization before and after gastric bypass surgery. JAMA 2005;294:1918.


Figure 30.22 General trend for the percentage composition of the weight lost during 4 weeks of caloric restriction.


Figure 30.23 General trend for the energy (caloric) equivalent of the weight lost in relation to the duration of caloric restriction. As caloric restriction progresses, the energy equivalent per unit of weight lost increases to about 7000 kCal per kilogram after 20 weeks. This occurs because of the large initial body water loss (no calorie value) early in weight loss.
produce a larger percentage of water and carbohydrate loss per unit weight reduction with only a minimal decrease in body fat.

## EXERCISE FOR WEIGHT CONTROL

Conventional wisdom views excessive food intake as the prime cause of the overfat condition. Most persons believe that the only way to reduce unwanted body fat entails caloric restriction by dieting. This overly simplistic strategy partly accounts for the dismal success in maintaining weight loss over the long term, refocusing debate on the contribution of food intake to obesity. ${ }^{85,198}$ Despite controversy about the precise contributions of physical inactivity and excessive caloric intake to body fat accretion, a sedentary lifestyle consistently emerges as an important factor in weight gain by children, adolescents, and adults. ${ }^{11,21,184,224}$

## Not Simply Gluttony

Excess weight gain often parallels reduced physical activity rather than increased caloric intake. Physically active individuals who eat the most often weigh the least and maintain the highest levels of physiologic fitness.

Obese infants do not characteristically ingest more calories than recommended dietary standards. For children ages 4 to 6 years, daily energy expenditure averaged $25 \%$ below the current recommendation for energy intake at this age. A low level of daily physical activity primarily caused the depressed energy output. ${ }^{25}$ More specifically, $50 \%$ of boys and $75 \%$ of girls in the United States fail to engage in even moderate physical activity three or more times weekly. ${ }^{1}$ Physically active children tend to be leaner than less active counterparts. For preschool children, no relationship
emerged between total energy intake, or the fat, carbohydrate, and protein composition of the diet and percentage body fat. ${ }^{8}$ Excessive fatness relates directly to the number of hours spent watching television (a consistent marker of inactivity) among children, adolescents, and adults. ${ }^{5,75}$ For example, 3 hours of television viewing a day led to a twofold increase in obesity and a $50 \%$ increase in diabetes. ${ }^{98}$ Each 2-hour-per-day increment of TV watching coincides with a $23 \%$ increase in obesity and a $14 \%$ rise in diabetes risk. Excessive television watching, playing video games, and otherwise remaining inactive characterizes overweight minority teens. Estimates indicate that reducing the amount of time spent watching television, playing video games, or using a computer could substantially reduce the incidence of metabolic syndrome. ${ }^{69}$ Minimizing time devoted to such behaviors can help combat childhood fat gain. ${ }^{74,182}$

The observation that overfat children often eat the same or even less than peers of average body weight also pertains to less physically active adults as they slowly, progressively gain weight. Overweight individuals often do not eat more on average than persons of normal weight. Consequently, it remains neither prudent nor justifiable to emphasize dieting alone to effectively induce long-term weight loss. ${ }^{87}$

## The Most Desirable Solutionłfacrease Energy Output

Physically active men and women usually maintain a desirable body composition. An increased level of regular physical activity combined with dietary restraint maintains weight loss more effectively than long-term caloric restriction alone. ${ }^{3,20,117,167,233}$ A negative energy balance induced by increased caloric expenditure, through either lifestyle activities or formal exercise programs, unbalances the energy balance equation for weight loss, improves physical fitness and the health risk profile, and favorably alters body composition and body fat distribution for children and adults. ${ }^{55,125,184,205,212,237}$ Regular exercise produces less accumulation of central adipose tissue associated with aging. ${ }^{108,120,185,232}$ Overweight women show a dose response relationship between amount of exercise and longterm weight loss. ${ }^{103}$ Obese adolescents and adults improve body composition and visceral fat distribution from both moderate physical activity or more vigorous exercise that improves cardiovascular fitness, with more intense physical activity being most effective. ${ }^{99}$ For obese boys and girls, the most favorable body composition changes occur with (1) long-duration exercise; (2) aerobic exercise combined with high-repetition resistance training; and (3) exercise programs combined with a behavior-modification component. ${ }^{81,139,147}$ Additional spin-off from regular exercise includes slowing of the age-related loss in muscle mass, possible prevention of adult-onset obesity, improvement in obesity-related comorbidities, decreased mortality, and beneficial effects on existing chronic diseases. ${ }^{17,84,137,144,215}$

## Two Misconceptions About Exercise

Two arguments attempt to counter the increased physical activity approach to weight loss. One maintains that exercise inevitably increases appetite to produce a proportionate increase in food intake that negates the caloric deficit that increased physical activity produces. The second argument claims that the relatively small calorie-burning effect of a normal exercise workout does not dent the bodys fat reserves as effectively as food restriction.

## Misconception 1: Increased Physical Activity Increases Food Intake

Sedentary persons often do not balance energy intake and energy expenditure. Failure to accurately regulate energy balance at the lower end of the physical activity spectrum contributes to the creeping obesity observed in highly mechanized and technically advanced societies. In contrast, regular exercisers maintain appetite control within a reactive zone where food intake more readily matches daily energy expenditure.

In considering the effects of exercise on appetite and food intake, one must distinguish exercise type and duration and the participants body fat status. Lumberjacks, farm laborers, and endurance athletes consume about twice as many daily calories as sedentary individuals. More specifically, marathon runners, cross-country skiers, and cyclists consume about 4000 to 5000 kCal daily, yet they are the leanest people in the population. Obviously, their large caloric intake meets the energy requirements of training while maintaining a relatively lean body composition.

For the overweight or obese person, the extra energy required for increased physical activity more than offsets moderate physical activitys small compensatory appetitestimulating effect. To some extent, the large energy reserve of the overfat person makes it easier to tolerate weight loss and exercise without the obligatory increase in caloric intake typically observed for leaner counterparts. ${ }^{116,192}$ No difference emerged in fat, carbohydrate, or protein intake or total calories consumed for overweight men and women during 16 months of supervised, moderate-intensity exercise training compared with a sedentary control group. ${ }^{52}$ In essence, a weak coupling exists between the short-term energy deficit induced by exercise and energy intake. Increased physical activity by overweight, sedentary individuals does not necessarily alter physiologic needs and automatically produce compensatory increases in food intake to balance additional energy expenditure.

## INTEGRATIVE QUESTION

Respond to the person who claims: The only way to lose weight is to stop eating. Its that simple!

## Misconception 2: Physical Activity Does Not Burn Many Calories

A common misconception concerns what is considered the negligible contribution to weight loss of the calories burned in typical exercise. Some argue correctly that it requires an inordinate amount of short-term exercise to lose just 0.45 kg of body fat: for example, chopping wood for 10 hours, playing golf for 20 hours, performing mild calisthenics for 22 hours, or playing ping pong for 28 hours or volleyball for 32 hours. Consequently, a 2- or 3-month exercise regimen produces only a small fat loss in an overfat person. From a different perspective, if one played golf (no cart) for 2 hours daily ( 350 kCal ) 2 days per week ( 700 kCal ), it would take about 5 weeks to lose 0.45 kg of body fat. Assuming the person plays year-round, golfing 2 days a week produces a $4.5-\mathrm{kg}$ yearly fat loss provided food intake remains constant. Even an activity as innocuous as chewing gum burns an extra 11 kCal each hour, a $20 \%$ increase over normal resting metabolism. Simply stated, the calorie-expending effects of increased physical activity add up. A caloric deficit of 3500 kCal equals a $0.45-\mathrm{kg}$ body fat loss, whether the deficit occurs rapidly or systematically over time.

In estimating the energy cost of performing various physical activities, one assumes that exercise energy expenditure remains constant among persons of a particular body size. In Chapter 8, we noted that the energy cost data for most physical activities represent averages, often based on only a few observations. A wide range of values exists because of individual differences in performance style and technique; terrain, temperature, and wind resistance (environmental factors); and intensity of participation. Consequently, energy expenditure values for the physical activities presented in Appendix C (available online at http://thepoint.lww.com/ mkk7e) do not represent constants. Rather, they reflect average values applicable under average conditions when applied to the average person of a given body mass. However, the data do provide useful approximations to establish the energy cost of diverse physical activities.

The Recovery Afterglow. Controversy exists about the quantitative contribution of excess postexercise oxygen consumption to the total energy expended in physical activity. With low-to-moderate exercise, as performed by most persons who exercise for weight control, the contribution of recovery metabolismthe so-called recovery afterglowtototal energy expenditure remains small relative to exercise energy expenditure, ranging up to 75 kCal for exercise durations of 80 minutes. ${ }^{175}$ In addition, exercise training induces faster adjustments in postexercise energetics that reduce the magnitude of the total recovery oxygen consumption. ${ }^{200}$ Calories burned during physical activity represent the most important factor in total exercise energy expenditure, not calories expended during recovery.

## Calories In Versus Calories Out: The Amount of Exercise Required for a 150-Pound Person to Burn Off the Calories in Some Popular Foods

## Caffe Mocha

 (20 oz., with

Playing Tennis
43 minutes


Brisk Walking 103 minutes


Bicycling
( 9.4 mph )
16 minutes

Calories in versus calories out: the amount of exercise required for a 150-pound person to burn off the calories in some popular foods.

## EFFECTIVENESS OF REGULAR PHYSICAL ACTIVITY

Adding physical activity to a weight-loss program favorably modifies the composition of the weight lost in the direction of greater fat loss and maintaining or even enhancing physical
performance capacity. ${ }^{9,242}$ This muscle-sparing effect of regular exercise is clearly illustrated in Figure 30.24, which compares the effect of about 10 pounds of weight loss over 12 months induced by either only caloric restriction or only exercise on MRI-assessed thigh muscle volume of 50- to 60-year old men and women. Decreases in thigh muscle volume of


Figure 30.24 Conserve the lean and lose the fat. Relationship between the magnitude of weight loss and the magnitude of change in thigh muscle volume (sum of right and left thighs) in a group losing weight by only caloric restriction (CR) and a group losing weight by only exercise (EX) (From Weiss $E P$, et al. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exerciseinduced weight loss. J Appl Physiol 2007;102:634.)
$6.8 \%$ and composite knee flexion strength ( $-7.2 \%$ ), and $\dot{\mathrm{V}}{ }_{2 \text { max }}(-6.8 \%)$ occurred only in the caloric restriction group, whereas $\dot{\mathrm{V}}_{2 \text { max }}$ increased $15.5 \%$ in the group losing weight via exercise. Clearly, muscle mass, muscle strength, and aerobic capacity decrease in response to 12 months of
weight loss by caloric restriction, but not in response to similar weight loss by exercise.

The effectiveness of regular physical activity for weight loss relates closely to the degree of excess body fat. Obese persons generally lose weight and fat more readily with increased physical activity than normal-weight persons. ${ }^{184}$ In addition, aerobic exercise and resistance training, even without dietary restriction, provide positive spin-off to the weight loss effort. They alter body composition favorably (reduced body fat with a small increase in FFM) for the otherwise healthy overweight person, postmenopausal woman, cardiac patient, and physically challenged individual. ${ }^{124,201,223}$ Overfat children who participated in 4 months of 40-minute aerobic exercise sessions 5 days a week without dietary restriction accumulated less visceral adipose tissue than nonexercising controls. ${ }^{163}$ The active children also gained more FFM and lost more total fat mass and percentage body fat. Adolescent males who engaged regularly in vigorous activities showed less abdominal fat than sedentary counterparts. ${ }^{47}$ This indicates that regular exercise and improved aerobic fitness may target excess fat accumulation in the abdominal visceral area to a greater extent than peripheral fat deposits. Even when an exercise program produces no loss in body weight, substantial reductions occur in abdominal subcutaneous and visceral fat. ${ }^{185}$ This response certainly diminishes a tendency toward insulin resistance and resulting predisposition to type 2 diabetes. Table 30.3 shows the effects of regular exercise for weight loss by six sedentary, overfat young men who exercised 5 days a week for 16 weeks by walking 90 minutes each session. The men lost nearly 6 kg of body fat, a decrease in percentage body fat from 23.5 to $18.6 \%$. Exercise capacity also improved as did HDL cholesterol (15.6\%) and the HDL-to-LDL cholesterol ratio (25.9\%).

Most of the health-related metabolic improvements in the obese with regular exercise relate to total exercise volume and quantity of fat loss rather than enhanced cardiorespiratory fitness. ${ }^{43,44}$ Ideal exercise consists of continuous, large-muscle

| TABLE 30.3 $\begin{array}{ll}\text { Effect } \\ & \text { Comp } \\ & \text { Young }\end{array}$ | s of a 16-Wee n and Blood | lking Program Changes in Six |  |
| :---: | :---: | :---: | :---: |
| Variable | Pre-Training ${ }^{\text {a }}$ | Post-Training ${ }^{\text {a }}$ | Difference |
| Body mass (kg) | 99.1 | 93.4 | $-5.7^{b}$ |
| Body density, $\mathrm{g} \cdot \mathrm{mL}^{-1}$ | 1.044 | 1.056 | $+0.012^{b}$ |
| Body fat (\%) | 23.5 | 18.6 | $-4.9{ }^{\text {b }}$ |
| Fat mass (kg) | 23.3 | 17.4 | $-5.9{ }^{\text {b }}$ |
| Fat-free body mass (kg) | 75.8 | 76.0 | +0.2 |
| Sum of skinfolds (mm) | 142.9 | 104.8 | $-38.1{ }^{\text {b }}$ |
| HDL cholesterol, $\mathrm{mg} \cdot \mathrm{dL}^{-1}$ |  |  | $5.0^{\text {b }}$ |
| HDL/LDL cholesterol | 0.27 | 0.34 | $+0.07^{\text {b }}$ |
| From Leon AS, et al. Effects of a vigorous walking program on body composition, and carbohydrate and lipid metabolism of obese young men. Am J Clin Nutr 1979;33:1776. <br> ${ }^{a}$ Values are means. <br> ${ }^{b}$ Statistically significant. |  |  |  |

activities with moderate-to-high caloric cost such as circuit resistance training, walking, running, rope skipping, stair stepping, cycling, and swimming. Many recreational sports and games also are effective in weight control, but precise quantification and regulation of energy expenditure becomes difficult. Aerobic exercise stimulates fat catabolism, establishes favorable blood pressure responses, and generally promotes cardiovascular fitness. Interestingly, aerobic exercise training may elevate resting metabolism independent of any FFM change. ${ }^{255}$ No selective effect exists for running, walking, or bicycling; each promotes fat loss with equal effectiveness. ${ }^{170}$ Expenditure of an extra 300 kCal daily (e.g., jogging for 30 minutes) should produce a $0.45-\mathrm{kg}$ fat loss in about 12 days. This represents a yearly caloric deficit equivalent to the energy in 13.6 kg of body fat.

Resistance Training. Resistance training provides an important adjunct to aerobic training for weight loss and weight maintenance. The energy expended in circuit-resistance trainingeentinuous exercise using low resistance and high repetitionsaverages about 9 kCal per minute. Consequently, this exercise mode burns substantial calories during a typical $30-$ to 60 -minute workout. Even conventional resistance training that involves less total energy expenditure positively affects muscular strength and FFM during weight loss compared with programs that rely solely on food restriction. ${ }^{10,234}$ Individuals who maintain high muscular strength levels tend to gain less weight than weaker counterparts. ${ }^{134}$ Additionally, standard resistance training performed regularly reduces coronary heart disease risk, improves glycemic control, favorably modifies the lipoprotein profile, and increases resting metabolic rate (when FFM increases). ${ }^{168,169,173,222}$

Comparisons of conventional resistance training with endurance training indicate unique resistance-training benefits on body composition. ${ }^{19,234}$ Table 30.4 summarizes the effects of 12 weeks of either endurance exercise or resistance training on nondieting, untrained young men. Endurance training reduced percentage body fat (hydrostatic weighing) from reduced fat mass ( 1.6 kg ; no change in FFM), while
resistance training decreased body fat mass ( 2.4 kg ) and increased the FFM ( +2.4 kg ). Because FFM remains metabolically more active than body fat, conserving or increasing this tissue depot with exercise training maintains a higher level of resting metabolism, average daily metabolic rate, and possibly fat oxidation during rest, all factors that counteract the age-related increase in adiposity. ${ }^{24,50,207}$

Figure 30.25 shows body composition changes for 40 obese women placed into one of four groups: (1) control, no exercise, and no diet; (2) diet only, no exercise (DO); (3) diet plus resistance exercise $(\mathrm{D}+\mathrm{E})$, and (4) resistance exercise only, no diet (EO). The women trained 3 days a week for 8 weeks. They performed 10 repetitions each of three sets of


Figure $\mathbf{3 0 . 2 5}$ Changes in body composition with combinations of resistance exercise and/or diet in obese females. (From Ballor DL, et al. Resistance weight training during caloric restriction enhances lean body weight maintenance. Am J Clin Nutr 1988;47:19.)

TABLE 30.4 Changes in Body Composition After 12 Weeks of Either Resistance Training or Endurance Training

| Variable | Controls |  | Resistance Trained |  | Endurance Trained |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | PreTreatment | PostTreatment | PreTreatment | PostTreatment | PreTreatment | PostTreatment |
| Relative body fat (\%) | $20.1 \pm 8.5$ | $20.2 \pm 8.5$ | $21.8 \pm 6.2$ | $18.7 \pm 6.6^{a}$ | $18.4 \pm 7.9$ | $16.5 \pm 6.4^{a}$ |
| Fat mass (kg) | $16.2 \pm 10.8$ | $16.3 \pm 10.5$ | $17.2 \pm 7.6$ | $14.8 \pm 6.2^{a}$ | $14.4 \pm 7.9$ | $12.8 \pm 7.1^{a}$ |
| Fat-free body mass (kg) | $64.3 \pm 5.4$ | $64.4 \pm 6.6$ | $61.9 \pm 8.3$ | $64.4 \pm 9.0^{a}$ | $64.1 \pm 8.2$ | $64.7 \pm 8.6$ |
| Total body mass (kg) | $80.5 \pm 8.1$ | $80.7 \pm 8.5$ | $79.4 \pm 8.3$ | $79.2 \pm 7.6$ | $78.5 \pm 8.2$ | $77.5 \pm 7.9$ |

[^55]eight strength exercises. Body mass decreased for DO $(4.5 \mathrm{~kg})$ and $\mathrm{D}+\mathrm{E}(3.9 \mathrm{~kg})$, compared with $\mathrm{EO}(+0.5 \mathrm{~kg})$ and controls $(0.4 \mathrm{~kg})$. Importantly, FFM increased for EO $(+1.1 \mathrm{~kg})$, whereas the DO group lost 0.9 kg of FFM. The authors concluded that augmenting a calorie-restriction program with resistance-exercise training preserves FFM better than dietary restriction alone.

## Dose Response Relationship of Energy Expended

The total energy expended in physical activity relates in a dose response manner to the effectiveness of exercise for weight loss. ${ }^{9,104}$ A reasonable goal progressively increases moderate exercise to between 60 and 90 minutes daily or a level that burns 2100 to 2800 kCal weekly. ${ }^{63,107}$ To combat the worldwide obesity epidemic, the public health perspective must promote a populations need to increase total daily energy expenditure substantially and regularly rather than increase exercise intensity to induce a training response. An overly fat person who starts out with light exercise such as
slow walking accrues a considerable caloric expenditure simply by extending exercise duration. The focus on exercise duration offsets the inadvisability of having a sedentary, obese individual begin a program with more strenuous exercise. Also, the energy cost of weight-bearing exercise relates directly to body mass; the overweight person expends considerably more calories in such exercise than someone of average weight.

## INTEGRATIVE QUESTION

Among physically active men and women, how can individuals who consume the most calories weigh less than those who consume fewer calories?

## Walking Running for Different Durations

The duration of exercise affects fat loss. Table 30.5 lists changes in body fat for three groups of men who exercised for 20 weeks by walking and running for either 15,30 , or

TABLE 30.5 Effects of Three Training Durations of Walking and Running on Body Composition Changes

| Variable | Control$(N=16)$ |  | Training Group |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  | 15 Minute$(N=14)$ |  |  | 30 Minute$(N=17)$ |  | 45 Minute$(N=12)$ |  |
|  | Pre | Post | Pre | Post |  | Pre | Post | Pre | Post |
| Body mass (kg) | 72.1 | 73.2 | 76.9 | 76.3 |  | 80.6 | 78.9 | 70.9 | 69.9 |
| Body fat (\%) | 12.5 | 13.0 | 13.7 | 13.2 |  | 14.2 | 13.6 | 13.2 | 12.0 |
| Sum skinfolds (mm) | 73.8 | 79.6 | 83.0 | 77.0 |  | 90.0 | 83.8 | 77.5 | 67.0 |
| Waist girth (cm) | 82.7 | 84.9 | 84.3 | 82.8 |  | 88.2 | 86.1 | 83.6 | 81.8 |
| Distance run per workout (mi) |  |  |  |  | 1.56 |  | 2.89 |  | 4.13 |
|  |  |  |  |  | 1.54 |  | 2.95 |  | 4.46 |
|  |  |  |  |  | 1.79 |  | 3.19 |  | 4.82 |
|  |  |  |  |  | 1.75 |  | 3.24 |  | 5.06 |
| Total time of exercise (min:s) |  |  |  |  | 14:58 |  | 30:25 |  | 41:18 |
|  |  |  |  |  | 14:11 |  | 28:40 |  | 42:48 |
|  |  |  |  |  | 15:51 |  | 29:43 |  | 43:19 |
|  |  |  |  |  | 14:53 |  | 30:12 |  | 42:27 |
| Training heart rate ( $\mathrm{b} \cdot \mathrm{min}^{-1}$ ) |  |  |  |  | 179 |  | 175 |  | 174 |
|  |  |  |  |  | 179 |  | 174 |  | 169 |
|  |  |  |  |  | 182 |  | 175 |  | 177 |
|  |  |  |  |  | 180 |  | 175 |  | 175 |
| Intensity (\%max HR) |  |  |  |  | 89.4 |  | 83.8 |  | 84.5 |
|  |  |  |  |  | 89.8 |  | 73.4 |  | 81.0 |
|  |  |  |  |  | 94.0 |  | 90.1 |  | 89.5 |
|  |  |  |  |  | 92.5 |  | 90.2 |  | 88.1 |

[^56]45 minutes per workout. Data also include distance run and total duration of weekly workouts, training heart rate, body mass, sum of six skinfolds, and waist girth.

The three exercise groups decreased body fat, skinfolds, and waist girth compared with sedentary controls. Body weight also decreased with exercise, except for the 15-minute group, whose weight remained stable. Comparing the three exercise groups, the 45 -minute group lost more body fat than either the 30 - or 15 -minute groups. This difference was closely linked to the greater caloric expenditure with longer exercise (i.e., a dose response relationship).

## Exercise Frequency

To determine the optimal exercise frequency for weight loss, subjects exercised for 30 to 47 minutes for 20 weeks by either running or walking, with exercise intensity maintained between 80 and $95 \%$ of maximum heart rate. ${ }^{171}$ Training twice weekly produced no changes in body mass, skinfolds, or percentage body fat, but training 3 and 4 days weekly did. Subjects who trained 4 days a week reduced body weight and skinfolds more than subjects who trained 3 days a week. Percentage body fat decreased similarly in both groups. These findings support a recommendation to exercise a minimum of 3 days per week to favorably alter body composition; the additional caloric expenditure with more frequent exercise produces even greater results. The threshold exercise energy expenditure for weight loss probably remains highly individualized. The calorie-burning effect of each exercise session should eventually reach at least 300 kCal whenever possible. This generally occurs with 30 minutes of moderate-tovigorous running, swimming, bicycling, or circuit-resistance training or 60 minutes of brisk walking.

## INTEGRATIVE QUESTION

Why should individuals limit weight loss to no more than 2 pounds of body weight weekly?

## Start Slowly and Progress Gradually

The initial stage of an exercise weight-loss program for a previously sedentary, overly fat person should be developmental with moderate energy demands. The individual should adopt long-term goals and personal discipline and restructure eating and exercise behaviors. Unduly rapid training progressions prove counterproductive because most overfat individuals initially resist increasing their physical activity. During the first few months, intervals of faster paced walking can replace slow walking. Meaningful changes in body weight and body composition require at least 12 weeks. Most overfat persons can realistically expect to reduce body weight by 5 to $15 \%$ with programs that focus on modifying eating and exercise behaviors. Behavioral approaches to exercise should foster lifestyle changes in daily physical activity. ${ }^{225}$ For example, walking or bicycling can replace the
auto, stair climbing can replace the elevator, and manual tools can replace power tools. ${ }^{4,53}$ Eating less and exercising more proves more effective in a group situation than going it alone. Persons who joined a weight-loss program with several friends or family members lost more weight than individuals who participated alone. ${ }^{254}$

## Self-Selected Energy Expenditures: Mode of Exercise

No selective effect exists among diverse modes of bigmuscle aerobic exercise with equivalent energy expenditures to favorably reduce body weight, body fat, skinfold thickness, and girths, yet other differences may emerge. For example, Figure 30.26A shows that men and women generally self-select a higher energy expenditure level (with accompanying higher heart rates) at similar ratings of perceived exertion when running for 20 minutes on a treadmill than when performing simulated cross-country skiing (NordicTrack), cycle ergometry, or aerobic riding (HealthRider). ${ }^{126}$ Men selected a higher absolute level of exercise intensity and oxygen consumption than women in each exercise mode (Fig. 30.26B); treadmill running generated the greatest total oxygen consumed (energy expended) for both groups. For individuals without physical activity limitations, running usually provides the most suitable exercise mode for maximizing energy expenditure during selfselected intensities of continuous exercise.

## Caloric Restraint Plus Exercise: The Ideal Combination

Combinations of increased physical activity and caloric restraint offer considerably more flexibility for achieving a negative caloric imbalance than either exercise alone or diet alone. ${ }^{54,132,253}$ Dietary restraint plus increased physical activity through lifestyle changes offer health and weight-loss benefits similar to those from combining dietary restraint and a vigorous program of structured exercise. ${ }^{4}$ Adding exercise to a weight-control program facilitates longer term maintenance of fat loss than total reliance on either food restriction alone or increased exercise alone. ${ }^{104,117,119,174}$ Moderate regular exercise also offsets the decrement in immunoprotective natural killer cell activity associated with weight loss. ${ }^{189}$ Table 30.6 summarizes the benefits of exercise to a weight-loss program.

## INTEGRATIVE QUESTION

Why might large-scale studies that compare diet only and exercise plus diet often show only a small, added weight loss benefit for the exercise-plus-diet group?

How can an overfat person using exercise and dietary restraint to maintain a weight loss of about 1 pound $(0.45 \mathrm{~kg})$ a week reduce body mass by 20 pounds $(9.1 \mathrm{~kg})$ ? A prudent 1 -pound per week fat loss requires 20 weeks. The weekly


Female subject




Exercise mode

Figure 30.26 A. Oxygen consumption and heart rate for a representative male and female subject during 20 minutes of selfselected exercise consisting of treadmill running, leg-cycle ergometry, simulated cross-country skiing, or aerobic riding. B. Total oxygen consumed by males and females during 20 minutes of each form of exercise at the same rating of perceived exertion. (From Kravitz L, et al. Exercise mode and gender comparisons of energy expenditure at self-selected intensities. Med Sci Sports Exerc 1997;29:1028.)

## TABLE 30.6 Benefits of Adding Exercise to Dietary Restriction for Weight Loss

Increases overall size of the energy deficit
Facilitates lipid mobilization and oxidation, especially from visceral adipose tissue depots
Increases relative body fat loss by preserving fat-free body mass
Bunts the drop in resting metabolism that accompanies weight loss by conserving and even increasing fat-free body mass
Requires less reliance on caloric restriction to create an energy deficit
Contributes to long-term success of the weight-loss effort
Provides significant health-related benefits
Offsets the deterioration in immune system function that often accompanies weight loss
energy deficit to achieve this goal must average 3500 kCal with a daily deficit of 500 kCal . One half-hour of moderate exercise (about 350 extra kCal ) performed 3 days a week adds 1050 kCal to the weekly deficit. Consequently, the weekly caloric intake need only decrease by 2400 kCal (about 350 kCal daily) instead of 3500 kCal to lose the desired pound of body fat each week. If the number of exercise days increases from 3 to 5, daily food intake requires only a $250-$ kCal decrease. Extending the duration of the 5-day-per-week workouts from 30 minutes to 1 hour produces the desired weight loss without reducing food intake. In this case, extra physical activity creates the entire 3500 kCal deficit. If the intensity of the 1 -hour exercise performed 5 days a week increases by only $10 \%$ (cycling at 22 mph instead of 20 mph ; running at 6.6 mph instead of 6.0 mph ), the number of calories expended each week through exercise increases by an additional $350 \mathrm{kCal}(3500 \mathrm{kCal} \times 0.10)$. This new weekly deficit of 3850 kCal ( 550 kCal per day) allows the dieter to increase daily food intake by 50 kCal and still maintain a 1 -pound weekly fat loss.

Clearly, physical activity combined with mild dietary restriction effectively unbalances the energy balance equation for weight loss. This approach produces less-intense feelings of hunger and less psychologic stress than one that relies exclusively on caloric restriction. Furthermore, both aerobic and resistance exercises protect against FFM loss that occurs with weight loss by diet alone. This results partly from the favorable effect of regular exercise on mobilization and use of fatty acids from adipose tissue depots. ${ }^{145}$ Combining exercise with weight loss produces desirable reductions in blood pressure at rest and in situations that typically elevate blood pressure such as intense physical activity and emotional distress. ${ }^{211}$ Exercise also facilitates protein retention in skeletal muscle and retards its rate of breakdown. The fat-burning, proteinsparing benefits of regular exercise contribute to facilitated fat loss in a weight-loss program.

Reality Check. Regardless of the approach to weight loss, a statement from the National Task Force on the

## How Much Physical Activity Is Enough? The Latest Recommendations

The following is the concluding summary statement of the American College of Sports Medicine (ACSM) as to the Appropriate Physical Activity Intervention Strategies for Weight Loss and Prevention of Weight Regain for Adults: ${ }^{\text {a }}$

On the basis of the available scientific literature, the ACSM recommends that adults participate in at least $150 \mathrm{~min} \cdot \mathrm{wk}^{-1}$ of moderate-intensity physical activity to prevent significant weight gain and reduce associated chronic disease risk factors. It is recommended that overweight and obese individuals participate in this level of physical activity to elicit modest reductions in body weight. However, there is likely a dose effect of physical activity, with greater weight loss and enhanced prevention of weight regained with doses of physical activity that approximate 250 to $300 \mathrm{~min} \cdot \mathrm{wk}^{-1}$ (approximately $2000 \mathrm{kCal} \cdot \mathrm{wk}^{-1}$ ) of moderateintensity physical activity.
${ }^{\text {a D Donnelly ED, Blair SN, Jakicic JM, et al. }}$ American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41:459.

Prevention and Treatment of Obesity (www.ncbi.nih.gov/ pubmed/10761953) best sums up the difficulty in solving the overly fat condition on a long-term basis: Obese individuals who undertake weight loss efforts should be ready to commit to lifelong changes in their behavioral patterns, diet, and physical activity. ${ }^{159}$ Unfortunately, despite the importance of regular physical activity, fewer than one-half the people (about $40 \%$ ) trying to lose or maintain weight were regularly active during leisure-time in a nationally representative sample. ${ }^{130,131}$

The benefits of regular physical activity in weight loss and weight maintenance outlined in Table 30.6 come primarily from highly structured experimental research on relatively small numbers of subjects who significantly increased physical activity with high compliance. On the other hand, large-scale intervention studies (randomized clinical trials) that compare diet only with a combination of diet and regular exercise produce generally less remarkable results. In some cases, adding exercise did not augment weight loss; when a benefit did occur, the extra weight loss remained small. Clearly, the relatively modest amount of extra physical activity in the exercise group combined with high noncompliance to the exercise regimen in large-scale studies accounts for some blunting of an exercise effect. The key to unlocking the benefits of regular exercise for weight control in the general population lies in effective implementation of psychologic behavioral factors that favor increased regular physical activity.

INTEGRATIVE QUESTION
Outline a prudent, effective plan for a middleaged woman who wants to shed 10 kg of excess weight. Provide the rationale for each recommendation.

## Spot Reduction Does Not Work to <br> Selectively Reduce Local Fat Deposits

The notion of spot reduction emanates from the belief that an increase in a muscles metabolic activity stimulates relatively greater fat mobilization from the adipose tissue in proximity to the active muscle. As such, exercising a specific body area region to sculpt it should selectively reduce more fat from that area than exercising a different muscle group at the same metabolic intensity. Advocates of spot reduction recommend performing large numbers of sit-ups or side-bends to reduce excessive abdominal and hip fat. The promise of spot reduction with exercise seems attractive from an aesthetic and health risk standpointmertunately, critical evaluation of the research evidence does not support its use. ${ }^{122,129,160}$

Physical Activity Prevents Fat Infiltration Into Muscle
Considerable evidence suggests that the loss of strength and muscle mass appear to be inevitable consequences of aging, and that body fat increases with aging. Eleven men and 31 women completed a randomized trial consisting of either a physical activity group ( $\mathrm{PA} ; N=22$ ) or successful aging health educational control group (SA; $N=20$ ). Isokinetic knee extensor strength and computed tomography-derived mid-thigh skeletal muscle and adipose tissue cross-sectional areas (CSA) were assessed at baseline and at 12 mo following randomization. Total body weight and muscle CSA decreased in both groups, but these losses were not different between groups. Strength adjusted for muscle mass decreased ( $-20.1 \pm 9.3 \%$ ) in SA. The loss of strength was completely prevented in $\mathrm{PA}(-2.5 \pm 8.3 \%)$. In addition, there was a significant increase ( $18.4 \pm 6.0 \%$ ) in muscle fat infiltration in SA, but this gain was nearly completely prevented in $\mathrm{PA}(2.3 \pm 5.7 \%)$. This study is one of the first to show that regular physical activity prevents both the age-associated loss of muscle strength and increase in muscle fat infiltration in older adults.

Goodpaster BH et al. Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol 2008;105: 1498.

INTEGRATIVE QUESTION
Give specific examples of how small adjustments in daily energy expenditure and daily food intake can alter body fat content over time.

To examine claims for spot reduction, researchers compared the girths and subcutaneous fat stores of the right and left forearms of high-caliber tennis players. ${ }^{82}$ As expected, the girth of the dominant or playing arm exceeded the nondominant arm because of a modest muscular hypertrophy from the exercise overload of tennis. Measurements of skinfold thickness, however, clearly showed that regular and prolonged tennis exercise did not reduce subcutaneous fat in the playing arm. Another study evaluated fat biopsy specimens from abdominal, subscapular, and buttock sites before and after 27 days of sit-up exercise training. ${ }^{112}$ The number of sit-ups increased from 140 at the end of the first week to 336 on day 27. Despite the considerable amount of localized exercise, adipocytes in the abdominal region were no smaller than adipocytes in the unexercised buttocks or subscapular control regions.

Undoubtedly, the negative energy balance created through regular exercise contributes to reducing total body fat. Exercise stimulates the mobilization of fatty acids via hormones and enzymes that act on fat depots throughout the body. Body areas of greatest fat concentration and/or lipidmobilizing enzyme activity supply the greatest amount of this energy. Exercise does not cause greater fatty acid release from the fat pads directly over the active muscle.

Where on the Body Does Fat Loss Occur?
Decreases in body fat with exercise training and/or caloric restriction preferentially mobilize and reduce upper-body subcutaneous and deep abdominal fat rather than the more resistant fat depots in gluteal and femoral regions. ${ }^{42,120}$

## Possible Gender Difference in Responsiveness to Exercise

An interesting question concerns the possibility of a gender difference in the responsiveness of weight loss to regular exercise. A meta-analysis of 53 research studies on this topic concluded that men generally respond more favorably than women to the effects of exercise on weight loss. ${ }^{9}$ One possible explanation involves the gender difference in body fat distribution. As discussed previously, fat distributed in the upper body and abdominal regions (central fat) shows active lipolysis to sympathetic nervous system stimulation and becomes preferentially mobilized for energy during exercise. ${ }^{6,236}$ Consequently, the greater upper-body fat distribution in men may contribute to a greater sensitivity to lose fat in the abdominal region with regular exercise. Women also may more
effectively preserve energy balance with increased physical activity. ${ }^{51,53,245}$ Men often reduce energy intake with exercise training, whereas the depression of food intake with exercise may be less for women.

## WEIGHT LOSS RECOMMENDATIONS FOR WRESTLERS AND OTHER POWER ATHLETES

Weightlifters, gymnasts, and other athletes in sports that require a high level of muscular strength and power per unit of body mass often must reduce body fat without compromising exercise performance. Any increase in relative muscular strength and short-term power output capacity should improve competitive performance. The following discussion focuses on wrestlers, but applies to all physically active individuals who desire to reduce body fat without negatively affecting health, safety, and exercise capacity.

To reduce injury and medical complications from shortand longer-term periods of weight loss and dehydration, the

ACSM, NCAA, and AMA recommend assessing each wrestlers body composition. The National Federation of State High School Associations required the adoption of weight certification beginning with the 2005 season. This assessment takes place several weeks prior to the competitive season to determine a minimal wrestling weight based on percentage body fat. Five percent body fat (determined using hydrostatic weighing or population-specific skinfold equations) represents the lowest acceptable level for safe wrestling competition. The hydrostatic weighing or skinfold assessment of body fat recommended by the NCAA has been crossvalidated by the more rigorous four-component body composition assessment and found to be acceptable for accuracy and precision. ${ }^{31,32}$ For wrestlers under age $16,7 \%$ body fat level represents the recommended lower limit. Importantly, percentage body fat must be determined in the euhydrated state because dehydration of between 2 and 5\% body weight through fluid restriction and exercise in a hot environment (techniques commonly used by wrestlers) violates the assumptions necessary for accurate and precise prediction of minimal wrestling weight. ${ }^{12}$ Table 30.7 outlines a practical

## TABLE 30.7 Using Anthropometric Equations to Predict a Minimal Wrestling Weight and to Select a Competitive Weight Class

A. To predict body density (BD), use one of the following equations. (For each skinfold, record the average of at least three trials in mm.)

1. Lohman equation ${ }^{a}$
$\mathrm{BD}=1.0982-(0.00815 \times[$ triceps + subscapular + abdominal skinfolds $])$
$+\left(0.00000084 \times[\text { triceps }+ \text { subscapular }+ \text { abdominal skinfolds }]^{2}\right)$
2. Katch and McArdle equation ${ }^{b}$
$\mathrm{BD}=1.09448-(0.00103 \times$ triceps skinfold $)-(0.00056 \times$ subscapular skinfold $)-(0.00054 \times$ abdominal skinfold $)$
3. Behnke and Wilmore equation ${ }^{c}$
$\mathrm{BD}=1.05721-(0.00052 \times$ abdominal skinfold $)+(0.00168 \times$ iliac diameter $)+(0.00114 \times$ neck circumference $)$
$+(0.00048 \times$ chest circumference $)+(0.00145 \times$ abdominal circumference $)$
4. Thorland equation ${ }^{d}$
$\mathrm{BD}=1.0982-(0.000815 \times[$ triceps + abdominal skinfolds $])+(0.00000084 \times[$ triceps + abdominal skinfolds $])$
B. To determine fat percentage, use the Brork equation:
$\%$ Fat $=[4.570 \div$ BD -4.142$] \times 100$
C. To determine fat-free weight and to identify a minimum weight class, follow the examples below:
5. Fifteen-year-old wrestler who weighs 132 lb has a body density of $1.075 \mathrm{~g} \cdot \mathrm{cc}^{-1}$, and hopes to compete in the $119-\mathrm{lb}$ weight class.
6. Percentage fat is $(4.570 \div 1.075-4.142) \times 100=10.9 \%$
7. Fat weight and fat-free weight are:
a. $132.0 \mathrm{lb} \times 0.109=14.4 \mathrm{lb}$ fat
b. $132.0 \mathrm{lb}-14.4 \mathrm{lb}$ fat $=117.6 \mathrm{lb}$ fat-free weight
D. To calculate a minimal wrestling weight:
8. Realize that the recommended minimum body weight for those 15 years and younger contains $93 \%$ ( 0.93 ) fat-free weight and $7 \%$ fat (0.07)
9. Divide the wrestlers calculated fat-free weight by the greatest allowable fraction of fat-free weight to estimate minimal wr estling weight: $117.6 \div(93 / 100)=117.6 \div 0.93=126.5 \mathrm{lb}$
E. To allow for a $2 \%$ error, perform the following calculations:
10. 126.5 minimal weight $\times 0.02=2.5 \mathrm{lb}$ error allowance
11. $126.5 \mathrm{lb}-2.5 \mathrm{lb}=124.0 \mathrm{lb}$ minimum wrestling weight
F. Conclusion: This boy cannot wrestle in the 119-pound weight class; rather he must compete in the 125 -pound class.

[^57]application to determine minimal wrestling weight and an appropriate competitive weight class. The ACSM also recommends that legitimate weight loss should progress gradually and not exceed a 1- to 2-pound reduction per week. At the same time, the athlete should continue to consume a wellbalanced, nutritious diet.

Prudent Recommendations for Wrestlers. The Gatorade Sports Science Institute (www.gssiweb.com) presents nutrition guidelines for wrestlers, with downloads available in PDF format. This includes general body composition and nutritional recommendations for wrestlers once the appropriate wrestling weight has been established and achieved. Coaches should regularly assess their wrestlers body composition and hydration and nutrition status. In response to the deaths of three collegiate wrestlers in 1997 from excessive weight loss (largely from dehydration), the NCAA introduced rule changes for the 199899 season to discourage dangerous weight-cutting practices and increase safe participation. ${ }^{33}$ In addition to establishing a minimal wrestling weight, another rule change measures urine specific gravity (density of urine to the density of water). This assessment of hydration status ensures euhydration of wrestlers at weight certification. Athletes with a urine specific gravity of 1.020 or less are considered euhydrated, while those with specific gravity in excess of 1.020 cannot have body fat measured to determine minimum competitive wrestling weight for the season. Urine-specific gravity reflects hydration status, but it lags behind true hydration status during rapid body fluid turnover with acute dehydration as used by wrestlers to make weight. Such a scenario would fail to detect a large number of dehydrated wrestlers. ${ }^{172}$

## GAINING WEIGHT: THE COMPETITIVE ATHLETES DILEMMA

Gaining weight to enhance body composition and exercise performance in activities that require muscular strength and power or aesthetic appearance poses a unique problem not easily resolved. Most persons focus on weight loss to reduce excess body fat and improve overall health and appearance. Weight (fat) gain per se occurs all too readily by tilting the bodys energy balance to favor greater caloric intake. Weight gain for athletes should represent muscle mass and accompanying connective tissue. Generally, this form of weight gain occurs if increased caloric intakeearbohydrate for adequate energy and protein sparing, plus the amino acid building blocks of protein for tissue synthesisaecompanies a balanced, progressive resistance-exercise regimen.

## Unsupported Hype

Athletes attempting to increase muscle mass often fall easy prey to health food and diet supplement manufacturers who market high-potency, tissue-building substanceschromium, boron, vanadyl sulfate, $\beta$-hydroxy-methyl butyrate, and various protein and amino acid mixtures, none of which reliably increases muscle mass. Concerning protein
supplementation, no evidence indicates that commercially prepared mixtures of powdered protein, predigested amino acids, or special high-protein cocktails promote muscle growth any more effectively than protein consumed in a wellbalanced diet (see Chapter 23). ${ }^{127}$

## Increase the Lean, Not the Fat

Endurance exercise training usually increases FFM only slightly, but the overall effect reduces body weight because of fat loss from the calorie-burning and possible appetitedepressing effects of this exercise mode. In contrast, muscular overload through resistance training, supported by adequate energy and protein intake (with sufficient recovery), increases muscle mass and strength. Adequate energy intake ensures that no catabolism of protein available for muscle growth occurs from an energy deficit. Thus, intense aerobic training should not coincide with resistance training to increase muscle mass. ${ }^{88}$ More than likely, the added energy (and perhaps protein) demands of concurrent resistance and aerobic exercise training impose a limit on muscle growth and responsiveness to resistance training. In addition, on the molecular level, aerobic exercise training may inhibit signaling to the protein synthesis machinery of skeletal muscle to negatively impact the muscles adaptive response to resistance training. ${ }^{14,155} \mathrm{~A}$ prudent recommendation increases daily protein intake to about 1.6 g per kg of body mass during the resistance-training period. ${ }^{138}$ The individual should consume a variety of plant and animal proteins; relying solely on animal protein (high in saturated fatty acids and cholesterol) potentially increases heart disease risk.

If all calories consumed in excess of the energy requirement during resistance training sustained muscle growth, then 2000 to 2500 extra kCal could supply each $0.5-\mathrm{kg}$ increase in lean tissue. In practical terms, 700 to 1000 kCal added to the well-balanced daily meal plan supports a weekly 0.5 - to $1.0-\mathrm{kg}$ gain in lean tissue and additional energy needs for training. This ideal situation presupposes that all extra calories synthesize lean tissue. Chapter 23 provided specific recommendations for nutrient timing to optimize muscle responsiveness to resistance training.

## How Much Gain to Expect

A 1-year program of heavy-resistance training for young, athletic men increases body mass by about $20 \%$, mostly from lean tissue accrual. The rate of lean tissue gain rapidly plateaus as training progresses beyond the first year. For athletic women, first-year gains in lean tissue mass average 50 to $75 \%$ of the absolute values for men, probably from the womens smaller initial lean body mass. Individual differences in the daily quantity of nitrogen incorporated into body protein (and protein incorporated into muscle) also limit and explain differences among persons in muscle mass increases with resistance training. Figure 30.27 lists eight specific factors that affect the responsiveness of lean tissue synthesis to resistance training.


Figure 30.27 Specific factors affecting the magnitude of lean tissue synthesis with resistance training. (Photo of Bill Pearl, courtesy of Bill Pearl.)

Individuals with relatively high androgen estrogen ratios and greater percentages of fast-twitch muscle fibers probably increase lean tissue to the greatest extent. Muscle mass increases most at the start of training in individuals with the largest relative FFM (FFM corrected for stature and body fat). ${ }^{234}$ Regularly monitoring body mass and body fat verifies whether the combination of training and additional food intake increases lean tissue and not body fat. This requires an accurate (valid) appraisal of body composition at regular intervals throughout the training period.

## INTEGRATIVE QUESTION

Outline recommendations to a high school student who wishes to increase body weight to improve physical appearance and sports performance.

## Summary

1. Three ways unbalance the energy-balance equation to produce weight loss: (1) reducing energy intake below energy expenditure, (2) maintaining normal energy intake and increasing energy expenditure,
and (3) decreasing energy intake and increasing energy expenditure.
2. Long-term maintenance of weight loss through dietary restriction has a success rate less than $20 \%$. Typically, one- to two-thirds of the lost weight returns within a year and almost all of it within 5 years.
3. A caloric deficit of 3500 kCal , created through either diet or exercise, represents the equivalent of the calories in 0.45 kg of adipose tissue.
4. Prudent dieting effectively promotes weight loss. Disadvantages of extremes of caloric restriction include loss of FFM, lethargy, malnutrition, and depressed resting metabolism. Some of these factors conserve energy and reduce the diets effectiveness.
5. Reduced resting metabolism represents a welldocumented response to weight loss through dieting.
6. Rapid weight loss during the first few days of caloric deficit mainly reflects loss of body water and stored glycogen; greater fat loss occurs per unit of weight lost as caloric restriction continues.
7. The calories burned in exercise accumulate. Over time, regular extra physical activity creates a considerable energy deficit.
8. The precise role of exercise in appetite suppression or stimulation remains unclear, but moderate increases in physical activity may depress appetite and energy intake of a previously sedentary, overweight person. Most athletes eventually consume enough calories to counterbalance trainings added caloric expenditure.
9. Exercise combined with caloric restriction offers a flexible and effective way to achieve weight loss. Exercise enhances fat mobilization and catabolism to accelerate body fat loss.
10. Regular aerobic exercise retards lean tissue loss while resistance training increases FFM.
11. Selective exercise of specific body regions by spot exercise proves no more effective for localized fat loss than more general physical activity of equivalent caloric expenditure.
12. Differences in body fat distribution partially explain gender difference in responsiveness to exer-cise-induced weight loss.
13. Athletes should gain weight as lean body tissue (muscle mass and connective tissue). Modest increases in caloric intake with systematic resistance training effectively produce this effect.
14. Ideally, 700 to 1000 extra kCal per day supports a weekly 0.5 - to $1.0-\mathrm{kg}$ gain in lean tissue and resistance training energy requirements.

References are available online at http://thepoint.lww.com/mkk7e.

## On the Internet

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# Exercise, Successful Aging, and Disease Prevention 

## OVERVIEW

The physiologic and exercise capacities of older persons usually rate below those of younger peers. It remains uncertain how these differences reflect true biologic aging or the effect of disuse from alterations in lifestyle and reduced physical activity. Recent research reveals that older men and women no longer conform to a sedentary stereotype with little or no initiative for active pursuits. Senior citizens now routinely participate in a broad range of physical activities and exercise programs. Maintenance of an active lifestyle into later years helps older adults retain a relatively high level of functional capacity. In addition, regular exercise offers considerable protection against and rehabilitation from a variety of disabilities, diseases, and risk factors, particularly those related to cardiovascular health. Within this framework, the exercise physiologist provides skills and contributions to encourage regular exercise in the clinical setting.

# Interview with Dr. Steven N. Blair 



Education: BA (Kansas Wesleyan University, Salina, KS); MS and PED (Indiana University, Bloomington, IN); postgraduate training (Scholar in Preventive Cardiology, Stanford University School of Medicine, Palo Alto, CA)

Current Affiliation: Director of Epidemiology and Clinical Applications, and Director of Research, The Cooper Institute for Aerobics Research, Dallas, TX

Honors and Awards: See Appendix E, online at http://thepoint.lww.com/mkk7e.
Research Focus: My research has two major foci: (1) The Aerobics Center Longitudinal Study, an investigation of the relation of physical activity, cardiorespiratory fitness, and health outcomes and (2) randomized clinical trials of physical activity interventions and their health-related outcomes.

Memorable Publication: Blair SN, et al. Physical fitness and all-cause mortality: a prospective study of healthy men and women. JAMA 1989;262:2395.

## STATEMENT OF CONTRIBUTIONS: ACSM Citation Award

In recognition of his outstanding contributions to the body of knowledge concerning the health implications of a physically active lifestyle.

Dr. Blair is recognized for his insightful, skillful, and persistent application of epidemiological research techniques in the exploration of the health effects of physical activity and physical fitness. His studies of the Cooper Clinic population have markedly advanced our knowledge of the
association between physical activity and risk of chronic disease morbidity and mortality. These studies, by demonstrating that moderate levels of physical activity and fitness provide important health benefits, have had a critical impact on public health policy.

Through his research, through his extensive service to the American College of Sports Medicine, and through his highly effective communication with health professionals and with the public, Dr. Blair has made an enormous contribution to exercise science.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

$>$ I participated in sports in high school and college, and decided during my college career that I wanted to be a physical education teacher and athletic coach.

## What influence did your undergraduate education have on your final career choice?

> My physical education teachers and coaches encouraged and influenced me to continue my education with graduate school. I had conducted a small, independent research project as an undergraduate and found that I liked defining a problem, collecting data, and trying to make sense of the results. In graduate school, I developed an interest in an academic research career, but I think it was the solid foundation in
the liberal arts and specific areas of physical education that influenced my career direction.

Who were the most influential people in your career, and why?
> Gene Bissell was a strong early mentor. He is a man of uncompromising principles, dedication, and genuine concern for his students. He once forfeited a win in football when, after the game was over, he realized that an official had missed a call. When Coach Bissell pointed out the infraction, the league office replied that sometimes calls are missed and that is just one of the breaks of the game. Coach Bissell refused to accept that ruling and insisted that his team be declared the loser.

I had several influential mentors at Indiana University. Karl and Carolyn Bookwalter gave me a research assistantship, helped me with my first
publication, and generally introduced me to the world of scientific writing. Arthur Slater-Hammel introduced me to the scientific process, taught me about experimental design, and was the director of my doctoral dissertation. George Cousins was inquisitive and skeptical-two traits I consider essential for a scientist.

My first academic job was at the University of South Carolina. My interests soon turned to preventive cardiology, with a specific interest in exercise as a preventive and therapeutic modality. In the early 1970s I wrote an application for the Multiple Risk Factor Intervention Trial (MRFIT), and we received a grant to serve as one of the 20 MRFIT clinical centers. I learned much from leaders of the MRFIT, including Professors Jerry Stamler, Henry Taylor, Paul Ogelsby, Henry Blackburn, Steve Hulley, Mark Kjelsburg, Lew Kuller, and many others.

In 1978, I had an opportunity to work with Bill Haskell and Peter Wood at the Stanford University Heart Disease Prevention Program. I have had literally hundreds of hours of discussion with them over the years about various issues in exercise science and public health, and I continue to learn from their work and examples.

I also had the great opportunity to develop a relationship with Dr. Ralph S. Paffenbarger, who has considerably influenced my research over the past 20 years. Paff has made enormous contributions to the epidemiology of physical activity and health. His work is a model of rigorous methodology, clear thinking, poetic writing, and carefully drawn conclusions. He continues to be a good friend, research collaborator, mentor, and inspiration.

Last, I will mention colleagues at the Cooper Institute. I feel very fortunate that Dr. Cooper had the vision to establish the database for the Aerobics Center Longitudinal Study. My many colleagues at the Cooper Institute have been instrumental in our work over the past 20 years. I have learned much from them, and any success we have had is due in large part to their hard work, dedication, and scientific expertise.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> The most interesting/enjoyable aspect of science for me is the discovery that accompanies research. Nothing is more exciting than seeing the results of an analysis that yield something new and perhaps unexpected.

The least desirable aspects of my scientific life are the constant scrambling for funds to support our research activities and the routine administrative tasks that are inherent in managing an enterprise of 25 to 30 people.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

$>$ I think that our work on low cardiorespiratory fitness as a predictor of morbidity and mortality in middle-aged and older women and men is a meaningful contribution to exercise science. Our report on fitness and mortality that was published in the Journal of the American Medical Association in 1989 seemed to come at the right time and struck a responsive chord in both the scientific and lay communities. This research helped influence several statements on the significance of physical inactivity on public health, which have had a substantial effect on exercise science, public health, and clinical medicine.

I also am proud of our research on lifestyle physical activity interventions. Our epidemiological studies revealed a curvilinear, dose response relation between cardiorespiratory fitness and mortality, with the steepest part of the curve at the low end of the fitness continuum. Moderate levels of fitness are associated with reduced risk, and moderate amounts and intensities of physical activity can produce these moderate levels of fitness. We designed a randomized clinical trial to test the hypothesis that behaviorally based lifestyle physical activity intervention would be as effective as a traditional, structured exercise program in increasing physical activity, improving cardiorespiratory fitness, and improving other health parameters. I am pleased that this work is leading to greater flexibility and more options for exercise programming to achieve health benefits.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

$>$ Obtain a strong foundation in science as an undergraduate. Read widely in your area of interest and become familiar with the leading researchers in this area of investigation. Talk to your professors about your plans and seek their advice. Do not be afraid to approach well-known researchers and ask for their advice in making your career choices. Most of them are very nice people and will be flattered if you come well prepared with good questions. As you begin to narrow your choice of institutions for graduate school, make up a visitation schedule and try to visit at least three or four programs that you think match your needs. Go to the very best program that will accept you.

## What interests have you pursued outside your professional career?

> I like to garden, and my wife and I are proud of our landscaping and flowers. We have season tickets to the symphony,

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opera, summer musicals, and one of the Dallas theaters. We both use running as our main form of exercise, and we run nearly every day and have over the past 30 years. We like to travel and feel fortunate that my work has afforded us many opportunities to travel in the United States and abroad.

## Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 30 years?

> Genetic epidemiology will make important contributions to our understanding of which individuals are at greatest risk of a sedentary way of life. We will work out in much greater detail the specific types, amounts, and intensities of activity that prevent or delay specific diseases or conditions. We will finally establish appropriate public health surveillance systems to monitor accurately patterns and trends of physical activity and physical fitness in people of all ages. Physical inactivity will be recognized as the major and most expensive public health problem in the United States.

We will learn much more about how to help sedentary individuals adopt and maintain physical activity. These advances, however, may not be sufficient to overcome the ever more toxic environment in which we live, as indicated by our continuing to engineer physical activity out of daily life. The threat posed to our public health and well-being by an increase in the prevalence of sedentary habits may finally cause us to seriously consider, develop, and implement policy and legislative solutions to encourage more physical activity.

## You have the opportunity to give a last lecture. Describe its primary focus.

$>$ I would describe the joys of scientific discovery and the pleasure of collaborating with colleagues to address important public health issues. I would illustrate how hazardous it is to be sedentary and unfit, and how a fit and active way of life can bring benefits to virtually all demographic groups. I would outline the seriousness of the public health problem of inactivity and try to issue a rousing call to action to encourage all to help address this problem. After accepting sustained applause, and even standing ovations and shouts of Bravo, I would exit the stage and leave the work to the younger generation.


## CHAPTER 31

## Physical Activity, Health, and Aging

## CHAPTER OBJECTIVES

> Summarize aging trends in the American population
> Describe the physical activity level of typical adult American men and women
> Outline the major findings of the Surgeon Generals report on the populations physical activity participation
> Answer the question: How safe is exercising?
> List factors that increase the likelihood of experiencing an exercise catastrophe
> Contrast physiologic responses to exercise of children and adults and their implications for evaluating physiologic function and exercise performance

- List important age-related changes in (1) muscular function, (2) nervous system function, (3) cardiovascular function, (4) pulmonary function, and (5) body composition components
> Summarize the potential benefits of moderate resistance training for the elderly
> Discuss the following statement: A sedentary lifestyle causes losses in functional capacity at least as great as the effects of aging itself
> Describe research about the role of regular physical activity in coronary heart disease prevention and life extension
> Indicate the types and levels of physical activity that induce the greatest improvement in riskfactor profile and overall health
> Describe vulnerable plaque and its proposed role in sudden death
> List the major modifiable heart disease risk factors and how regular physical activity affects each
> Outline the normal dynamics of homocysteine, its proposed role in coronary heart disease, and factors that affect plasma levels
> Discuss the prevalence of heart disease risk factors in children


## THE GRAYING OF AMERICA

Elderly persons-those 85 and older-make up the fastest growing segment of American society. Thirty years ago, age 65 represented the onset of old age. Gerontologists now consider 85 the demarcation of oldest-old and age 75, youngold. Currently, nearly $13 \%$ of the country s population, or approximately 38 million U.S. citizens, exceed age 65 , and by the year 2030, $20 \%$, or 70 million, will exceed age 85 . Assuming consistent mortality rates, the number of citizens over age 85 will more than triple during the next four decades, reaching 15 million by 2040 . While the life expectancy for men is less than that for women, the gap has narrowed; for white males and females, it has declined from 7.5 years in 1980 to 5.5 years in 2001, and to 5.0 years in 2008 (www.cdc.gov). For black males and females in 2008, the gap is somewhat larger, at 6.6 years. Some demographers project that half of the girls and a third of the boys born in developed countries near the end of the 20th century will live in three centuries. In the short term, disease prevention, water purification and better sanitation, improved nutrition and health care, and more effective treatment of age-related heart disease and osteoporosis help people to live longer. Far fewer persons now die from infectious childhood diseases, so those with the genetic potential actualize their proclivity for longevity. On a different but parallel front, anticipated breakthroughs in genetic therapies may slow the aging of individual cells. Gene therapies and rapid progress in stem cell research could boost human life spans to a much greater extent than improved medical treatment or even eradication of some diseases.

Figure 31.1A shows that, proportionately, centenarians are the fastest growing age group in the United States. In 2005, there were 71,000 centenarians, up from the estimate of 15,000 in 1980 and almost none at the beginning of the 20th century. According to the U.S. Census Bureau (www .census.gov), this number will swell to 114,000 by 2010 and then exceed 241,000 by 2020 . No longer viewed as a quirk of nature, 2 in 10,000 Americans now live to age 100. Demographers project that by the middle of this century, more than 800,000 Americans will exceed age 100, with many maintaining relatively good health. Figures 31.1B D depict longevity statistics retirement-pension organizations use to calculate the payout of annuity dividends. For example, a 55-year-old person today can expect to live on average an additional 31.4 years, for a life span of 86 years (Fig. 31.1B). But if this 55-year-old lives an additional 15 years to age 70, life expectancy extends to almost 89 years. Figure 31.1C indicates the proportion of individuals age 65 years who are expected to survive to specified ages. Among current 65-year-olds, $95.5 \%$ will live to age $70,63.3 \%$ to age 85 , and nearly $10 \%$ will achieve 100 years. Estimates indicate that by the middle of this century there will be more than 835,000 worldwide centenarians. Web sites that offer life-expectancy calculators include the National Center for Health Statistics (www.cdc.gov/nchs/ fastats/lifexpec.htm) and Northwestern Mutual Life Insurance Company (www.nmfn.com/tn/learnctr-lifeevents-longevity). Extension of life expectancy is not limited to the U.S. population;
instead, it represents a worldwide phenomenon. Figure 31.2 provides the latest World Health Organization (WHO; www.who.int/whr/) projections of geographical distribution of older adults ( $<60$ y) throughout the world in 2008. By 2025, a large increase will occur in the proportion of the population who exceed age 60 in most industrialized nations.

Physical inactivity relates causally to nearly $30 \%$ of all deaths from heart disease, colon cancer, and diabetes. Lifestyle changes could reduce mortality from these ailments and greatly improve cardiovascular and functional capacities, quality of life, and independent living. ${ }^{30,78,163}$ The greatest health benefits would come from strategies that promote regular physical activity. 2,3,70,137 At any age, behavioral changes-becoming more physically active, quitting cigarette smoking, and controlling body weight and blood pressureact independently to delay all-cause mortality. ${ }^{182}$ Persons with more healthful lifestyles survive longer, and the risk of disability and the necessity to seek home health care is postponed and compressed into fewer years at the end of life. ${ }^{216,217}$ The increased number of 65 -and-over participants in marathons (and even ultramarathons) aptly illustrates the exercise capacities of active older individuals. For example, there were 42 male and 22 female finishers of the 2007 New York City Marathon in the 70 - to $90+$-year age group. This represents the largest number of aged participants in the history of the event.

## fyi

## Physical Activity Modifications for the Elderly

Physical activity recommendations for the elderly are similar to those of the updated American College of Sports Medicine/American Heart Association recommendations for healthy adults but with several important differences. For example, the level of exercise intensity takes into account the older adult s relatively lower level of aerobic fitness. Recommended activities also focus on joint flexibility and balance to reduce risks of falls. Physical activity in this population emphasizes moderate-intensity aerobic activity, musclestrengthening exercises, reduction of sedentary behavior, and lifestyle risk management.

From Nelson ME, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2006;39:1435.

## THE NEW GERONTOLOGY

Many gerontologists maintain that research on the elderly should focus on improving healthspan (total number of years a person remains in excellent health), not simply on increasing lifespan. This new gerontology addresses areas beyond age-related diseases and prevention to recognize that


Figure 31.1 The graying of America. A. Growth in number of centenarians in the United States. B. Additional life expectancy in years for individuals currently at a specific age. C. Probability that a current 65 -year-old will live to a certain age. D. Average life expectancy at birth has increased by more than $60 \%$ since 1900. (Data from U.S. Bureau of the Census, National Center for Health Statistics, Centers for Disease Control and Prevention: Washington, DC, and actuarial tables from insurance companies.)
successful aging requires maintenance of enhanced physiologic function and physical fitness. Vitality, not longevity per se, remains the primary goal. Researchers now view much of the physiologic deterioration previously considered normal aging as dependent on lifestyle and environmental influences subject to considerable modification with proper diet and physical activity. ${ }^{32,55}$ For those who achieve older age, low muscular strength, diminished cardiovascular function, and poor joint range of motion, as well as sleep disturbances, relate directly to functional limitations regardless of disease status. ${ }^{78,87,132,178}$ Gerontologists now consider that successful aging includes four main components:

1. Physical health
2. Spirituality
3. Emotional and educational health
4. Social satisfaction

Maintaining and even enhancing physical and cognitive functions, fully engaging in life, and participating in productive activities and interpersonal relations contribute to achieving these goals.

## Healthy Life Expectancy: A New Concept

The Centers for Disease Control and Prevention (CDC; www.cdc.gov/) reports that nearly 1 in 10 Americans over age 70 needs help with daily activities such as bathing, and 4 in 10 use assistive walkers or hearing aids. Approximately one-half of men and two-thirds of women above age 70 suffer from arthritis; one-third of all Americans in this age group also have high blood pressure and $11 \%$ have diabetes. Of all seniors, women over age 85 are the most likely to need everyday help; $23 \%$ require assistance with at least one basic activity (e.g., dressing or going to the toilet).


Figure 31.2 World Health Organization projection of the geographical distribution of elderly population in 2007 (A) and in year 2025 (B). Color code indicates the proportion of the country population exceeding 60 years of age. The blue shade indicates countries with greater than $20 \%$ of the population above 60 years of age.

To estimate healthful longevity, the WHO has introduced the concept of healthy life expectancy-the expected number of years a person might live in the equivalent with full health. This involves disability-adjusted life expectancy (DALE), which considers the years of ill health, weighted according to severity and subtracted from expected overall life expectancy to compute the equivalent years of healthy life. The WHO rankings by country show substantially more years lost to disability in poorer countries from the impact of injury, blindness, and paralysis and from the debilitating effects of tropical disease malaria that strikes children and young adults more frequently. Figure 31.3 shows the DALE for a sample of 14 countries. Of the 191 countries evaluated, DALE estimates of healthy life expectancy reached 70 years in 24 countries and 60 years in more than half. Thirty-two countries fell at the lower extreme, where DALE estimates were less than 40 years. Many of these countries experience major epidemics of HIV/ AIDS including other causes of death and disability.

Japanese citizens experience the longest healthy life expectancy of 74.5 years. Surprisingly, the United States rates 24th, with 70.0 years of healthy life for babies born in 1999 ( 72.6 y for females and 67.5 y for males). Native Americans, rural African Americans, and inner-city poor experience


## Five Lifestyle Behaviors That Add Years to Life

1. Do not smoke.
2. Drink moderately (no more than a glass of wine, a half-pint of beer, or one shot of liquor per day).
3. Keep physically active, either on the job or in leisure time.
4. Eat five servings of fruits and vegetables daily.
5. Control body weight and blood pressure.

From Khaw KT, et al. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. PLoS Med 2008;5:e12; Yates LB, et al. Exceptional longevity in men: modifiable factors associated with survival and function to age 90 years. Arch Intern Med 2008;168:294; Cherkas LF, et al. The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med 2008;168:154.


Figure 31.3 Disability-adjusted life expectancy rankings (DALE; an estimate of healthy life expectancy) of populations of selected countries as assessed by the World Health Organization. Of all countries surveyed, the United States ranked 24th, with Japan ranked at the top.
health characteristics similar to those of underdeveloped countries. The HIV/AIDS epidemic, tobacco-related diseases, violent deaths, and prevalence of coronary heart disease all contribute to the United States lower ranking than other industrialized nations.

## Part 1 PHYSICALACTIVITY IN THE POPULATION

## PHYSICAL ACTIVITY EPIDEMIOLOGY

Epidemiology involves quantifying factors that influence the occurrence of illness to better understand, modify, and/or control a disease pattern in the general population. The specific field of physical activity epidemiology applies the general research strategies of epidemiology to study physical activity as a health-related behavior linked to disease and other outcomes.

## Terminology

Physical activity epidemiology applies specific definitions to characterize behavioral patterns and outcomes of the group(s) under investigation. Relevant terminology includes the following:

Physical activity: Body movement produced by muscle action that increases energy expenditure
Exercise: Planned, structured, repetitive, and purposeful physical activity
Physical fitness: Attributes related to how well one performs physical activity

Health: Physical, mental, and social well-being, not simply absence of disease
Health-related physical fitness: Components of physical fitness associated with some aspect of good health and/or disease prevention
Longevity: Length of life
Within this framework, physical activity becomes a generic term, with exercise its major component. Similarly, the definition of health focuses on the broad spectrum of well-being that ranges from complete absence of health (near death) to the highest levels of physiologic function. Such definitions often challenge how we measure and quantify health and physical activity objectively. They provide a broad perspective to study the role of physical activity in health and disease.

The trend in physical fitness assessment during the past 40 years deemphasizes tests that stress motor performance and athletic fitness (i.e., speed, power, balance, and agility). Instead, current assessment focuses on functional capacities related to overall good health and disease prevention. The four most common components of health-related physical fitness are aerobic and/or cardiovascular fitness, body composition, abdominal muscular strength and endurance, and lower back and hamstring flexibility (Fig. 31.4; see In a Practical Sense, p. 837).

## Physical Activity Participation

More than 30 different methods can assess diverse aspects of physical activity. They include direct and indirect calorimetry, self-reports and questionnaires, job classifications, physiologic


Figure 31.4 Health-related physical fitness components.
markers, behavioral observations, mechanical or electronic monitors, and activity surveys. Each approach offers unique advantages but also has disadvantages depending on the situation and population studied. Obtaining valid estimates of physical activity of large groups is difficult because such studies, by necessity, apply self-reports of daily activity and exercise participation rather than direct monitoring or objective measurement.

A discouraging picture of physical activity participation worldwide, both of work/occupational and of leisure-time activity, emerges consistently, as emphasized for United States citizens in the Surgeon General s report on physical activity and data provided by others: ${ }^{131,143,153,200,207}$

## U.S. Adult Population

Only about 15\% engage in vigorous physical activity during leisure time, 3 times a week for at least 30 minutes.
More than $60 \%$ do not engage in physical activity regularly.
Twenty-five percent lead sedentary lives (i.e., do not exercise at all).
Walking, gardening, and yard work are the most popular leisure-time activities.
Twenty-two percent engage in light-to-moderate physical activity regularly during leisure time ( 5 times/week for at least 30 min ).
Physical inactivity occurs more among women than men, blacks and Hispanics than whites, older than younger adults, and less-affluent than wealthier persons.
Physical inactivity contributes to 300,000 preventable deaths a year in the United States. Moderate
daily physical activity can substantially reduce the risk of developing or dying from cardiovascular disease, type 2 diabetes, and some cancers. Daily physical activity lowers blood pressure and cholesterol levels, retards osteoporosis, and reduces obesity, symptoms of anxiety and depression, and arthritis.
Participation in fitness activities declines with age; a large number of older citizens have such poor functional capacity they cannot rise from a chair or bed, walk to the bathroom, or climb a single stair without assistance.
At best, no more than $20 \%$ and possibly less than $10 \%$ of adults in the United States (including Australia, Canada, and England) obtain sufficient regular physical activity at an intensity that imparts discernible health and fitness benefits.

## U.S. Children and Teenagers

The most recent physical activity data from a longitudinal study of boys and girls between ages 9 and 15 indicate that moderate-to-vigorous physical activity declined with age over the study period. ${ }^{134}$ By age 15, daily physical activity decreased to just 49 minutes on weekdays and about 30 minutes per weekend day, well below the government s recommended 60-minute duration. Overall, boys were only slightly more active than girls, moving an average of 18 more minutes a day. The percentage of children who met the government s 1 hour recommendation of moderate daily activity shifted markedly over time. Between ages 9 and 11, almost every child in the study was moving at least an hour a day. But by age 15 , only $31 \%$ met the guideline during the week, and just $17 \%$ on the weekend.

Other data on the physical activity patterns of children, adolescents, and teenagers indicate the following:

Nearly one-half of those between ages 12 and 21 do not exercise vigorously on a regular basis; a sharp decline in physical activity occurs during adolescence regardless of gender.
Fourteen percent report no recent physical activitymore prevalent among females, particularly black females.
Twenty-five percent engage in light-to-moderate physical activity (e.g., walk or bicycle) nearly every day.
Participation in all types of physical activity declines strikingly with increasing age and school grade.
More males participate in vigorous physical activity, strengthening activities, and walking or bicycling than females.
Daily attendance in school physical education programs declined from $42 \%$ in early 1990 to less than $25 \%$ in 2005.

## IN A PRACTICAL SENSE

## Assessing Lower Back, Hamstring, and Shoulder Wrist Flexibility

Two types of flexibility include (1) static flexibility, full range of motion (ROM) of a specific joint and (2) dynamic flexibility, torque or resistance encountered as the joint moves through its ROM. Field tests commonly assess static flexibility indirectly through linear measurement of ROM.

## FIELD TESTS OF HIP-AND-TRUNK AND <br> SHOULDER WRIST STATIC FLEXIBILITY

Administer a minimum of three trials following a standardized warm-up.

## TEST 1: HIP-AND-TRUNK FLEXIBILITY (MODIFIED SIT-AND-REACH TEST)

## Starting Position

Sit on the floor with the back and head against a wall, legs fully extended, with the bottoms of the feet against the sit-and-reach box. Place hands on top of each other, stretching the arms forward while
keeping the head and back against the wall. Measure the distance from the fingertips to the box edge with a yardstick. This represents the zero, or starting, point (Fig. A).

## Movement

Slowly bend and reach forward as far as possible (move head and back away from the wall), sliding the fingers along the yardstick; hold the final position for 2 seconds (FIG. B).

## Score

Total distance reached to the nearest $1 / 4$ inch represents the final score.

Modified Sit-and-Reach Ratings

| Age Range (Y) | Men |  | Rating | Women |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\leq 35$ | 3649 |  | $\leq 35$ | 3649 |
|  | $>17.9$ | $>16.1$ | Excellent | $>17.9$ | $>17.4$ |
|  | $17.0 \quad 17.9$ | 14.616 .1 | Good | 16.717 .9 | 16.217 .4 |
|  | 15.817 .0 | 13.914 .6 | Average | 16.216 .7 | 15.216 .2 |
|  | 15.015 .8 | 13.413 .9 | Fair | 15.816 .2 | 14.515 .2 |
|  | $<15.0$ | $<13.4$ | Poor | <15.4 | $<14.5$ |

Test 1: Hip-and-trunk flexibility (modified sit-and-reach test)

(A)


B

Test 2: Shoulder-wrist flexibility (shoulder-and-wrist elevation test)


## IN A PRACTICALSENSE

## TEST 2: SHOULDER WRIST FLEXIBILITY (SHOULDER-AND-WRIST ELEVATION TEST)

## Starting Position

Lie prone on the floor with the arms fully extended overhead; grasp a yardstick with the hands shoulder-width apart.

## Movement

Raise the stick as high as possible (Fig. C).
Measure the vertical distance (nearest 0.5 in ) the yardstick rises from the floor.
Measure arm length from the acromial process to the tip of longest finger.
Subtract the average vertical score from arm length.

## Score

Arm length - average vertical score (nearest 0.25 in)

Continued

| Shoulder-and-Wrist Elevation Ratings |  |  |
| :--- | :--- | :--- |
| Men | Rating | Women |
| 6.00 or less | Excellent | 5.50 or less |
| 8.256 .25 | Good | 7.505 .75 |
| 11.5088 .50 | Average | 10.757 .75 |
| 12.5011 .75 | Fair | 11.7511 .00 |
| 12.75 or more | Poor | 12.00 or more |

Modified from Johnson BL, Nelson JK. Practical measurements for evaluation in physical education. 4th ed. New York: Macmillan, 1986.

## Healthy People 2010

A widespread erosion of physical activity patterns becomes particularly apparent with increasing age among American adolescents and adults; the decline is greater for adolescent and adult females than for males. ${ }^{34}$ Regardless of the cause for progressive inactivity as adults age, increased levels of physical activity predict decreased levels of all-cause morbidity and mortality and the relationship appears to be graded. ${ }^{27,88}$

The Physical Activity Pyramid illustrated in Figure 31.5 summarizes major goals for increasing the level of regular physical activity in the general population and emphasizes diverse forms of behavioral and lifestyle options.

The Healthy People 2010 initiative launched on January 25,2000 , builds on the initiatives of the previous two decades of public health concern to improve national health for the first decade of the 21st century. The Healthy People 2010 initiative outlines a comprehensive, nationwide health promotion and disease prevention agenda as a roadmap to promote health and prevent illness, disability, and premature death among all persons in the United States. ${ }^{184}$

Healthy People 2010 is designed to achieve two primary goals:

1. Increase quality and years of healthy life
2. Eliminate health disparities among the nation s citizens

Progress will be monitored through achievements for 467 objectives within the 28 focus areas. Many goals and objectives-several of which either directly or indirectly involve upgrading the national level of regular physical activity-converge on interventions designed to reduce or eliminate illness, disability, and premature death among individuals and communities. Other objectives focus on broader issues such as improving access to quality health care, strengthening public health services, and improving
availability and dissemination of health-related information. Each objective has a target for specific improvements and explicit guidelines on how to achieve the stated goal by 2010.

Activities of Those Americans Who Report Exercising Regularly

|  | Percentage |  |
| :--- | :---: | :---: |
| Activity | Male | Female |
| Walking | 39 | 48 |
| Resistance training | 20 | 9 |
| Cycling | 16 | 15 |
| Running | 12 | 6 |
| Stair climbing | 10 | 12 |
| Aerobics | 3 | 10 |

## Safety of Exercising

Several well-publicized reports of sudden death during exercise raised the question of exercise safety. ${ }^{107,181}$ Actually, the death rate during exercise has declined over the past 30 years despite an overall increase in exercise participation. In one report of cardiovascular episodes over a 65 -month period, 2935 exercisers recorded 374,798 hours of exercise that included $2,726,272 \mathrm{~km}$ of running and walking. No deaths occurred during this time, with only two nonfatal cardiovascular complications. This amounted to two complications per 100,000 hours of exercise for women and three complications for men.

Intense physical exertion raises a small risk of sudden death (e.g., one sudden death per 1.51 million episodes of exertion) during the activity compared with resting an equivalent


Physical Activity Pyramid
Figure 31.5 The Physical Activity Pyramid: Prudent goals for increasing daily physical activity.
time, particularly for sedentary persons as shown in Figure 31.6. Nonetheless, the longer-term reduction in overall death risk from regular exercise outweighs any small potential for acute cardiovascular complications. Regular exercisers have considerably less risk of death during physical activity. ${ }^{6}$ A 12-year follow-up of more than 21,000 male physicians showed that men who exercised at least 5 times a week had a much lower sudden death risk during vigorous exertion-about sevenfold less-than those who exercised only once weekly. ${ }^{9}$ The likelihood of an exercise catastrophe-cerebrovascular accident, aortic dissection and rupture, lethal arrhythmias, myocardial infarction-increases under the following eight conditions:

1. Genetic predisposition (family history of sudden death at a relatively young age)
2. History of fainting or chest pain with exercise
3. Unaccustomed vigorous exercise
4. Exercise performed with accompanying psychologic stress
5. Extremes of environmental temperature
6. Straining-type exercise that requires a considerable static muscle-action component (e.g., shoveling wet snow)
7. Exercise during viral infection or when feeling ill
8. Co-mingling of prescription drugs or dietary supplements (e.g., ephedra)

Musculoskeletal injuries represent the most prevalent exercise complications. A longitudinal study of aerobic dance injuries in 351 participants and 60 instructors during nearly 30,000 hours of activity reported 327 medical complaints. ${ }^{63}$ Just 84 of the injuries caused disability ( 2.8 per 1000 personhours of participation) and only $2.1 \%$ required medical attention. National estimates from self-reported frequency and


Figure 31.6 Triggering acute cardiac events. Relative risk of myocardial infarction associated with vigorous exertion ( $\geq 6$ METs) according to habitual frequency of vigorous physical activity. The horizontal solid line indicates risk of myocardial infarction with no exertion. (From Mittleman MA. Trigger of acute cardiac events: new insights. Am J Med Sports 2005;4:99.)
severity of injuries in five common physical activitieswalking, gardening, weightlifting, outdoor bicycling, and aerobics-report relatively low injury rates. ${ }^{116,157}$ Most injuries required no treatment or reduction in physical activity. Age does not affect incidence of orthopedic problems for exercise of moderate intensity and duration. For activities that involve running, the greatest orthopedic injury risk occurs in those who exercise for prolonged durations. ${ }^{11}$

Prospective epidemiologic research evaluated clinically significant medical incidents and emergencies for 7725 lowrisk, apparently healthy corporate fitness enrollees in a supervised facility at a major medical center. ${ }^{133}$ Almost three years of surveillance reported 15 medically significant events ( 0.048 per 1000 participant-hours) and two medical emergencies (both recovered), which equaled a rate of 0.0063 per 1000 participanthours. Such a low rate of medical incidents in a supervised health-fitness facility illustrates convincingly that the healthrelated fitness benefits outweigh any small risk of participation.

A published report from the National Electronic Injury Surveillance System All Injury Program (NEISS-AIP; www.icpsr.umich.edu/ICPSR/STUDY/21280.xml) that characterizes sports- and recreation-related injuries among the U.S. population revealed 4.3 million nonfatal injuries were treated in U.S. hospital emergency departments (comprising $6 \%$ of all unintentional injury-related emergency room visits). ${ }^{136}$ Injury rates varied by sex and age and were highest for persons ages 10 to 14 years ( $51.5 \%$ for boys, $38 \%$ for girls) and lowest for persons
over age 45 ( $6.4 \%$ for men, $3.1 \%$ for women.) The overall rate of sports- and recreation-related injuries was 15.4 per 1000 population. For persons 20 to 24 years, basketball- and bicycle-related injuries ranked among the three leading types of injury. Basketball-related injuries ranked highest for men ages 25 to 44 years (see accompanying inset Figure). Exercise (e.g., weightlifting, aerobics, stretching, walking, jogging, and running) was the leading injury-related activity for women over age 20 and ranked among the top four types of injuries for men over age 20. The most frequent injury diagnosis included strains/sprains (29.1\%), fractures (20.5\%), contusions/abrasions (20.1\%), and lacerations ( $13.8 \%$ ). The body parts injured most commonly were ankles ( $12.2 \%$ ), fingers ( $9.5 \%$ ), face ( $9.2 \%$ ), head ( $8.2 \%$ ), and knees $(8.1 \%)$. Overall, hospitalizations included $2.3 \%$ of persons with sports- and recreation-related injuries.


## Prehabilitation Reduces Sports and Recreational Injuries

For most individuals, participation in sports/athletic/recreational activities poses little risk, particularly in younger individuals. For individuals older than 40 years, and particularly those 60 years and older, a carefully planned and systematic prehabilitation program to ensure readiness for participation reduces exercise-induced disability further. Prehabilitation exercises emphasize joint stretching, muscle activation, core stability and strength, balance and muscle coordination. Such an approach ensures maximum motor unit recruitment and joint stability. Figure 31.7 shows examples of four exercises to promote stability


Figure 31.7 Sample of suspension-sling exercises that emphasize different levels of body weight loading and instability to develop core stability and strength.
and core muscular strength development to reduce injury potential. This example of sling-suspension exercise, originally popularized in Norway in the early 1900s and now practiced worldwide, applies different levels of body weight loading combined with controlled instability and range of motion movements to emphasize core musculature development.

## Sedentary Environmental Death Syndrome (SeDS)

A review of the world literature over the last 50 years concludes that inactivity alone results in a constellation of problems and conditions eventually leading to premature death. The term sedentary environmental death syndrome (SeDS), coined by Dr. Frank Booth (p. 936), aptly identifies this deteriorating condition. ${ }^{27}$ Research evidence reveals the following:

SeDS will cause 2.5 million Americans to die prematurely in the next decade.
SeDS will cost $\$ 2$ to 3 trillion in health care expenses in the United States in the next decade.
Chronic diseases have increased because of physical inactivity. In the United States, type 2 diabetes has increased ninefold since 1958, obesity has doubled since 1980, and heart disease remains the number one cause of death.
U.S. children are now getting SeDS-related diseasesthey are increasingly overweight, showing fatty streaks in their arteries, and developing type 2 diabetes (a disease formerly restricted to adults).
SeDS relates to the following conditions: high blood triacylglycerol, high blood cholesterol, high blood glucose, type 2 diabetes, hypertension, myocardial ischemia, arrhythmias, congestive heart failure, obesity, breast cancer, depression, chronic back pain, spinal cord injury, stroke, disease cachexia, debilitating illnesses, fall resulting in broken hips, vertebral/ femoral fractures.
Efforts to lessen the time watching television or videos or using a computer, if coupled with increases in physical activity above daily routines, could substantially decrease the prevalence of metabolic syndrome.
Individuals who do not engage in any moderate or vigorous physical activity during leisure time have about twice the odds of having metabolic syndrome as those who exercise up to 150 minutes a week or more.

## Summary

1. Physical activity epidemiology evaluates the nature, extent, and demographics of exercise participation in a large population. Such data often reflect disease occurrence and other health-related outcomes.
2. A discouraging picture exists about physical activity participation by adult Americans. Only 10 to $15 \%$ of adults in the United States obtain enough regular physical activity of adequate intensity to impart health and fitness benefits.
3. Health benefits accrue from including a moderate amount of physical activity on most if not all days of the week.
4. Intense physical effort raises a small risk of sudden death during the activity compared with resting for an equivalent time, particularly for sedentary people. The longer term health benefits of regular exercise far outweigh the risk of acute cardiovascular complications.
5. The current Healthy People 2010 goals and objectives for the nation include 226 targeted health objectives in 28 focus areas. Several of these either directly or indirectly aim at increasing regular physical activity among all citizens.
6. For activities that involve running, the greatest orthopedic injury potential exists among individuals who exercise for extended durations.
7. Prehabilitation, particularly among older individuals, that utilizes body weight loading and core stability training can reduce injury potential in exercising.
8. Physical inactivity promotes unhealthy gene expression; increasing regular exercise in the population must become a top public health priority.

## Part 2 AGING AND PHYSIOLOGIC FUNCTION

## AGE TRENDS

Physiologic and performance measures improve rapidly during childhood and achieve a maximum between late adolescence and approximately age 30 . Functional capacity declines thereafter, with deterioration varying at any age depending on lifestyle and genetic characteristics.

## Differences in Exercise Physiology Between Children and Adults

One must consider the interaction between physical activity and aging when evaluating physiologic responses and exercise performance across a broad age span. The distinct differences between children and adults can be summarized as follows:

During weight-bearing walking and running, oxygen consumption ( $\mathrm{mL} \cdot \mathrm{kg}^{1} \cdot \mathrm{~min}^{1}$ ) of children averages 10 to $30 \%$ higher than adults at a designated submaximal pace. ${ }^{219}$ The lower exercise economy from children s lower ventilatory efficiency, greater body surface area mass ratio, shorter stride length, and greater stride frequency, makes a standard walking or running pace physiologically more stressful and performance scores poorer.
Exercise performance disadvantages exist even though children typically maintain equal or somewhat
higher aerobic powers than adults. Also, walking and running economy and percentage $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ sustainable during exercise at the lactate threshold continually improve as children age, independent of aerobic power changes. This limits the usefulness of a single walking or running performance test to predict $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ throughout childhood and adolescence. ${ }^{42}$
Children exhibit lower absolute aerobic power values ( $\mathrm{L} \cdot \min { }^{1}$ ) than adults from a smaller fat-free body mass (FFM; Fig. 11.13). Consequently, children are disadvantaged when exercising against a standard external resistance (unadjusted for body size) in stationary cycling and arm cranking. The fixed oxygen cost $\left(\mathrm{L} \cdot \min ^{1}\right)$ of this exercise represents a greater percentage of children s smaller absolute aerobic power. During weight-bearing exercise, energy expenditure relates directly to body mass, so children are not disadvantaged by a smaller body size.
Children score lower than adults on tests of anaerobic power because they cannot generate a high level of blood lactate during maximal exercise. Lower intramuscular levels of the glycolytic enzyme phosphofructokinase may contribute to children s poorer anaerobic exercise performance.
Children breathe larger air volumes (greater ventilatory equivalent) than adults at any level of submaximal exercise oxygen consumption.
Adults score higher than children on perception of effort (rating of perceived exertion, or RPE) when both exercise at equivalent percentages of aerobic power. Greater pulmonary discomfort owing to the higher respiratory rate and ventilatory equivalent of children may produce this effect. ${ }^{202}$
Children and adults increase muscle strength with resistance training. Prepubescent children, unlike pubescent children and adults, have limited ability to increase muscle mass, presumably because of their relatively low androgen levels.

## INTEGRATIVE QUESTION

What factors would explain the relatively poor performances of children in a 10-k run compared with adults of equal aerobic power?

## Muscular Strength

Age and gender affect muscular strength and muscular power, with the magnitude of each effect influenced by the muscle group studied and the type of muscle action. General trends in muscular strength and power of adults with increasing age can be summarized as follows:

Men and women attain their highest strength levels between ages 20 and 40, the time when muscle crosssectional area is largest. Thereafter, concentric
strength of most muscle groups declines, slowly at first and then more rapidly after middle age.
Accelerated strength loss in middle age coincides with weight loss and increase in chronic diseases such as stroke, diabetes, arthritis, and coronary heart disease.
The capacity for power generation declines faster than that for maximal strength. ${ }^{84}$
Declines in eccentric strength begin at a later age and progress more slowly than for concentric strength.
Strength loss begins at a later age for women than for men. ${ }^{119}$
Arm strength for men and women deteriorates more slowly than leg strength. ${ }^{122}$
Rate of decline in muscular power with aging is similar among male and female weightlifters including world record holders, elite master athletes, and healthy, untrained individuals. ${ }^{197}$
Strength loss among the elderly directly relates to limited mobility and fitness status and potential for increased incidence of accidents from muscle weakness, fatigue, and poor balance. ${ }^{92,196}$

## Age Trends Among Elite Weightlifters and Powerlifters

Master athletes more accurately reflect the effects of physiologic aging because these healthy, motivated athletes maintain a rigorous training schedule to compete at the highest level. Figure 31.8 illustrates age trends for weightlifting and powerlifting records of the U.S. weightlifting and U.S. powerlifting organizations (www.usawa.com/; www.usapowerlifting.com/). These findings indicate the following:

Peak lifting performance declines for men and women with aging. Weightlifting performance follows a curvilinear trend, while powerlifting performance declines linearly with age.
The rate and overall magnitude of decline in performance with age are markedly greater in weightlifting than powerlifting.
The magnitude of decline in peak muscular power is greater in lifting tasks that require more complex and explosive power movements (weightlifting).
Sex differences in age-related performance decrements emerge only in events that require more complex and explosive power movements, with performance declining in women to a greater extent than in men.

These findings indicate a gender- and task-specific influence of age on muscular performance among elite resistancetrained athletes. More powerful and complex tasks undergo greater decline with age than tasks that require simpler movement patterns; women experience greater age-related declines in such tasks.


## $\square$ Men $\square$ Women

Figure 31.8 Age-related sex differences in (A) weightlifting (average snatch and clean and jerk scores) and (B) powerlifting (average deadlift, squat, and bench press scores) based on analysis of top age-group records of the U.S. Weightlifting and U.S. Powerlifting Organizations. (From Anton MA, et al. Age-related declines in anaerobic muscular performance: weightlifting and powerlifting. Med Sci Sports Exerc 2004;36:143.)

## Muscle Mass Decrease

Motor unit remodeling represents a normal, continuous process that involves motor endplate repair and reconstruction. Remodeling progresses by selective denervation of muscle fibers, followed by terminal sprouting of axons from adjacent motor units. Motor unit remodeling gradually deteriorates in old age. This leads to denervation muscle atrophy, an irreversible degeneration of muscle fibers, particularly type II fibers, which associates with chronic inflammation and reduction in circulating growth hormone (GH), insulin-like growth factor-1 (IGF-1), muscle-specific isoforms of IGF, mitochondria number and capacity, cell nuclei, and endplate structures. ${ }^{12,38,67,68}$

This deterioration (termed sarcopenia), magnified by reduced physical activity, progressively reduces muscle cross section, mass, and function even after adjustment for changes in body mass and stature. ${ }^{28,62,89}$ Muscle fibers also tend to type group, in that fast- and slow-twitch fibers lose their typical chessboard distribution and cluster within groups of similar type-perhaps from denervation and subsequent fiber death. Older adults have more than twice the noncontractile content in locomotor muscles as younger adults. ${ }^{96}$ Impaired neural drive does not explain the decline in muscle strength with age because older adults achieve full muscle activation during a maximal voluntary muscle action. ${ }^{44}$

## fyi

Potassium-rich Foods May Blunt Loss
of Muscle with Aging
With aging, a mild but slowly increasing metabolic acidosis develops, which may trigger a musclewasting response that contributes to the incidence of slips, falls, and fractures. This response might be neutralized by alkaline-producing plant foods high in potassium. To test this hypothesis, 384 male and female volunteers ages 65 or older were evaluated to determine the association of 24-h urinary potassium and an index of fruit and vegetable content of the diet and percentage of lean body mass at the start of the study and 3 years later. Subjects whose diets were potassium rich averaged 3.6 pounds of lean tissue mass more than those with only half that potassium intake. This conservation of lean tissue mass almost offsets the 4.4 pounds of lean tissue typically lost in a decade in this age group. Federal dietary guidelines emphasize the importance of older adults ingesting at least 4700 mg of potassium daily, an amount double that typically consumed.

From Dawson-Hughes B, et al. Alkaline diets favor lean tissue mass in older adults Am J Clin Nutr 2008;87:662.

The primary cause of reduced strength between ages 25 and 80 relates to a 40 to $50 \%$ reduction in muscle mass from muscle fiber atrophy and loss of motor units, even among healthy, physically active adults. Figure 31.9A shows that muscle-fiber loss begins near ages 50 to 60 . Reduction in total muscle area (Fig. 31.9B) usually parallels reduced fiber size, particularly fast-twitch fibers in the lower extremities. This proportionately increases the area occupied by slow-twitch (type I) muscle fibers.

In a longitudinal study of age-related declines in muscular strength, nine men initially evaluated for muscular strength and muscle fiber composition 12 years earlier were remeasured. ${ }^{61}$ Knee and elbow extensor and flexor strengths tested at slow and fast angular velocities decreased by 20 to $30 \%$. Muscle cross-sectional area for the same muscle groups evaluated by CT scans decreased between 13 and $16 \%$.


Figure 31.9 Relationship between age and (A) total number of muscle fibers and (B) muscle cross-sectional area. Muscle size begins to decrease at approximately age 30, decreasing $10 \%$ by age 50 . Thereafter, muscle area declines more precipitously, largely from decreased total number of muscle fibers. (From Lexell J, et al. What is the cause of the ageing atrophy? Total number, size, and proportion of different fiber types studied in whole vastus lateralis muscle from 15 - to 83 -year-old men. J Neurol Sci 1988;84:275.)

Muscle biopsies from the vastus lateralis muscle showed a $42 \%$ reduction in type I fibers without changes in mean fiber type area. Capillary-to-fiber ratio decreased with aging ( 0.31 units lower after 12 y ). The researchers concluded that changes in muscle cross-sectional area largely contributed to the strength decline from ages 65 to 77 .

## Resistance Training for the Elderly

Moderate resistance training provides a remarkably safe way to stimulate protein synthesis and retention while slowing the normal and somewhat inevitable loss of muscle mass and strength with aging. ${ }^{3,60,83,123}$ Muscle fiber size and mechanical performance, particularly the rate of force development, were consistently elevated in elderly individuals exposed to lifelong resistance training. ${ }^{1}$ Older men who resistance train demonstrate greater absolute gains in muscle
size and strength than women, but the percentage improvement is similar between genders (although gains are somewhat less than those of younger counterparts). ${ }^{102,205}$

Healthy men between ages 60 and 72 years who trained for 12 weeks with standard-resistance exercise at loads equivalent to $80 \%$ of 1-RM demonstrate how well the elderly respond to resistance training. Figure 31.10 shows that muscle strength increased progressively throughout training. At week 12, knee extension strength increased by $107 \%$ and knee flexion strength by $227 \%$. Improvement rate of $5 \%$ per training session matched similar increases reported for young adults. Fast- and slow-twitch muscle fiber hypertrophy accompanied dramatic strength improvements. In other research, muscle crosssectional area and strength in 70-year-olds who had resistance trained since age 50 equaled values for a group of 28-year-old university students. ${ }^{99}$ Older individuals possess impressive plasticity in physiologic, structural, and performance characteristics. Muscle responds to vigorous training with rapid improvement into the ninth decade of life (Fig. 31.11). Improved muscle strength, bone density, dynamic balance, and overall functional status with regular exercise can minimize or reverse the syndrome of physical frailty. For men and women between ages 70 and 89 years, a regular program of aerobic, strength, flexibility, and balance training prevented both loss of muscle strength and increase in muscle fat infiltration associated with advancing age. ${ }^{64}$ Regular strengthening and balance exercises provide the most effective way to reduce orthopedic injury (e.g., high prevalence of falls) in older men and women. ${ }^{161}$ Even for older persons disabled with osteoarthritis of the knee, regular aerobic or resistance exercises induce beneficial effects on measures of disability, pain, and physical performance. ${ }^{52}$ For disabled older female cardiac patients, a 6-month program of resistance training improved muscular strength and physical capacity in a wide range of household physical activities and also improved endurance, balance, coordination, and flexibility. ${ }^{7}$ This relative preservation in muscle structure and function may provide an important physical reserve capacity to retain muscle mass and function above the critical threshold for independent living at old age.

Mechanisms that explain how middle-aged and elderly persons respond to resistance training include enhanced motor unit recruitment and innervation patterns and muscular hypertrophy (see Chapter 22). As with younger adults, the number of sets and repetitions and intensity, duration, and frequency of training determine the magnitude of strength adaptations.

## Neural Function

A nearly $40 \%$ decline in the number of spinal cord axons and a $10 \%$ decline in nerve conduction velocity reflect the cumulative effects of aging on central nervous system function. These changes likely contribute to the age-related decrement in neuromuscular performance assessed by simple and complex reaction and movement times. Partitioning reaction time into central processing time and muscle action time, aging most adversely affects the time to detect a stimulus and


Figure 31.10 Weekly measurements of dynamic muscle strength (1-RM) in left knee extension (green) and flexion (orange) during resistance training in older men. (From Frontera WR, et al. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol 1988;64:1038.)
process the information to produce the response. Knee-jerk reflexes do not involve neural processing in the brain, so aging affects them less than voluntary responses that involve reaction and movement. Physical inactivity may also be responsible for a large portion of the loss of neuromuscular function seen in older adults. Highly active versus low-active elderly women achieve greater peak torque, faster rate of torque development, shorter motor time, faster rate of EMG rise, and greater onset of EMG magnitude. ${ }^{110}$ Figure 31.12 shows slower movement times for simple and complex tasks
by older subjects than by younger subjects with similar physical activity levels. In all instances, the young or old active groups moved considerably faster than the less-active age group. A physically active lifestyle and specific exercise training (combined aerobic, balance, coordination and strength) affects neuromuscular functions positively at any age to slow the age-related decline in cognitive performance associated with speed of information processing. ${ }^{211}$ Physically active older adults who have relatively high cardiorespiratory fitness are less likely to experience cognitive


Figure 31.11 Plasticity in physiologic response to resistance training among the elderly. Magnetic resonance images taken at the mid-thigh region of a male subject 92 years of age before (left) and after (right) 112 weeks of resistance training of the knee extensor and flexor muscles. Quadriceps lean cross-sectional area increased by $44 \%$ in this individual. (From Harridge SD, et al. Knee extensor strength, activation, and size in very elderly people following strength training. Muscle Nerve 1999;22:831.)


Figure 31.12 Simple and complex movement time in subjects classified as young active, old active, young nonactive, and old nonactive. Note the slower movement times (higher scores) in simple and complex tasks by the old and young nonactive subjects than by their active counterparts. (From Spirduso WW. Reaction and movement time as a function of age and physical activity level. J Gerontol 1975;30:435.)
decline and dementia. Biologic mechanisms for such protection include reduced vascular risk, body fat, and levels of inflammatory markers and enhanced neuronal health and function (Fig. 31.13). Exercise interventions associate with short-term improvements in cognitive function in sedentary elders. ${ }^{17,21,35}$ Older individuals who remain physically active for 20 years or longer show reaction speeds that equal or exceed inactive younger adults. These findings support regular physical activity for slowing biologic aging of select neuromuscular functions. The potential magnitude of these changes and amount of physical activity required to induce meaningful responses remain controversial. ${ }^{180}$

## Endocrine Changes

Endocrine function changes with age. Approximately $40 \%$ of individuals ages 65 and 75 years and $50 \%$ of those older than
age 80 have impaired glucose tolerance that leads to the most common form of the disease-type 2 diabetes (see Chapter 20). Increased disease prevalence among the elderly largely relates to the controllable factors of poor diet quality, inadequate physical activity, and increased body fat, particularly in the visceral abdominal region. ${ }^{4}$

A lowered pituitary gland release of the thyroid-stimulating hormone thyrotropin (and reduced output of thyroxine) occurs with advancing age. Thyroid dysfunction directly affects metabolic function including decreased metabolic rate, glucose metabolism, and protein synthesis.

Figure 31.14 depicts changes in three hormonal systems associated with aging: (1) hypothalamic pituitary gonadal axis, (2) adrenal cortex, and (3) GH/IGF axis.


Figure 31.13 Potential mechanisms that may underlie the association between physical activity and reduced risk of cognitive decline and dementia in older adults.


Figure 31.14 Age-related decline in three hormone systems that affect the rate of biologic aging. Left. Decreased growth hormone (GH) release by the anterior pituitary depresses production of IGF-1 by the liver and other tissues, which inhibits cellular growth (a condition of aging termed somatopause). Middle. Decreased output of gonadotropic luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary, coupled with reduced estradiol secretion from the ovaries and testosterone from the testes, causes menopause (females) and andropause (males). Right. Adrenocortical cells responsible for DHEA production decrease their activity (termed adrenopause) without clinically evident changes in this glands corticotropin (ACTH) and cortisol secretion. A central pacemaker in the hypothalamus and/or higher brain areas mediates these processes to produce aging-related changes in peripheral organs (ovaries, testicles, and adrenal cortex).

## Hypothalamic Pituitary Gonadal Axis

In females, alteration in the interaction between stimulating hormones from the hypothalamus and anterior pituitary gland and gonads decreases estradiol output from the ovaries. This effect probably initiates permanent cessation of menses (menopause). Changes in hypothalamic pituitary gonadal axis activity in males occur more slowly. Serum total and free testosterone, for example, gradually decline with aging in males. Decreases in gonadotropic secretions from the anterior pituitary gland characterize male andropause.

## Adrenal Cortex

Adrenopause refers to reduced adrenal cortex output of dehydroepiandrosterone (DHEA) and its sulfated ester DHEAS. In contrast to glucocorticoid and mineralocorticoid
adrenal steroids whose plasma levels remain relatively high with aging, DHEA exhibits a long, progressive decline after age 30 . By age 75, the plasma levels are only 20 to $30 \%$ of the value in young adults. This has evoked speculation that plasma DHEA levels might serve as a biochemical marker of biologic aging and disease susceptibility. Research with animals suggests that exogenous DHEA protects against cancer, atherosclerosis, viral infections, obesity, and diabetes; enhances immune function; and even extends life. Despite its quantitative significance as a hormone in humans, researchers know little about DHEA s (1) role in health and aging, (2) cellular or molecular mechanism(s) of action, (3) possible receptor sites, or (4) potential for adverse effects from supplemental use among young adults with normal DHEA levels. Chapter 23 discusses the case for ergogenic effects of DHEA supplements (and potential risks) on adult men and women.

## Growth Hormone/Insulin-Like Growth Factor Axis

Mean pulse amplitude, duration, and fraction of secreted GH gradually decrease with aging, a condition termed somatopause. A parallel decrease also occurs in circulating levels of IGF-1. IGF-1 stimulates tissue growth and protein synthesis. The interaction between the hypothalamus and anterior pituitary gland probably triggers the age-related GH decrease.

The extent to which changes in gonadal function (menopause and andropause) contribute to adrenopause and somatopause (present in both sexes) remains uncertain. Evidence indicates that muscle size and strength, body composition and bone mass alterations, and progression of atherosclerosis relate directly to hormonal changes with aging. Hormone replacement therapy, nutritional supplementation, and regular physical activity can delay or even prevent aspects of immune function deterioration and hormone-related aging dysfunction. ${ }^{152}$

## Pulmonary Function

Mechanical constraints on the pulmonary system progress with age to cause deterioration in static and dynamic lung function. Also, pulmonary ventilation and gas exchange kinetics during the transition from rest to submaximal exercise slow substantially. ${ }^{41}$ In elderly men, aerobic training increases gas exchange kinetics to levels that approach values for fit young adults. ${ }^{16}$ Likewise, older endurance-trained athletes demonstrate greater pulmonary functional capacity than sedentary peers. Values for vital capacity, total lung capacity, residual lung volume, maximum voluntary ventilation, $\mathrm{FEV}_{1.0}$, and $\mathrm{FEV}_{1.0} / \mathrm{FVC}$ in athletes above age 60 remain higher than predicted from body size and higher than values for sedentary, healthy individuals. ${ }^{65}$ Such findings indicate that regular exercise retards pulmonary function decline with aging.

## Cardiovascular Function

Cardiovascular function and aerobic power do not escape age-related decrements.

## Aerobic Power

The precise effect of regular aerobic training on the agerelated decline in aerobic power remains unresolved. Crosssectional data reveal that $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ declines between 0.4 and $0.5 \mathrm{~mL} \cdot \mathrm{~kg}{ }^{1}$ each year (approximately $1 \%$ per year) in adult men and women, although the rate of decline accelerates somewhat in advancing age particularly for men. ${ }^{58,86,222}$ Extrapolating this average rate of decline reduces aerobic power by age 100 to a level that equals the resting oxygen consumption. This represents a somewhat severe and unrealistic estimate because differences exist in the age-related rate of decline in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ in sedentary and active individuals. ${ }^{169}$ The decline in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ with advancing age occurs nearly twice as fast in sedentary compared to physically active men and women. Studies of men who varied considerably in age, aerobic power, body composition, and lifestyle revealed that
maintaining relatively stable physical activity and body composition levels over time produced an average yearly decline in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ of $0.25 \mathrm{~mL} \cdot \mathrm{~kg}^{1} \cdot \min { }^{1}$. No decline in aerobic power occurred in individuals who maintained constant training during a 10-year period. ${ }^{95,154}$

For most individuals, regular aerobic exercise cannot fully prevent the age-related decline in aerobic power with aging. ${ }^{56,193,206}$ For example, aerobic power of 50 -year-old endurance athletes decreased between 8 and $15 \%$ per decade despite continued exercise over a 20-year period. ${ }^{155}$ Despite this disparity, research consistently shows that physically active older men and women maintain a 10 to $50 \%$ higher aerobic power than sedentary counterparts.

Factors other than physical activity level influence the agerelated decline in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$. Heredity undoubtedly plays a crucial role, as does an increase in body fat and decrease in skeletal muscle mass. ${ }^{169}$ In the later decades of life, declines in maximal cardiac output and $\mathrm{a}-\mathrm{vO}_{2}$ difference contribute equally to the age-related decrease in $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}{ }^{220}$ Aging also relates to a decline in a muscle s oxidative function from reduced synthesis of mitochondrial and other proteins. ${ }^{179}$ An analysis of aerobic power of young and older endurance-trained men and women (Fig. 31.15) indicates an average $0.5 \mathrm{~L} \cdot \mathrm{~min}^{-1}$ lower $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ per kilogram of limb (appendicular) muscle mass for older athletes, independent of age-associated decreases in muscle and increases in fat. No clear answer exists as to how much the lower aerobic power per kilogram of limb muscle mass in the older subjects reflects reduced oxygen extraction by active muscles and/or reduced oxygen delivery via decreased cardiac output and/or active muscle blood flow. However, leg blood flow and vascular conductance during cycle ergometer exercise averaged 20 to $30 \%$ lower in older endurance-trained men than in younger peers at similar submaximal oxygen consumptions. ${ }^{158}$ Consequently, older athletes achieve an equivalent submaximal oxygen consumption at reduced leg blood flows by means of an increased local oxygen extraction ( $\mathrm{a}-\mathrm{vO}_{2}$ difference) from the available blood supply. For a group of older untrained women, a diminished leg blood flow during peak exercise contributed considerably to their lower $\dot{\mathrm{V}} \mathrm{O}_{\text {2peak }}$ than untrained younger counterparts. The diminished leg blood flow occurred from both central (cardiac output) and peripheral (reduced vascular conductance) limitations. ${ }^{159}$

## Central and Peripheral Functions

Decrements in central and peripheral functions linked to oxygen transport and use influence the age-related decline in aerobic power.

Heart Rate. A decline in maximum exercise heart rate represents a well-documented change with age. This age effect reflects reduced medullary outflow of sympathetic activity (depressed $\beta$-adrenergic stimulation) that occurs similarly in men and women. Several longitudinal studies of elite athletes reveal that decreases in maximum heart rate over a 20-year period (from ages 50 to 70 y ) are smaller than typically predicted and indicative of a training response. ${ }^{155,195}$


Figure 31.15 Individual maximal oxygen consumption values $\left(\dot{\mathrm{VO}}_{2 \text { max }}\right)$ related to appendicular muscle mass in young (top line) and older (bottom line) endurance-trained women and men. For an equivalent appendicular muscle mass, $\dot{\mathrm{VO}} 2_{\text {max }}$ averaged $0.5 \mathrm{I} \cdot \mathrm{Min}^{-1}$ less for older subjects. These data suggest that aerobic power per kilogram of appendicular muscle mass decreases with age in highly trained men and women. (From Procter DN, Joyner MJ. Skeletal muscle mass and the reduction of $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ in trained older subjects. J Appl Physiol 1997;82:1411.)

Cardiac Output. Maximum cardiac output decreases with age in trained and untrained men and women because of a lower maximum heart rate and stroke volume. The stroke volume decline reflects the combined effects of reduced left ventricular systolic and diastolic myocardial performance, although some physically active individuals maintain contractile function. Healthy elderly individuals often compensate for a diminished maximum heart rate with increased cardiac filling (end-diastolic volume), which subsequently increases stroke volume by the Frank-Starling mechanism. ${ }^{57,222}$

Large Artery Compliance. Compliance of large arteries in the cardiothoracic circulation declines with age from changes in the arterial wall s structural and nonstructural properties. ${ }^{151,175}$ The inability of the internal diameter of an artery to expand and recoil in response to fluctuations in intravascular pressure during the cardiac cycle associates with impaired cardiovascular function and elevated heart disease risk factors-hypertension, stroke, atherosclerosis, thrombosis, myocardial infarction, and congestive heart failure. Regular endurance exercise slows or prevents the stiffening
of the large arteries with advancing age and slows the decline in limb vasodilator capacity with healthy aging. ${ }^{160,190,194}$

Peripheral Factors. Reduced peripheral blood flow capacity accompanies age-related decreases in muscle mass. A decrease in the capillary-to-muscle fiber ratio and reduced arterial cross-sectional area produces lower blood flow to active muscle. ${ }^{185}$ An unanswered question concerns how aging and regular exercise interact to affect a muscle s oxidative enzymes.

## Physiologic Loss with Aging: Lifestyle or Chronologic Age?

Sedentary living produces losses in functional capacity at least as great as the effects of aging. A high degree of trainability exists among older men and women and may not only slow but even reverse the decline in functional capacity with aging. ${ }^{177}$ Positive training-induced adaptations in skeletal muscle structure and function, substrate metabolism, and cardiovascular function often equal those for younger individuals. Both low- and higher intensity exercise enable older individuals to retain cardiovascular functions at a higher level than age-paired sedentary subjects. Active middle-aged men who endurance trained over a 10-year period forestalled the usual 9 to $15 \%$ decline in aerobic power. ${ }^{94}$ At age 55, the men maintained the same values for blood pressure, body mass, and $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ as 10 years earlier.

## Endurance Performance

Comparing endurance performance of athletes of different ages provides further evidence for the impressive effects of regular exercise on preservation of cardiovascular function throughout life. Age-group, world-record times for 50-, 100-, and $200-\mathrm{km}$ runs for men and women are always recorded by the youngest athletes. The world record marathon time for men set in 2008 by 35 -year-old Haile Gebrselassie of Ethiopia was 2 hours 3 minutes and 59 seconds ( $4: 44$ per mile pace); the world record for women of 2 hours, 15 minutes, 25 seconds was set by Paula Radcliff (age 31) of Great Britain in 2003, and corresponds to an average running speed of 5 minutes 10 seconds per mile.

Run times for the marathons are particularly noteworthy for the older runners. The data for the 70- to 74 -year-old group are illustrative; the record- 2 hours, 54 minutes, 49 seconds ( $6: 40$ per mile pace), set in 2003 by 73 -year old Canadian Ed Whitlock-was the first time anyone over age 70 ran a sub- 3 hour marathon. This time would have placed him 608th in the 2008 New York City Marathon, or at the top $1.6 \%$ of the 38,111 finishers; 994 runners bettered 3 hours in this marathon. That individuals in their eighth and ninth decades of life successfully run for 12 to 14 hours affirms the tremendous cardiovascular potential of older men and women who continue vigorous training as they age.

## Sprint Performance

Figure 31.16 illustrates the relationship between age and 100-m sprint performance in male and female master sprinters ages 35 to 88 years. Performance declined in both groups

$\square$ Men $\quad \square$ Women
Figure 31.16 Individual values of $100-\mathrm{m}$ running time as a
Figure 31.16 Individual values of $100-\mathrm{m}$ running time as a function of age in male and female sprinters. (From Korhonen MT, et al. Age-related differences in 100-m sprint performance in male and female master runners. Med Sci Sports Exerc 2003;35:1419.)
of athletes with age, the decreases becoming more evident after age 60. Remarkable similarities exist for age-related decrements in running velocity between sexes. Running velocity during the different phases of the run declined from 5 to $6 \%$ per decade in men and 5 to $7 \%$ per decade for women. Reduced stride length and increase in contact time of the foot with the ground primarily accounted for the overall performance deterioration with age.

## Body Composition

Cross-sectional studies indicate that after age 18 , men and women progressively gain body weight and fat until the fifth or sixth decade of life, at which time total body mass decreases despite increasing body fat. This results partly from a disproportionately greater death rate among the obese in the upperage group, leaving fewer of these individuals to measure.

Most age-trend studies do not track the same subjects over time; instead, they evaluate different subjects in different age categories at the same time. From such cross-sectional data, one attempts to generalize about an individual s expected agerelated changes, but sometimes this creates misleading generalizations. For example, today s 70- and 80-year-olds typically are shorter than 20-year-old college students. This observation does not necessarily mean that individuals become shorter with age (although this does happen to some extent). Instead, the young adults of the current generation receive better nourishment than 80-year-olds received at age 20.

The limited longitudinal data (collected on the same subjects over time) show trends in body fat changes similar to data from cross-sectional studies. It is not known whether
body fat increases during adulthood represent a normal biologic pattern or simply reflect sedentary lifestyle choices. Longitudinal observations of individuals who maintain a physically active lifestyle support a biologic tendency to gain fat with age. Figure 31.17 shows body composition


Figure 31.17 Changes in (A) waist girth, (B) waist hip girth ratio, (C) sum of skinfolds, (D) percentage body fat, and (E) FFM for 21 endurance athletes who continued to train over a 20-year period, starting at age 50. (From Pollock ML, et al. Twenty-year follow-up of aerobic power and body composition of older track athletes. J Appl Physiol 1997;82:1508.)
changes for 21 endurance athletes who continued to train over a 20 -year period starting at age 50 . Despite maintaining a relatively constant body mass during the prolonged period of training, gains occurred in body fat and abdominal obesity while FFM declined. The roughly $3 \%$ body fat unit increase per decade paralleled increases in waist girth. The magnitude of increase in body fat and decrease in FFM, while discouraging to some, averages at least $20 \%$ less than reported for nonathletes. Habitual endurance exercise confers at least some protection from the effects of aging on body composition.

## Bone Mass

Osteoporosis poses a major problem with aging, particularly among postmenopausal women. This condition produces loss of bone mass as the aging skeleton demineralizes and becomes porous. Bone mass can decrease by 30 to $50 \%$ in persons above age 60. As emphasized in Chapter 2, regular weight-bearing exercise and resistance exercise not only retard bone loss but also often increase bone mass in elderly men and women. ${ }^{5}$ In postmenopausal women, regular exercise augments hormone replacement therapy to increase total bone mineral density and preserve these gains. ${ }^{66,101}$

## TRAINABILITY AND AGE

Exercise training improves physiologic responses at any age. Several factors affect the magnitude of the training response, including initial fitness status, genetics, and specific type of training.

Research over the past 40 years has modified the classic view of the diminished improvements from physical conditioning with aging (Fig. 31.18). The current view maintains


Figure 31.18 New view of old beliefs. Traditional (classic) versus the more current view of the expected improvements from physical training with aging.
that over a broad age range, improvements in physiologic function result from an appropriate training stimulus, often at a rate and magnitude independent of age. Older men and women and younger adults show similar adaptations of muscle fiber size, capillarization, and glycolytic and respiratory enzymes to specific endurance or resistance-training exercise. These adaptations emerge most readily with relatively intense exercise that continuously adjusts to training improvements.

## Aerobic Trainability Among the Elderly: Perhaps a Gender Difference

Exercise training for healthy elderly men enhances the heart s systolic and diastolic properties and increases aerobic power to the same relative extent (15 30\%) as in younger adults. ${ }^{29,49,174}$ Research has evaluated the contribution of training-induced increases in stroke volume and a-vO $\mathrm{O}_{2}$ difference to aerobic fitness improvements in healthy older men and women. Nine to 12 months of endurance training increased $\dot{\mathrm{VO}} 2_{2 \text { max }}$ by $19 \%$ in men and $22 \%$ in women (Table 31.1). These values represent the high end of improvement typically observed for younger adults. Gender differences emerged in certain aspects of the training response. For men, improved aerobic power was associated with a $15 \%$ larger maximum stroke volume (corresponding cardiac output increase represented two-thirds of the $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ increase) and $7 \%$ greater maximum $\mathrm{a}-\mathrm{vO}_{2}$ difference (representing onethird of the $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ increase).

For the women, the a- $\mathrm{vO}_{2}$ difference explained the total $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ increase, with no change in left ventricular performance at maximal exercise. This indicates that training-induced increases in aerobic power for older women depend on peripheral adaptations in trained muscle and suggests that sex hormones influence gender-related adaptations to endurance training. ${ }^{98}$ The lack of a stroke volume increase among older women with training may result from (1) blunting of the normal increase in plasma volume, (2) depression of cardiopulmonary baroreflex sensitivity, and (3) estrogen deficiency related decrease in vascular compliance (i.e., increased vascular stiffness). ${ }^{185} 187$ These apparent gender differences in physiology do not impair endurance performance in older women as reflected by male female similarities in ultradistance running performance.

## Summary

1. Physiologic and performance capabilities usually decline after age 30. Many factors, including diminished physical activity level, affect the rate of decline.
2. Regular physical activity and exercise training enable older persons to retain higher levels of functional capacity, notably cardiovascular and muscular function.

TABLE 31.1 Effects of 9 Months of Endurance Training on Maximal Oxygen Consumption and Cardiovascular Function in 15 Men (Age, $63 \pm 3$ y)

|  | $\begin{gathered} \dot{\mathrm{VO}}_{2 \mathrm{MAx}} \\ \mathrm{~L} \cdot \mathrm{Min}^{-1} \end{gathered}$ | $\begin{gathered} \dot{\mathrm{Q}}_{\mathrm{MAX}} \\ \mathrm{~L} \cdot \mathrm{Min}^{-1} \end{gathered}$ | $\begin{gathered} \mathrm{HR}_{\mathrm{MAX}} \\ \mathrm{~B} \cdot \mathrm{Min}^{-1} \end{gathered}$ | $\begin{gathered} \mathrm{SV}_{\mathrm{MAX}} \\ \mathrm{~mL} \end{gathered}$ | $\begin{gathered} \mathrm{a}-\mathrm{vO}_{2 \text { diff }} \\ \mathrm{mL} \cdot \mathrm{dL}^{-1} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Men |  |  |  |  |  |
| Before | 2.35 | 17 | 170 | 101 | 13.8 |
| After | $2.8{ }^{\text {a }}$ | $19^{a}$ | $164{ }^{a}$ | $116^{a}$ | $14.8{ }^{\text {a }}$ |
| Women |  |  |  |  |  |
| Before | 1.36 | 11.2 | 161 | 70 | 12.2 |
| After | $1.66{ }^{\text {a }}$ | 11.5 | 164 | 70 | $14.4{ }^{\text {a }}$ |

From Spina RJ, et al. Differences in cardiovascular adaptations to endurance-exercise training between older men and women. J Appl Physiol 1993;75:849.
Values are means; $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, maximal $\mathrm{O}_{2}$ consumption; $\dot{\mathrm{Q}}_{\text {max }}$, maximal cardiac output; $\mathrm{HR}_{\text {max }}$, maximal heart rate; $\mathrm{SV}_{\text {max }}$, stroke volume at maximal exercise; $\mathrm{a}-\overline{\mathrm{v}} \mathrm{O}_{2 \text { diff }}$, arteriovenous $\mathrm{O}_{2}$ content difference at maximal exercise. ${ }^{a} p \pm 0.01 \mathrm{vs}$. before training.
3. Biologic aging relates to changes in three hormonal systems: hypothalamic pituitary gonadal axis, adrenal cortex, and growth hormone insulin-like growth factor axis.
4. Four factors are important when evaluating physiologic and performance differences between children and adults: (1) exercise economy, (2) FFM, (3) anaerobic power, and (4) anabolic hormone levels.
5. The primary cause of the age-associated reduction in muscle strength between ages 25 and 80 is a 40 to $50 \%$ reduction in muscle mass from a loss of motor units and muscle fiber atrophy.
6. Considerable plasticity exists in physiologic, structural, and performance characteristics among older individuals that enable marked and rapid strength improvement with training into the ninth decade of life.
7. A physically active lifestyle affects neuromuscular functions positively at any age and possibly slows the age-related decline in cognitive performance associated with speed of information processing.
8. $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ declines approximately $1 \%$ each year in adult men and women. Physically active older men and women maintain a higher aerobic power than sedentary peers at any age.
9. Sedentary living causes losses in functional capacity at least as great as aging itself. Regular exercise improves physiologic function at any age; initial fitness, genetics, and type and amount of training control the magnitude of change.
10. Active older athletes average at least $20 \%$ less body fat and $20 \%$ more FFM than nonathletic peers; this suggests that habitual physical activity confers some protection from the negative effects of aging on body composition.

## Part 3 PHYSICAL ACTIVITY, HEALTH, AND LONGEVITY

Physical activity may not necessarily represent a fountain of youth, yet the preponderance of evidence shows that regular physical activity retards the decline in functional capacity associated with aging and disuse. Exercise participation can reverse the loss of function regardless of when a person becomes more physically active.

## The Federal Government Takes a Stand

The Physical Activity Guidelines for Americans, released by the Health and Human Services Department in October 2008, are based on the first federal-sponsored review of scientific research about physical activity and health. Key guidelines, by group, are:
Children and Adolescents-One hour or more of moderate or vigorous aerobic physical activity a day, including vigorous-intensity physical activity at least 3 days a week. Examples of moderateintensity aerobic activities include hiking, skateboarding, bicycle riding, and brisk walking. Vigorous-intensity aerobic activities include bicycle riding, jumping rope, running, and sports such as soccer, basketball, and ice or field hockey. Children and adolescents should incorporate musclestrengthening activities, such as rope climbing, sit-ups, and tug-of war, 3 days a week. Bonestrengthening activities, such as jumping rope, running, and skipping, are recommended 3 days a week.

Adults-Adults gain substantial health benefits from 2.5 hours a week of moderate-intensity aerobic physical activity, or 1 hour and 15 minutes of vigorous physical activity. Walking briskly, water aerobics, ballroom dancing, and general gardening are examples of moderate-intensity aerobic activities. Vigorous-intensity aerobic activities include race walking, jogging or running, swimming laps, jumping rope, and hiking uphill or with a heavy backpack. Aerobic activity should be performed in episodes of at least 10 minutes. For more extensive health benefits, adults should increase their aerobic physical activity to 5 hours a week of moderate-intensity or 2.5 hours a week of vigorous-intensity aerobic physical activity. Adults should incorporate muscle-strengthening activities, such as weight training, push-ups, sit-ups, and carrying heavy loads or doing heavy gardening, at least 2 days a week.
Older adults-Older adults should follow the guidelines for other adults when it is within their physical capacity. If a chronic condition prohibits their ability to follow those guidelines, they should be as physically active as their abilities and conditions allow. If they are at risk of falling, they should also do exercises that maintain or improve balance.
Women during pregnancy-Healthy women should get at least 2.5 hours of moderate-intensity aerobic activity a week during pregnancy and the time after delivery, preferably spread through the week. Pregnant women who habitually engage in vigorous aerobic activity or who are highly active can continue during pregnancy and the time after delivery, provided they remain healthy and discuss with their health care provider how and when activity should be adjusted over time.
Adults with disabilities-Those who are able should get at least 2.5 hours of moderate aerobic activity a week, or 1 hour and 15 minutes of vigorous aerobic activity a week. They should incorporate muscle-strengthening activities involving all major muscle groups 2 or more days a week. When they are not able to meet the guidelines, they should engage in regular physical activity according to their abilities and should avoid inactivity.
People with chronic medical conditions-Adults with chronic conditions get important health benefits from regular physical activity. They should do so with the guidance of a health care provider.

For more information about the Physical Activity Guidelines for Americans, visit www.hhs.gov or www.health.gov/paguidelines.

## CAUSES OF DEATH IN THE UNITED STATES

Substantial changes in lifestyle during the last two to three decades have led to variations in causes of death in the United States. Mortality rates from heart disease, stroke, and cancer have declined. Concurrently, behavioral changes have increased the prevalence of obesity and type 2 diabetes. Table 31.2 summarizes the 10 leading causes of death in the United States. Diseases of the heart $(652,091)$, malignant neoplasm cancers $(559,312)$, and cerebrovascular disease $(143,579)$ account for the vast majority of the deaths (www.cdc.gov/nchs/FASTATS/lcod.htm). Estimates attribute approximately one-half of all these deaths to a limited number of largely preventable behaviors and exposures, most of which relate directly to physical inactivity and overweight and obesity.

## EXERCISE, HEALTH, AND LONGEVITY

In one of the first studies of the possibility that sport and regular exercise prolongs life, former Harvard oarsmen exceeded their predicted longevity by 5.1 years per man. ${ }^{74}$ Other early studies showed similar but more modest life span extensions. ${ }^{13}$ Methodologic problems in this research included inadequate record keeping, small sample size, improper statistical procedures to estimate expected longevity, and no accounting for socioeconomic status, body type, tobacco use, and family background.

Subsequent research contradicted these findings and showed that participation in athletics as a young adult does not ensure good health and longevity later in life. ${ }^{162}$ In contrast, maintaining increased physical activity and fitness throughout life provides significant health and longevity benefits. ${ }^{24,172,201,226}$ A continuing longitudinal study of the health consequences of different fitness levels in 25,341 men and 7080 women revealed that low aerobic fitness was a more important precursor of all-cause mortality than any of the other

TABLE 31.2 Ten Leading Causes of Death in the United States in 2005

| Cause of Death | Number of Deaths |
| :--- | ---: |
| Heart disease | 652,091 |
| Cancer | 559,312 |
| Stroke (cerebrovascular disease) | 143,579 |
| Chronic lower respiratory diseases | 130,933 |
| Accidents (unintentional injuries) | 117,809 |
| Diabetes | 75,119 |
| Alzheimer s disease | 71,559 |
| Influenza/pneumonia | 63,001 |
| Nephritis, nephritic syndrome, | 43,901 |
| $\quad$ and nephrosis | 34,136 |
| Septicemia |  |
|  |  |



Figure 31.19 Comparative influence of low physical fitness as a precursor of all-cause mortality in men and women. (From Blair S, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996;276:205.)
risk factors (FIG. 31.19). In addition, inverse risk gradients emerged across categories of low, moderate, and high fitness, with a lower death rate among moderately fit individuals compared to the low-fitness group. The least fit men and women were nearly twice as likely to die from all causes as the most fit counterparts during an 8-year follow-up. Increased physical fitness countered the negative effects of other important risk factors. Moderately fit smokers with hypertension and high cholesterol lived longer than healthy but sedentary nonsmokers. Low physical fitness emerged as a more powerful risk factor than high blood pressure, high cholesterol, obesity, and family history.

## Enhanced Quality to a Longer Life: The Harvard Alumni Study

The lifestyles and exercise habits of 17,000 Harvard alumni who entered college between 1916 and 1950 provide evidence that moderate aerobic exercise equivalent to jogging

3 miles daily at a pace slightly faster than fast walking promotes good health and adds several years to life. The results of long-term studies show four direct benefits from regular exercise:

1. Counters the life-shortening effects of cigarette smoking and excess body weight
2. Reduces death rate by one-half in individuals with hypertension who exercise regularly
3. Counters genetic tendencies toward early death with a lifestyle of regular exercise; reduces death risk by $25 \%$ for individuals with one or both parents who died before age 65 (a significant health risk)
4. Decreases mortality rate by $50 \%$ for physically active men whose parents live beyond age 65

Figure 31.20 illustrates that persons who do more physical activity further reduce their risk of dying (from any cause). Men who walked nine or more miles each week, for


Figure 31.20 Reduced death risk for individuals who participate in regular exercise. (Adapted from Paffenbarger RS Jr, et al. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med 1986;314:605.)
example, had a $21 \%$ lower mortality rate than men who walked three miles or less. Life expectancy was higher for men who exercised at the equivalent of light sport activity than sedentary men. Life expectancy of Harvard alumni increased steadily from a weekly exercise energy expenditure of 500 kCal up to 3500 kCal , a value equivalent to 6 to 8 hours of strenuous exercise. The active men lived an average of 1 to 2 years longer than sedentary classmates. Weekly exercise beyond 3500 kCal conferred no additional health or longevity benefits.

## Vigorous Exercise and Longevity

The Harvard alumni study examined only the total amount of weekly physical activity, not its intensity, in relation to heart disease and mortality. Further research from the same population revealed that vigorous regular exercise exerts the greatest effect on extending life. ${ }^{113}$ Men who expended at least 1500 kCal weekly in vigorous exercise during the 20-year study-equivalent to 6 METs or more (jogging or walking briskly, lap swimming, singles tennis, fast cycling, or heavy yard chores for 1 hour, performed 3 or 4 times weekly)—had a $25 \%$ lower death rate than the most sedentary men. The most active men showed the greatest life expectancies, largely from reduced deaths from cardiovascular disease. The benefits of vigorous exercise also extended to overweight smokers. Risk associated with a sedentary lifestyle equaled the risk of smoking one pack of cigarettes daily or being $20 \%$ overweight. Subsequent research with these men (and others) ${ }^{8}$ showed that the exercise equivalent of a 1-hour brisk walk 5 days weekly or a vigorous workout at least once weekly cut stroke risk almost in half; brisk walking for 30 minutes 5 days weekly reduced stroke risk by $24 \%$. ${ }^{114,115}$ Other stroke-protective activities included stair climbing or participating in moderate activities such as gardening, dancing, and bicycling. An intensive poststroke exercise program also facilitates the stroke survivor s recovery of motor skills.

## Epidemiologic Evidence

A critique of 43 studies of the relationship between physical inactivity and coronary heart disease concluded that lack of regular exercise contributes to heart disease in a cause-andeffect manner; the sedentary person has about twice the risk of developing heart disease as the most active individual. ${ }^{156}$ The strength of the association between lack of exercise and heart disease risk equals that for hypertension, cigarette smoking, and high serum cholesterol. This makes physical inactivity the greater heart disease risk because more people lead sedentary lifestyles than possess one or more of the other primary risk factors. The life-protecting benefits of exercise link more with preventing early mortality than extending life span. Surprisingly, only light-to-moderate regular walking, gardening, stair climbing, and household chores produce health benefits for previously sedentary middle-aged and older men and women. ${ }^{22,100,116,168}$ These sedentary individuals represent the
largest percentage of the population at greatest risk for chronic disease.

## INTEGRATIVE QUESTION

Discuss whether physical activity benefits a persons health profile even if exercise intensity does not produce a training effect.

## REGULAR MODERATE EXERCISE PROVIDES SIGNIFICANT BENEFITS

A sedentary lifestyle represents an independent and powerful predictor of coronary heart disease risk and mortality, so encouraging the most sedentary $25 \%$ of the American adult population to become only moderately active would yield substantial public health benefits. ${ }^{23,33,108,164}$ Moderate exercise such as walking even reduces the level of diabetic, hypertensive, and cholesterol medication required by patients. ${ }^{225}$ For postmenopausal women, walking briskly for 2.5 hours weekly (about 30 min a day 5 days a week) reduced heart disease risk by $30 \%$-a reduction comparable to that achieved with cholesterol-lowering drugs-regardless of race, age, or how much the women weighed. ${ }^{127}$ Women who did the most exercise reduced risk by $63 \%$. Figure 31.21


Figure 31.21 Cumulative mortality by year of follow-up and distance walked per day. (To convert distances to kilometers, multiply by 1.609.) (From Hakim AA, et al. Effects of walking on mortality among nonsmoking retired men. N Engl J Med 1998;338:94.)

TABLE 31.3 Moderate- and High-Intensity Leisure-Time Physical Activity (LTPA) and Risk of Primary Cardiac Arrest

| Type of LTPA | Cases |  | Odds Ratio Cardiac Arrest Risk |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Patients, No. (\%) | Controls, No. (\%) | Unadjusted | Adjusted ${ }^{\text {a }}$ |
| No activity | 45 (14) | 18 (4) | 1.0 (Reference) | 1.0 (Reference) |
| Moderate intensity | 160 (48) | 192 (38) | 0.36 | 0.36 |
| High intensity | 128 (38) | 293 (58) | 0.19 | 0.36 |

From Lemaitre RN, et al. Leisure-time physical activity and the risk of primary cardiac arrest. Arch Intern Med 1999;159:686.
${ }^{a}$ Adjusted for age, smoking, education, diabetes, hypertension, and health status.
further illustrates the health-related benefits of regular physical activity. The analysis assessed the effect of miles walked each day on overall mortality rate in 707 nonsmoking men ages 61 to 81 years. An inverse relationship between distance walked and mortality emerged after adjusting for overall physical activity and other risk factors. Men who walked less than 1 mile daily had a cumulative death incidence in 7 years that required 12 years for the most active men who walked at least 2 miles daily. Over 7 years, $43.1 \%$ of the less active men died compared with $21.5 \%$ of the most active walkers.

TABLE 31.3 presents corroborative research findings for leisure-time physical activity of 333 patients ages 25 to 74 years who suffered a first heart attack and 503 control subjects without a heart attack selected randomly and matched for age and gender. After adjustments for heart disease risks (age, smoking, diabetes, hypertension), regular walkers reduced cardiac arrest risk by $73 \%$, and those who gardened regularly reduced risk by $66 \%$ compared with sedentary peers (risk ratio set at 1.00 ). Walking or gardening for more than 60 minutes a week reduced risk similarly to highintensity leisure-time physical activity. The benefits of walking also applied to women who regularly walked 3 mph or faster for at least 3 hours weekly; cardiac arrest risk decreased up to $40 \%$ below the risk for sedentary women. Risk reduced by one-half for women who walked briskly ( $\geq 3.0 \mathrm{mph}$ ) for 5 hours a week. ${ }^{126}$ These findings complement and further support exercise recommendations from the CDC and ACSM to accumulate 30 minutes or more of moderate-intensity physical activity on most days of the week.

## Influence of Physiologic Factors

In addition to simple physical activity data, physiologic measures like a low level of cardiorespiratory fitness (including low exercise capacity, low $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$, low heart rate recovery, and failure to achieve target heart rate) provide a strong independent predictor of increased risk for cardiovascular disease and all-cause mortality. ${ }^{36,224,226}$

One study directly examined aerobic fitness (rather than verbal or written reports of physical activity habits) and heart disease risk in more than 13,000 men and women observed over an average of 8 years. To isolate the effect of physical fitness, the study accounted for cigarette smoking, high cholesterol and blood sugar levels, hypertension, and family history of heart disease. Based on age-adjusted death rates per 10,000 person-years, the least-fit group averaged more than three times the death rate of the most-fit individuals (Fig. 31.22). The greatest health benefits emerged for the group rated just above the most sedentary category. For men, the decrease in death rate from the least-fit category to the next category exceeded 38 ( 64.0 vs. 25.5 deaths per 10,000 person-years), whereas the drop in mortality between the second group and most fit group was only 7 . Enhanced aerobic fitness benefits women to a similar if not greater extent. ${ }^{142}$ For every increased score of 1 MET in exercise capacity, the risk of death from all causes decreased by $17 \%$. ${ }^{127}$ To move from the most sedentary category to the next highest group-the change that produced the greatest health benefits-requires only such moderate-intensity exercise as walking briskly for 30 minutes twice weekly.

Studies of Finnish men complement the above findings. ${ }^{93}$ Aerobic power and leisure-time physical activity showed an inverse, graded, independent association with risk for acute myocardial infarction. Even after adjusting for genetic effects and other familial factors that predict mortality, current aerobic fitness and physical activity level offered significant protection from death. ${ }^{106}$ Physical fitness also counters the negative impact of existing disease. For example, an inverse and independent relationship emerges between aerobic power and incidence of fatal and nonfatal cardiovascular events and all-cause mortality in male and female hypertensives followed over 16.5 years. ${ }^{149}$

Table 31.4 summarizes 30 years of research relating physical activity level or physical fitness to chronic disease or medical conditions. Clearly, a strong inverse association exists between regular exercise and level of aerobic fitness and all causes of death. Moderate-intensity regular exercise substantially reduces the risk of dying from heart disease, cancer, and other causes.


Figure 31.22 Aerobic fitness and longevity. Going from the low fitness category to a moderate level produces the greatest reduction in death risk with only a small but additional benefit from further fitness improvements. Inset figure shows a generalized curve that depicts health benefits from increased daily physical activity and aerobic fitness. (Modified from Blair SN, et al. Physical fitness and all-cause mortality: a prospective study of healthy men and women. JAMA 1989;262:2395.)

## TABLE 31.4 General Trend for Effects of Regular Physical Activity and/or Increased Physical Fitness and Risk for Chronic Disease Conditions

## Disease or

 ConditionTrends Across Activity or Fitness Categories and Strength of Evidence ${ }^{a}$

| All-cause mortality | $\uparrow \uparrow \uparrow$ |
| :---: | :---: |
| Coronary artery disease | $\uparrow \uparrow \uparrow$ |
| Hypertension | $\uparrow \uparrow$ |
| Obesity | $\uparrow \uparrow \uparrow$ |
| Stroke | $\uparrow$ |
| Peripheral vascular disease | $\rightarrow$ |
| Cancer |  |
| Colon | $\uparrow \uparrow$ |
| Rectum | $\rightarrow$ |
| Stomach | $\rightarrow$ |
| Breast | $\uparrow$ |
| Prostate | $\uparrow$ |
| Lung | $\uparrow$ |
| Pancreas | $\rightarrow$ |
| Type 2 diabetes | $\uparrow \uparrow \uparrow$ |
| Osteoarthritis | $\rightarrow$ |
| Osteoporosis | $\uparrow \uparrow$ |
| ${ }^{a} \rightarrow$, No apparent difference in disease rates across activity or fitness categories; $\uparrow$, some evidence of reduced disease rates across activity or fitness categories; $\uparrow \uparrow$, good evidence of reduced disease rates across activity or fitness categories, control of potential confounders, good methods, some evidence of biologic mechanisms; $\uparrow \uparrow \uparrow$, excellent evidence of reduced disease rates across activity or fitness categories, good control of potential confounders, excellent methods, extensive evidence of biologic mechanisms, relationship is considered causal. |  |

## Structured Physical Activity Not Necessary

Researchers monitored two groups of 116 sedentary men and 119 women ages 35 to 60 years during a 2 -year randomized clinical trial. ${ }^{48}$ One group spent 20 to 60 minutes vigorously exercising by swimming, stair stepping, walking, or biking at a fitness center up to 5 days a week. The other group incorporated 30 minutes a day of lifestyle exercises such as extra walking, raking leaves, stair climbing, walking around the airport while waiting for a plane, and participating in a walking club most days of the week. The lifestyle participants also learned cognitive and behavioral strategies to increase daily physical activity. For each of the programs, the intervention consisted of 6 months of intensive exercise followed by 18 months of maintenance. At the end of 24 months, both groups showed similar improvements in physical activity, cardiorespiratory fitness, systolic and diastolic blood pressure, and body fat percentage. These findings reinforce the conclusion that the healthderived benefits from regular exercise do not require highly structured or vigorous exercise.

## INTEGRATIVE QUESTION

Respond to the statement: The fact that overwhelming epidemiologic evidence links on-the-job or leisure-time physical activity to reduced coronary heart disease risk does not necessarily prove that exercise causes improved cardiovascular health.


Figure 31.23 Adjusted relative risks for CHD mortality from changes in lifestyle characteristics. Each relative risk is adjusted for age and all other variables in the figure. First bar of each pair represents men with initial unfavorable characteristics (in 1962 or 1966) and at follow-up in 1977. The second bar of the pair shows adjusted relative risks for men who achieved favorable changes in the variable of interest between baseline and 1977 follow-up. BMI, body mass index; Yes and No refer to presence or absence of trait at date indicated. (Modified from Blair SN. Physical activity, physical fitness, and health. Res Q Exerc Sport 1993;64:365. Data from Paffenbarger RS Jr, et al. The association between changes in physical-activity level and other lifestyle characteristics with mortality among men. N Engl J Med 1993;328:538.)

## CAN INCREASING PHYSICAL ACTIVITY LEVEL IMPROVE HEALTH AND EXTEND LIFE?

Current level of physical activity and physical fitness relates to health risk, but an important question concerns whether a sustained increase in regular activity can reduce disease risk. To answer this question, previously sedentary, apparently healthy male Harvard alumni reported whether they changed their typical physical activity and other lifestyle habits over an 11- to 15 -year period. Figure 31.23 relates changes in health-related lifestyle characteristics to changes in mortality risk. Regardless of age, sedentary men who adopted a more moderate to vigorous level of regular activity had a $51 \%$ lower risk of dying than men who remained sedentary. For lifestyle change and heart disease mortality risk, becoming more physically active on a regular basis provided risk reduction benefits equivalent to quitting cigarette smoking, reducing body weight, or controlling blood pressure.

## Summary

1. Vigorous physical activity early in life contributes little to increased longevity or health in later life. A
physically active lifestyle throughout life confers significant health benefits.
2. Regular, moderate exercise counters the lifeshortening effects of coronary heart disease risks that include cigarette smoking and excess body weight. A sedentary person runs almost twice the risk of developing heart disease as the most active individuals.
3. The risk of coronary heart disease from sedentary living equals that for hypertension, cigarette smoking, and high serum cholesterol. The lifeprotecting benefits of exercise relate more to preventing early mortality than to extending overall life span.
4. A moderate amount of regular exercise substantially reduces the risk of dying from heart disease, cancer, and other medically related maladies. The greatest health benefits emerge when a person alters a sedentary lifestyle and becomes just moderately physically active.
5. Strategies that modify lifestyle toward increased daily physical activity beneficially alter factors associated with coronary heart disease risk.

## Part 4 CORONARY HEART DISEASE

Coronary heart disease (CHD) involves degenerative changes in the intima, or inner lining, of the larger arteries that supply the myocardium.

## CHANGES ON THE CELLULAR LEVEL

Damage to arterial walls begins as a multifactorial, largely immunologically mediated, inflammatory response to injury, perhaps from hypertension, cigarette smoking, infection, homocysteine, elevated cholesterol, or free radicals. One response triggers the chemical modification of various compounds, which includes oxidation of lowdensity lipoprotein cholesterol (LDL-C). This initiates a complex series of changes that produce lesions that sometimes bulge into the vessel lumen or protrude outward into the arterial wall. Lesions initially take the form of fatty streaks, the first signs of atherosclerosis. With further inflammatory damage from continued lipid deposition and proliferation of smooth muscle cells and connective tissue, the vessel congests with lipid-filled plaques, fibrous scar tissue, or both. Progressive occlusion gradually reduces blood flow capacity with ensuing myocardial ischemia (reduced supply of oxygen).

## C-Reactive Protein: An Indication of Arterial Inflammation

About half of persons with heart disease have normal or just moderately elevated cholesterol levels, which has led researchers to consider other factors in the heart disease process. Guidelines issued by the AHA (www.aha.org) and the CDC (www.cdc.gov) propose an important role for inflammation testing to judge whether persons need aggressive treatment to protect their hearts and vascular system. Mounting evidence indicates that painless chronic lowgrade arterial inflammation, including that of the coronary arteries, is central to every stage of atherosclerotic disease and a major trigger for heart attack-more substantial even than high cholesterol. The inflammation produces heart attacks by weakening blood vessels walls, making plaque burst, and interfering with substances that increase myocardial circulation. C-reactive protein (CRP), a plasma protein discovered in 1930, is produced by the liver and adipocytes, and helps to fight injury, inflammation, and infection. The levels of this protein rises dramatically during acute and more chronic inflammatory reactions in the body. This compound may be just as important an independent coronary artery disease risk factor as elevated LDL-cholesterol. In fact, CRP reduction with statin drugs (and associated reduction in plaque size) is at least as crucial as cholesterol reduction in preventing heart attacks. ${ }^{141,166}$ CRP frequently rises when arteries begin to accumulate plaque. High CRP
levels also associate with the development of hypertension, ${ }^{176}$ a finding that suggests that hypertension is part of an inflammatory disorder. Normal CRP levels average $1.5 \mathrm{mg} \cdot \mathrm{dL}^{1}$ of blood. Individuals with abnormally high CRP levels ( $>3.0$ to $4.0 \mathrm{mg} \cdot \mathrm{dL}^{1}$ ) are four times more likely to experience impaired blood flow to the heart. They also are twice as likely to die from heart attacks and strokes as individuals with high cholesterol-a finding that explains why some persons with low cholesterol develop heart disease or why lowering cholesterol sometimes fails to prevent serious heart problems.

Guidelines suggest limiting CRP testing to those already judged to be at intermediate risk ( 10 to $20 \%$ risk of heart disease over the next 10 years; about $40 \%$ of U.S. adults), based on risk factors of age, cholesterol level, and blood pressure. Individuals with CRP levels above $1.0 \mathrm{mg} \cdot$ $\mathrm{dL}^{1}$ should take aggressive action to reduce the level, which is also elevated in children and adolescents with the metabolic syndrome. ${ }^{59}$ Strategies to lower CRP include weight loss, abstinence from cigarette smoking, consuming a healthful diet, and regular exercise (e.g., combined aerobic/ resistance training). ${ }^{191}$

## Inflammation Attacks Arterial Vessels

An arterial wall injury (magnified by cigarette smoking, hypertension, and high blood sugar) initiates an inflammatory response as the body s immune system mobilizes to repair the damage as follows:

1. Abnormal oxidized LDL cholesterol moves into the arterial wall to cause injury.
2. The injured tissue stimulates the immune system to recruit to the area inflammatory cytokine cells, which include white blood cells (monocytes).
3. Monocytes migrate into the arterial wall. Here they form macrophages, which fill with the LDL cholesterol.
4. The LDL-laden macrophages become foam cells, which form a fatty streak within the arterial wall.
5. Over time, cholesterol, connective and elastic tissue, calcium, and cell debris build up to turn the fatty streak into plaque. As a natural defense against oxidized LDL cholesterol and to heal itself, smooth muscle cells migrate to the area to form a fibrous cap around the plaque.
6. Continued inflammation releases enzymes that weaken the fibrous cap.
7. The fibrous cap eventually ruptures.
8. The formation of a clot around the rupture blocks the normal flow of blood. Blockage within a coronary artery triggers a heart attack, whereas a blockage of an artery that feeds the brain causes a stroke.

## FOCUS ON RESEARCH

## Physical Inactivity: A Significant Coronary Heart Disease Risk

Morris JN, et al. Coronary heart disease and physical activity of work. Lancet 1953;265:1053.

- Epidemiologists of the 1940s and 1950s did not consider regular exercise a way to protect against early development of coronary heart disease (CHD). Morris and colleagues demonstrated an impressive link between physical activity in specialized occupations and reduced CHD risk. The researchers compiled statistics on CHD incidence for two groups of workers. One group consisted of 31,000 men ages 35 to 64 years employed by the London Transport Authority. Job classifications included drivers and conductors of trams and trolley buses and motormen and guards on the underground railway system. Drivers and motormen classified as sedentary, while a conductor represented a more physically demanding occupation (e.g., walking through a doubledecker bus, collecting tickets). The second work group consisted of 110,000 postal workers and civil servants. Physical activity level composed the basic differences between these workers in job requirements: Postmen maintained a moderate physical activity level walking delivering mail, while civil servants (postal and telegraph officers, telephone operators, clerks) remained sedentary in office jobs.

The figure shows the CHD incidence (rate per 1000 per age group determined from medical records) for the first clinical episode of CHD-angina pectoris, myocardial infarction, or death directly attributable to CHD. The London Transport workers exhibited 119 total CHD episodes ( $3.8 \%$ per 1000). In $25 \%$ of these episodes, death occurred within 3 days ( 34 of

119 cases); in $40 \%$, death ensued within 3 months (49 of 119 cases). Nonetheless, the pattern of CHD incidence differed between conductors and drivers. Drivers contracted the disease at a younger age and had a higher incidence ( 2.7 vs . 1.9) than conductors; also, drivers showed a rate of immediate mortality twice that of conductors. In contrast, angina occurred twice as frequently in the conductors ( 0.8 vs. 0.4 per 1000). Overall, conductors exhibited less CHD than drivers and the disease appeared at a later age. Like the transport workers, the physically active postmen averaged a substantially lower total incidence of CHD and mortality than sedentary clerks. The physically active group experienced less CHD; when disease did occur, it remained less severe.

Morris offered three possible explanations for the findings:

1. Differences in constitution (e.g., CHD susceptibility) affected existing health status, causing the men to selfselect a job category based on its physical requirements.
2. Differences in mental strains from a specific job affected the progression of CHD.
3. Differences in job-related physical activity caused group differences in CHD incidence.

While all three explanations seemed plausible, the researchers suggested that differences in on-the-job physical effort provided protection against CHD. More than 50 years of subsequent cross-sectional and longitudinal research confirms that increased physical activity confers a protective effect against CHD.


Coronary heart disease (CHD) incidence per 1000 persons for drivers, conductors, postmen, and clerks. Note that within each age and job classification, the mostactive workers (conductors and postmen) exhibit the lowest CHD incidence.

## Vulnerable Plaque: Difficult to Detect Yet Lethal

Vulnerable plaque, a soft type of metabolically active, unstable plaque, does not necessarily produce coronary artery narrowing but tends to fissure and burst. The rupture of unstable plaque-the sudden breakdown of fatty plaques in the lining of coronary arteries-exposes the blood to thrombogenic compounds. This triggers a cascade of chemical events that can produce clot formation (thrombus) and subsequent myocardial infarction and possible death. The sudden, complete obstruction of a coronary artery frequently occurs in blood vessels with only mild-to-moderate obstructions ( $<70 \%$ blockage). Arterial blockage often occurs before a coronary vessel has narrowed enough to produce angina symptoms or electrocardiographic (ECG) abnormalities or to indicate the need for revascularization procedures (e.g., coronary bypass surgery or balloon angioplasty). Acute disruption and rupture of arterial plaque provides a plausible explanation for sudden death from acute physical and emotional exertion in middle-aged men with coronary artery disease compared with sudden death under resting conditions. The beneficial effects of cholesterol-lowering strategies on heart disease risk do not always improve coronary blood flow. Stability of vulnerable plaque may improve with reduction in overall blood cholesterol. ${ }^{118}$ This stabilizing effect would reduce the likelihood of rupture of existing coronary artery plaque.

## Vascular Degeneration Begins Early in Life

Landmark studies of atherosclerosis in young American soldiers killed in Korea (1950s) showed advanced lesions in men whose ages averaged 22 years. ${ }^{51}$ These surprising findings focused attention on the possible childhood origins of atherosclerosis. Researchers now know that fatty streaks and clinically significant fibrous plaques develop rapidly during adolescence through the third decade of life. Autopsies of 93 young persons ages 2 to 39 years, most of whom died from trauma, revealed that fatty streaks and fibrous plaques in the aorta and coronary arteries appear early and progress in severity with aging. ${ }^{19}$ Body mass index, systolic and diastolic blood pressure, and total serum cholesterol, triacylglycerols, and LDL-C were strongly and positively related to the extent of vascular lesions in the deceased young people (high-density lipoprotein cholesterol [HDL-C] related negatively). History of cigarette smoking magnified the vascular damage, a disconcerting fact in light of data that indicate tobacco use is common and on the increase among college students. ${ }^{167}$ As the number of risk factors increased, so also did the severity of atherosclerosis in these asymptomatic individuals. Analyses of microscopic qualities of coronary atherosclerosis in 760 teenagers and young adults who died from accidents, suicide, and murder indicated that many had arteries so clogged that they could suffer a myocardial infarction. ${ }^{130}$ Two percent of those ages 15 to 19 and $20 \%$ of those 30 to 34 had advanced plaque formation,
the blockages considered most likely to break off and precipitate a heart attack or stroke. Collectively, the autopsy findings support the wisdom of primary prevention of atherosclerosis through risk factor identification and intervention early in childhood or adolescence.

Figure 31.24 shows the progressive occlusion of an artery from a buildup of calcified fatty substances in atherosclerosis. The first overt sign of atherosclerotic change occurs when lipid-laden macrophage cells cluster under the endothelial lining in the artery to form a bulge (fatty streak). Over time, proliferating smooth muscle cells migrate to the inner endothelial layer and accumulate to narrow the lumen (center) of the artery. A thrombus forms and plugs the artery, depriving the myocardium of normal blood flow and oxygen supply. When the thrombus blocks one of the smaller coronary vessels, a portion of the heart muscle dies (necrosis) and the person suffers a heart attack or myocardial infarction (MI). MIs are caused by blockage in one or more arteries that supply the heart, cutting off myocardial blood supply or sudden spasms (constrictions) of a coronary vessel that causes tissue necrosis from oxygen deprivation. MI contrasts with cardiac arrest from irregular neural electrical transmission within the myocardium. Cardiac arrest results from chaotic, unregulated beating of the heart s upper chambers (atrial fibrillation) or lower chambers (ventricular fibrillation).

If coronary artery narrowing progresses to produce brief periods of inadequate myocardial perfusion, the person may experience temporary chest pains termed angina pectoris (see Chapter 32). These pains usually emerge during exertion because physical activity increases myocardial blood flow demand. Anginal attacks provide painful, dramatic evidence of the importance of adequate myocardial oxygen supply.

## INTEGRATIVE QUESTION

Design an experiment to evaluate the effects of (1) aerobic exercise training and (2) standard resistance-exercise training on cardiovascular risk factors in middle-aged women. Indicate controls, measurement variables, and tests to show a training effect.

## Cardiovascular Disease Epidemic

Cardiovascular disease (CVD) currently ranks second only to cancer as the leading health problem and the primary cause of death among Americans younger than age 85. The primary reason for this reversal in rank is that while the number of deaths from both causes has fallen, the detection and treatment improvements have been more dramatic for heart disease than for cancer. Heart disease is an expensive condition to treat and a resource-intensive chronic condition. Consider the most recent (2005) statistics from the AHA. CVD claimed 869,724 lives in 2004 ( $36.3 \%$ of all deaths or 1 of every 2.8 deaths). Estimates for the year 2005 are that


Figure 31.24 A. Deterioration of a coronary artery from deposits of fatty substances that roughen the vessels center. When a thrombus (blood clot) forms above the plaque, complete blockage of the artery produces a myocardial infarction or heart attack. A coronary artery bypass graft (CABG) creates a new transportation route around the blocked region to allow the required blood flow to deliver oxygen and nutrients to the previously starved surrounding heart muscle. The saphenous vein from the leg is the most commonly used bypass vessel. CABG involves sewing the graft vessels to the coronary arteries beyond the narrowing or blockage, with the other end of the vein attached to the aorta. Medications (statins) lower total and LDLcholesterol, and daily low-dose aspirin ( 81 mg ) reduces post-CABG artery narrowing beyond the insertion site of the graft. Repeat CABG surgical mortality averages 5 to $10 \%$. B. Cast of coronary artery vasculature.

80,700,000 people in the United States had one or more forms of CVD, including:

High blood pressure- 73 million
Coronary heart disease-16 million
Myocardial infarction (acute heart attack)-
8.1 million

Angina pectoris (chest pain or discomfort caused by reduced blood supply to the heart muscle)-9.1 million Stroke-5.8 million
Heart Failure-5.3 million
Over 148,000 Americans killed by CVD in 2004 were under age 65.

Final death rates per 100,000 population from CVD in 2004 were 335.1 for white males and 454.0 for black males; for white females 238.0 and for black females 333.6.

## Coronary Heart Disease Statistics

CHD caused 451,326 deaths in 2004 and represents the single leading cause of death in America today. 16 million people alive today have a history of heart attack, angina pectoris, or both. This is about 8.7 million males and 7.3 million females.

An estimated 1.2 million Americans will have a new or recurrent coronary attack.
About 310,000 people a year die of coronary attack in an emergency department or without being hospitalized. Most of these are sudden deaths caused by cardiac arrest, usually resulting from ventricular fibrillation.
In 2004, CHD death rates per 100,000 people were 194.2 for white males and 223.9 for black males; and 114.7 for white females and 148.7 for black females.

Despite these rather discouraging statistics, age-adjusted death rate from CVD has decreased by approximately $60 \%$ since 1950. Still, heart diseases account for approximately $32 \%$ of the total mortality in the United States. When a heart attack does strike, its severity has decreased over the past decade. A large portion of the decline in incidence and severity relates to risk factor reduction (e.g., $25 \%$ of adults smoking now vs. $42 \% 30$ years ago, better pharmacologic control of high blood pressure and cholesterol levels, improved exercise behaviors), more effective pharmacologic therapies, and more intense treatment immediately after a heart attack. Survival rates can reach $96 \%$ for those who receive immediate hospital treatment. ${ }^{82}$

## CORONARY HEART DISEASE RISK FACTORS

Research over the past 50 to 60 years has identified various personal characteristics, behaviors, and environmental factors linked to increased CHD susceptibility. Although many of these factors relate strongly to CHD risk, the associations do not necessarily imply a causal relationship (e.g., male-pattern baldness). ${ }^{120}$ In some instances, it remains unclear whether risk-factor modification offers effective disease protection.

Until definite proof emerges, it seems prudent to assume that either elimination or reduction of one or more of the modifiable risk factors will reduce the likelihood of CHD and cumulative disability in later years. For example, a radical heart risk reduction program that includes a vegetarian diet limiting fat intake to no more than $10 \%$ of total calories and including regular exercise, stress-management training, and support meetings substantially reduces subsequent heart attack rate and other adverse heart events (e.g., bypass operations and angioplasty procedures). ${ }^{146}$ In contrast, patients in conventional care steadily worsened over the same 5 -year period. The following lists contain the most frequently implicated CHD risk factors:

Modifiable risk factors

## Diet

## Elevated blood lipids

Hypertension
Personality and behavior patterns
Cigarette smoking
High serum uric acid
Sedentary lifestyle
Pulmonary function abnormalities

Excessive body fat
Diabetes mellitus
ECG abnormalities
Tension and stress
Poor education
Elevated homocysteine

## Nonmodifiable risk factors

Age
Gender
Ethnic background
Male-pattern baldness, particularly lack of hair on the crown of the head; possibly from raised androgen levels
Family history
Determining the quantitative importance of any single CHD risk factor remains difficult because of the interrelationships among blood lipid abnormalities, type 2 diabetes, heredity (gene polymorphism), and obesity. ${ }^{26,215}$

## Age, Gender, and Heredity

Age represents a CHD risk factor largely because of its association with hypertension, elevated blood lipid levels, and glucose intolerance. After age 35 in men and age 45 in women, the chances of dying from CHD increase progressively and dramatically.

In contrast to the beliefs of many physicians who still adhere to the antiquated notion that cardiovascular disease is primarily a man s illness, Figure 31.25 shows that as of 1984, women show greater risk of death from cardiovascular diseases (heart disease, stroke, hypertension) than men. Women also have more lethal and severe first-time heart attacks and suffer a 70 to $100 \%$ greater risk of dying within months of a first heart attack than men, particularly women under age 50 (approximately $6 \%$ of all heart attacks in women). ${ }^{76,128,209}$ Specifically, $17 \%$ of women who suffer heart attacks die while still in the hospital compared with $12 \%$ of men, and $38 \%$ of women die within a year compared with $25 \%$ of men. A troubling and enduring gap still remains in treatment for women. Women account for about half of the coronary artery disease deaths in the United States, yet they receive only about one-third of the nearly 1 million annual intervention procedures. To close this gap, the AHA has issued new gen-der-specific guidelines that encourage doctors to make greater use of new cardiac imaging tests in women (the same high diagnostic accuracy as in men), which includes single photon emission computed tomography and stress echocardiography (see Chapter 32). ${ }^{85}$ Also recommended is an increase in the application of life-saving procedures such as balloon angioplasty and drug-coated stents to open blocked arteries. Special attention should be paid to women with diabetes, who have particularly high heart disease risk, as do women with metabolic syndrome and polycystic ovary syndrome (hormonal disorder among women of reproductive age). The pattern of coronary artery blockage may also differ between sexes. Men exhibit discrete blockages at distinct focal points,


1 in 4: Proportion of women with cardiovascular disease (heart disease, stroke, hypertension)

38\%: Percentage of women who die within one year of a heart attack versus $25 \%$ of men

54\%: Percentage of cardiovascular disease patients who are women

Figure 31.25 U.S. deaths from cardiovascular disease for men and women: 1979 to 2002.
making them more amenable to stenting, while women show a more diffuse blockage that occupies a longer segment of the vessel. The good news is that current trends in smoking cessation, diet improvement, and increase in postmenopausal hormone prescriptions largely account for the current decline in coronary artery disease in middle-aged women. ${ }^{77}$

Heart attacks that strike at an early age tend to run in families. Familial predisposition relates to a genetic role in determining risk of heart disease. In the following sections, we examine blood lipid abnormalities, obesity, cigarette smoking, and physical inactivity related to CHD (Chapters 15 and 32 discuss hypertension). These modifiable factors represent the big five heart disease risks proposed by the AHA. Each exists as a potent, independent CHD risk that can change considerably with lifestyle modification.

## INTEGRATIVE QUESTION

## Explain how risk factor modification can affect change in disease risk.

## Blood Lipid Abnormalities

Serum cholesterol levels in adults have declined substantially in the United States over the past 35 years, a decline that coincides with a decreased national incidence of CHD. Despite this support for the effectiveness of public health programs geared to lowering heart disease risks, nearly $30 \%$ of adults still require intervention for high cholesterol levels. ${ }^{91}$

Unfortunately, data from the CDC indicate that approximately $60 \%$ of persons with high cholesterol levels did not know they were high. Of those who knew, only $14 \%$ were taking a cholesterol-lowering drug. An abnormal blood lipid level, or hyperlipidemia, is a crucial component in the genesis of atherosclerosis.

## AHA Recommendations for Cholesterol and Triacylglycerol

Figure 31.26 shows the rate of increase in death risk from CHD related to total serum cholesterol. The inset table presents AHA serum cholesterol and lipoprotein and triacylglycerol level classifications for adults (www.americanheart.org). Recommendations also include that individuals above age 20 have a fasting lipoprotein profile every 5 years ( 9 to 12 h following the last meal and without liquids or pills). Current guidelines focus less on total cholesterol and more on its lipoprotein components. The new guidelines, based on findings concerning effects of the powerful cholesterol-lowering statin drugs on heart health (i.e., reduced risk of heart attack, bypass surgery, plaque growth in coronary vessels, angioplasty), ${ }^{25,140,173}$ are more stringent than prior recommendations. Adherence to the guidelines will nearly triple the number of adults taking cholesterol-lowering drugs to 36 million Americans and raise by $25 \%$ the number who should be on a cholesterol-lowering diet. ${ }^{111}$ Early treatment becomes crucial because of a strong association between high serum cholesterol as a young adult and cardiovascular disease in middle age. A cholesterol level of $200 \mathrm{mg} \cdot \mathrm{dL}^{1}$ or lower is

Risk of Death from CHD According to Blood Cholesterol Level


American Heart Association Recommendations and Classifications for Total Cholesterol and HDL and LDL cholesterol and Triacylglycerol

| Total cholesterol level* | Category |
| :---: | :--- |
| $\geq 240$ | High blood cholesterol. A person with this <br> level has more than twice the risk of heart <br> disease as someone with cholesterol below |
| 200 to 239 | 200. |
| $\leq 200$ | Borderline high <br> Desirable level that puts you at a lower risk <br> for heart disease. Cholesterol level of 200 <br> or higher raises risk. |

HDL cholesterol level
Category
$<40$
40 to 59

Low HDL cholesterol. A major risk factor for heart disease. Higher HDL levels are better. $\geq 60$ High HDL cholesterol. An HDL of $60 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ and above is considered protective against heart disease.

## LDL cholesterol level

Category
> 190
Very high; cholesterol-lowering drug therapies even if no heart disease and no risk factors.**
160-189

130-159
100-129
< 100

High; cholesterol-lowering drug therapies even if there is no heart disease but 2 or more risk factors present.
Borderline high; cholesterol-lowering drug therapies if heart disease is present. Near optimal; doctor may consider cholesterol-lowering drug therapies plus dietary modification if heart disease is present.
Optimal; no therapy needed.

Triacylglycerol level
Category
<

200-499
$\geq 500$

* All levels in $\mathrm{mg} \cdot \mathrm{dL}^{-1}$.
** In men under age 35 and premenopausal women with LDL cholesterol levels of 190 to $219 \mathrm{mg}^{-\mathrm{dL}^{-1}}$, drug therapy should be delayed except in high-risk patients like those with diabetes.
usually desirable, although risk for a fatal heart attack begins to rise at $150 \mathrm{mg} \cdot \mathrm{dL}^{1}$. A cholesterol level of $230 \mathrm{mg} \cdot \mathrm{dL}^{1}$ increases heart attack risk to about twice that of $180 \mathrm{mg} \cdot \mathrm{dL}^{1}$, and $300 \mathrm{mg} \cdot \mathrm{dL}{ }^{1}$ increases the risk fourfold. For triacylglycerol, $150199 \mathrm{mg} \cdot \mathrm{dL}^{1}$ is considered as an upper-limit normal level, with 200 to 499 considered high. The latter requires changes in exercise, diet, and possibly drug intervention if accompanied by other CHD risk factors.

Lipids do not circulate freely in blood plasma; they combine with a carrier protein to form lipoproteins composed of a hydrophobic cholesterol core and a coat of free cholesterol, phospholipid, and regulatory protein (apolipoprotein [Apo]). Table 31.5 lists the four different lipoproteins, their approximate gravitational densities, and percentage composition in the blood. Serum cholesterol is a composite of the total cholesterol contained in each of the different lipoproteins. Discussions commonly refer to hyperlipidemia, but the more meaningful focus addresses the different types of hyperlipoproteinemia.

Cholesterol distribution among the various lipoproteins provides a more powerful predictor of heart disease risk than total blood cholesterol. Specifically, elevated HDL-C levels relate causally with a lower heart disease risk even among individuals with total cholesterol below $200 \mathrm{mg} \cdot \mathrm{dL}^{1}$. Overwhelming evidence links high LDL-C and apolipoprotein (B) levels with increased CHD risk. ${ }^{109}$ A more effective evaluation of heart disease risk than either total cholesterol or LDL-C levels divides total cholesterol by HDL-C. A ratio greater than 4.5 indicates high heart disease risk; a ratio of 3.5 or lower represents a more desirable risk level.

LDL-C (synthesized in the liver) and very low-density lipoprotein cholesterol (VLDL-C) transport fats to cells, including the smooth muscle walls of arteries. Upon oxidation, LDL-C participates in artery-clogging, plaque-forming atherosclerosis by stimulating monocyte macrophage infiltration and lipoprotein deposition. ${ }^{189}$ LDL-C s surface coat contains the specific apolipoprotein (Apo B) that facilitates cholesterol removal from the LDL-C molecule by binding to LDL-C receptors of specific cells. Prevention of LDL-C oxidation, in contrast, slows CHD progression. In this case, any potential benefit of dietary antioxidants such as vitamins C and E and $\beta$-carotene (within a food matrix and not as isolated dietary supplements) on heart disease risk may lie in their ability to blunt LDL-C oxidation (see Chapter 2). ${ }^{45,69,105}$

Whereas LDL-C targets peripheral tissue and contributes to arterial damage, HDL-C (also produced in the liver and whose levels relate to genetic factors) ${ }^{90}$ facilitates reverse cholesterol transport. HDL-C promotes surplus cholesterol removal from peripheral tissues (including arterial walls) for

Figure 31.26 Top. Death risk from coronary heart disease (CHD) in relation to total serum cholesterol level in middleaged men. Inset table. The American Heart Association recommendations and classifications for serum cholesterol, lipoproteins, and triacylglycerol levels for adults.

## TABLE 31.5 Approximate Composition of Serum Lipoproteins

|  | Very Low-Density <br> Lipoproteins <br> (VLDL:Prebeta) | Low-Density <br> Lipoproteins <br> (LDL:Beta) | High-Density <br> Lipoproteins <br> (HDL:Alpha) |  |
| :--- | :---: | :---: | :---: | :---: |
| Chylomicrons | 0.95 | 0.951 .006 | 1.0061 .019 | 1.0631 .210 |
| Density $\left(\mathrm{g} \cdot \mathrm{cm}^{3}\right)$ | 515 | 25 | 45 |  |
| Lipid $(\%)$ | 1.0 | 95 | 75 | 50 |
| Cholesterol $(\%)$ | 99 | 1020 | 4045 | 18 |
| Triacylglycerol (\%) | 25 | 5070 | 510 | 2 |
| Phospholipid $(\%)$ | 1020 | 2025 | 30 |  |

transport to the liver for bile synthesis and subsequent excretion via the digestive tract. The apolipoprotein A-1 (Apo A-1) in HDL-C activates lecithin acetyl transferase (LCAT). This enzyme converts free cholesterol into cholesterol esters, facilitating cholesterol removal from lipoproteins and diverse tissues. ${ }^{147}$

## Factors That Affect Blood Lipids

Six behaviors that favorably affect cholesterol and lipoprotein levels include:

1. Weight loss
2. Regular aerobic exercise (independent of weight loss)
3. Increased dietary intake of water-soluble fibers (fibers in beans, legumes, and oat bran)
4. Increased dietary intake of polyunsaturated-tosaturated fatty acid ratio and monounsaturated fatty acids
5. Increased dietary intake of unique polyunsaturated fatty acids in fish oils (omega-3 fatty acids) and elimination of trans-fatty acids
6. Moderate alcohol consumption

Four variables that adversely affect cholesterol and lipoprotein levels include:

1. Cigarette smoking
2. Diet high in saturated fatty acids and preformed cholesterol and trans-fatty acids
3. Emotionally stressful situations
4. Oral contraceptives

## Specific Exercise Effects

Short-Term Effects. Reaching the threshold that changes blood lipid and lipoprotein levels in a single exercise session requires considerable physical activity. For example, healthy trained men needed to expend 1100 kCal in one exercise bout to elevate HDL-C, 1300 kCal of exercise to lower LDL-C, and 800 kCal of exercise to decrease triacylglycerol levels. ${ }^{53}$

Long-Term Effects. A single exercise session produces only transient favorable changes in lipid and apolipoprotein
concentrations, yet the change persists with exercising at least every other day. ${ }^{40}$
$\boldsymbol{L D L} \boldsymbol{C}$. Exercising regularly usually produces only small reductions in LDL-C level when controlling for serum cholesterol-related factors of body fat and dietary lipid and cholesterol intake. Regular exercise may improve the quality of this circulating lipoprotein by promoting a less oxidized form of LDL-C to reduce atherosclerosis risk. ${ }^{213}$ In addition, regular aerobic exercise increases the success of dietary efforts to favorably alter high-risk lipoprotein profiles. ${ }^{188}$

HDL-C. Endurance athletes usually maintain relatively high HDL-C levels, while favorable alterations occur for sedentary men and women of all ages who engage in regular moderate-to-vigorous aerobic exercise. ${ }^{46}$ To some extent, exercise intensity and duration exert independent effects in modifying specific CHD risk factors. In general, exercise duration exerts the greatest effect on HDL-C, while exercise intensity most favorably modifies blood pressure and waist girth. ${ }^{223}$ A favorable change in lipoprotein profile does not necessarily require that exercise intensity reach a level to improve cardiovascular fitness. With the exception of triacylglycerols, exer-cise-induced lipid alterations usually progress independent of body weight changes. ${ }^{112}$ For overweight individuals, the typical increase in HDL-C with exercise training diminishes without concomitant weight loss. ${ }^{138,199}$ Favorable exercise-related lipoprotein changes probably result from enhanced triacylglycerol clearance from plasma in response to exercise.

Protection from Gallstones. The benefits of regular aerobic exercise on modifying cholesterol and lipoprotein profiles extend to protection against painful gallstones and accompanying gallbladder removal (the usual treatment for 500,000 Americans yearly, of whom two-thirds are women). The NIH reports that gallstone formation and its consequences are the most common and costly (\$5 billion yearly) digestive disease requiring hospitalization and surgery. Increased physical activity protects against the development of gall bladder disease. ${ }^{104}$ Overall, women who exercised 30 minutes daily reduced their need for gallbladder surgery by $31 \%$. ${ }^{17}$ Physical activity increases the movement of the large intestine and improves blood
glucose and insulin regulation; both factors reduce gallstone risk. Regular exercise also may reduce the cholesterol content of bile, the digestive juice stored in the gallbladder. Eight percent of gallstones are solid cholesterol.

## Other Influences

Even trained endurance athletes exhibit considerable variability in HDL-C levels, with some elite runners values approaching the median value for the general population. No single factor-nutrition, body composition, or training statusdistinguishes runners with high HDL-C values from runners with lower values. This suggests that genetic factors exert a strong influence on the blood lipid profile. In fact, a specific gene produces endothelial lipase (EL), an enzyme that may affect HDL-C production. ${ }^{90}$ Turning on this gene increases EL synthesis, which may lower HDL-C and subsequently increase cardiovascular risk.

Standard resistance training exerts little or no effect on serum levels of triacylglycerol, cholesterol, or lipoproteins. From a dietary perspective, substituting soy-derived protein for protein from animal sources improves the cholesterol and lipoprotein profile, particularly in persons with high blood cholesterol. ${ }^{14}$ A moderate daily alcohol intake- 2 oz or 30 mL of 90 -proof alcohol, three $6-\mathrm{oz}$ glasses of wine, or slightly less than three $12-\mathrm{oz}$ beers-reduces an otherwise healthy person s risk of heart attack and stroke independent of their physical activity level. ${ }^{37,171}$ The heart-protective benefit of alcohol consumption also applies to individuals with type 2 diabetes. ${ }^{210}$ The mechanism for the benefit remains elusive, yet a moderate alcohol intake increases HDL-C and its subfractions $\mathrm{HDL}_{2}$ and $\mathrm{HDL}_{3}$. The polyphenols in red wine may inhibit LDL-C oxidation, thus blunting a critical step in plaque formation. ${ }^{139}$ Moderate wine intake also tends to associate with more heart-healthy dietary choices, with a positive impact on plasma lipids. Excessive alcohol consumption offers no lipoprotein benefit and increases liver disease and cancer risk.
$\operatorname{Lipoprotein}(\mathbf{a}) . \operatorname{Lipoprotein}(\mathbf{a})[\mathbf{L p ( a )}]$ represents a diverse class of protein particles formed in the liver when two distinct apolipoproteins unite. $\mathrm{Lp}(\mathrm{a})$ structurally resembles LDL-C but contains an additional unique apolipoprotein(a) coat. Heredity determines elevated Lp(a) levels, which occur in approximately $20 \%$ of the population. The independent risk for atherosclerosis, thrombosis, and acute MI increases when $\mathrm{Lp}(\mathrm{a})$ levels exceed 25 to $30 \mathrm{mg} \cdot \mathrm{dL}^{1}$ with raised LDL-C levels. ${ }^{20}$ Dietary changes and either short- or long-term exercise exert little or no effect on serum $\mathrm{Lp}(\mathrm{a})$ concentrations. ${ }^{75,80,81,124}$

Dietary Fiber, Insulin, and CHD Risk. Insulin resistance and associated hyperinsulinemia relate to CHD risk factors of age, obesity, central body fat distribution, smoking, physical inactivity, hypertension, dyslipidemia, and abnormalities in blood-clotting factors. Many researchers and clinicians now consider insulin resistance and consequent hyperinsulinemia as independent CHD risk factors. ${ }^{170}$

The combined effects of established CHD risk factors account for approximately $50 \%$ of the observed variability in insulin resistance and hyperinsulinemia within the population. The question then is what other factors might contribute to excessive insulin output and, by implication, increased CHD risk. Perhaps total lipid or saturated fatty acid intake and dietary carbohydrates are possible causal factors. Dietary fiber also may play a key role in optimizing insulin response. ${ }^{121}$ For example, dietary fiber reduces insulin secretion by slowing the rate of nutrient digestion and glucose absorption following a meal. A low-fiber meal with its inherently high glycemic index stimulates more insulin secretion than a high-fiber meal of equivalent carbohydrate content. Thus, dietary fiber can serve a dual role in heart-disease prevention by (1) attenuating the insulin response to a carbohydrate-containing meal and (2) reducing the tendency to accumulate body fat from insulin s facilitatory role in fat synthesis. Excessive body fat increases insulin resistance, which ultimately leads to hyperinsulinemia.

Immunologic Factors. An immune response likely triggers plaque development within arterial walls. During this process, mononuclear immune cells produce proteins called cytokines, some of which stimulate plaque buildup while others inhibit plaque formation. Regular exercise may stimulate the immune system to inhibit agents that facilitate arterial disease. For example, 2.5 hours of weekly exercise for 6 months decreased cytokine production that aids in plaque development by $58 \%$, while cytokines that inhibit plaque formation increased by nearly $36 \%$. ${ }^{183}$

## Beyond Cholesterol: Homocysteine and Coronary Heart Disease

Homocysteine, a highly reactive, sulfur-containing amino acid, forms as a byproduct of methionine metabolism. Researchers in the 1960s and 1970s described three different inborn errors of homocysteine metabolism that involved B-vitamin enzymes. High levels of homocysteine in the blood and urine were common to all three disorders of the afflicted individuals, and half of these persons developed arterial or venous thrombosis by age 30. Researchers postulated that moderate elevation of homocysteine in the general population predisposes individuals to atherosclerosis in a manner similar to elevated cholesterol concentration.

A nearly lockstep association occurs between plasma homocysteine levels and heart attack and mortality in men and women. ${ }^{50,165,218,221}$ This metabolic abnormality occurs in nearly $30 \%$ of CHD patients and $40 \%$ of patients with cerebrovascular disease. Excessive homocysteine causes blood platelets to clump, fostering blood clots and deterioration of smooth muscle cells that line the arterial wall. Chronic homocysteine exposure eventually scars and thickens arteries and provides a fertile medium for circulating LDL-C to initiate damage. In the presence of other conventional CHD risks (e.g., smoking and hypertension), synergistic effects magnify the negative impact of homocysteine on cardiovascular health. ${ }^{125,228}$ Resting homocysteine levels exerted an inde-


Figure 31.27 A. Proposed mechanism for how the amino acid homocysteine damages the lining of arteries and sets the stage for cholesterol infiltration into a vessel. B. Proposed defense against the possible harmful effects of elevated homocysteine levels. C. Relative risk of all vascular diseases defined by the presence of classic risk factors with and without elevated plasma total homocysteine levels adjusted for age, gender, and research center. (Graphs from Graham IM, et al. Plasma homocysteine as a risk factor for vascular disease: The European Concerted Action Project. JAMA 1997;277:1775.)
pendent increased risk on a continuum for vascular disease similar to that of smoking and hyperlipidemia. A powerful multiplicative interaction effect also emerged in the presence of other risks, particularly cigarette smoking and hypertension. In general, persons in the highest quartile for homocysteine levels experience nearly twice the risk of heart attack or stroke of those in the lowest quartile. Why some persons accumulate homocysteine remains uncertain, but evidence points to a deficiency of $B$ vitamins ( $\mathrm{B}_{6}, \mathrm{~B}_{12}$, and particularly
folic acid; FIG. 31.27B); lifestyle factors of cigarette smoking and coffee and high meat intake also associate with elevated homocysteine concentrations. ${ }^{31,135,145,192}$

Figure 31.27A proposes a mechanism for homocysteine s negative impact on cardiovascular health. The homocysteine model helps explain why some persons with low-to-normal cholesterol levels contract heart disease. Figure 31.27C gives the relative risk for vascular disease in groups defined by the presence or absence of classic risk
factors and elevated plasma homocysteine levels adjusted for age, gender, and research center.

## fyi <br> Diseases and Disorders Linked to Elevated Plasma Homocysteine Levels

Heart attack<br>Stroke<br>Dementia from Alzheimer s disease<br>Blood clots in veins (venous thrombosis)<br>Osteoporosis<br>Recurrent early miscarriage<br>Birth defects<br>Premature delivery and abnormally low birth weight

No clear standard currently exists for normal or desirable homocysteine levels, although most evidence indicates that the current normal range of 8 to $20 \mu \mathrm{~mol}$ per liter of plasma is too high. Evidence suggests as little as $12 \mu \mathrm{~mol}$ can double heart disease risk. Until recently, debate has focused on whether normalizing homocysteine reduces risk of arterial occlusive disease that precipitates heart attack and stroke. Consequently, little is known regarding whether an elevated homocysteine level is simply a CHD risk factor or an actual cause (not an effect) of CHD. ${ }^{129,144}$ The first study of its kind, a double-blind, randomized, controlled trial, determined whether once-daily high doses of folic acid ( 2.5 mg ), vitamin $\mathrm{B}_{6}(25 \mathrm{mg})$, and vitamin $\mathrm{B}_{12}(0.4$ mg ) over a 2-year period lowered homocysteine levels and reduced recurrent stroke risk in patients with ischemic stroke. ${ }^{204}$ Reduction of total homocysteine averaged $2.0 \mu \mathrm{~mol} \cdot \mathrm{~L}^{1}$ greater in the group that received the high-dose supplement than in the group receiving lower doses. The moderate homocysteine reduction produced no effect on vascular outcomes during a 2year follow-up. The researchers concluded that the consistent findings of other researchers of an association of total homocysteine with vascular risk justified longer trials in different populations with elevated homocysteine.

Research on the effects of exercise on homocysteine levels remains inconclusive. Intense exercise training may increase homocysteine levels accompanied by changes in vita$\min B_{12}$ and folate status. ${ }^{47,72,73}$ Other data indicate that individuals who engage in long-term exercise (and who exhibit higher plasma folate levels) show reduced homocysteine levels. ${ }^{71,103,148}$ Also, resistance training reduced homocysteine in the elderly. ${ }^{214}$ The American Heart Association does not recommend taking folic acid or other B vitamins to lower CHD risk.

## INTEGRATIVE QUESTION

In addition to extending life span, what other reasons would make sense for maintaining a physically active lifestyle throughout middle and older age?

## CHD Risk Factor Interactions

Many risk factors interact with each other and with CHD. Figure 31.28 shows that the presence of three primary CHD risk factors in the same person magnify individual effects. With one risk factor, a 45-year-old man s chance of CHD during the year averages twice the risk for a man without risk factors. With three risk factors, this man s chance for angina, heart attack, or sudden death increases to nearly 10 times the level for those without risk factors.

Some argue that the five major modifiable cardiovascular risk factorscigarette smoking, physical inactivity, diabetes mellitus, hypertension, and hypercholesterolemiaaccount for only about $50 \%$ of individuals who subsequently develop CHD. Thus, researchers have investigated novel markers and other nontraditional risk factor candidates to increase cardiovascular risk predictability. ${ }^{26,215}$ Table 31.6 presents different novel risk factors that independently associate with atherosclerotic vascular disease.

Several reports directly challenge this only 50\% claim for the aforementioned five risk factors. Analysis of data from 14 randomized clinical trials $(N=122,458)$ and three observational studies $(N=386,915)$ showed that in contrast to previous belief, 80 to $90 \%$ of patients who developed clinically significant CHD and more than $95 \%$ of patients who experienced a fatal CHD event had at least one of the five traditional major risk factors, including overweight/obesity. Remarkably, these finding may even underestimate the true extent of the relationship, given the self-report design of the observational studies and number of patients unaware or not diagnosed as having risk factors at the time of evaluation. These findings have enormous public health implications for targeting a large segment of the population at risk of developing CHD. Smoking is arguably the single most important modifiable


Figure 31.28 General relation between a combination of abnormal risk factors (cholesterol $\geq 250 \mathrm{mg} \cdot \mathrm{dL}^{1}$; systolic blood pressure $\geq 160 \mathrm{~mm} \mathrm{Hg}$; smoking $\geq 1$ pack of cigarettes per day) and incidence of coronary heart disease (CHD).

| TABLE 31.6 | Novel Risk Factors for Atherosclerotic Vascular Disease |  |  |  |
| :--- | :--- | :--- | :--- | :--- |
| Inflammatory <br> Markers | Hemostatic/ <br> Thrombosis Markers | Platelet-Related <br> Factors | Lipid-Related <br> Factors | Other Factors |

and preventable cardiovascular disease risk factor and one of the strongest predictors of premature CHD. Obesity and physical inactivity are equally important CHD predictors.

Many CHD risks link in common to behavioral patterns; they become influenced by similar and, in some cases, identical interventions. For example, regular exercise exerts a posi-
tive influence on obesity, hypertension, type 2 diabetes, stress, and elevated blood lipid profile. No other modifiable behavior exerts such a potent positive effect for the greatest number of persons, causing many to argue that regular physical activity constitutes the most important behavioral intervention to reduce CHD.

## An Underdiagnosed and Undertreated CHD Risk Factor: Sleep Disorders

The prevalence of sleeping disorders worldwide continues to increase (www.wrongdiagnosis.com/s/ sleep_disorders/stats-country.htm). In the United States, approximately 1 in 6 individuals, or 43 million Americans, suffer from sleep loss (an additional 20 to 30 million experience intermittent sleep-related problems) that directly or indirectly impacts CHD—insulin resistance and hypertension, ${ }^{b}$ obesity and diabetes, ${ }^{c}$ increased carotid wall thickness, ${ }^{a}$ and nocturnal myocardial ischemia from apnea-associated oxygen desaturation. ${ }^{d, e}$ The National Commission on Sleep Disorders Research (www.nhlbi.nih.gov/health/prof/sleep/reschpln.htm) attributed $\$ 15.9$ billion as the direct cost of sleeping conditions, with an estimated $\$ 50$ to $\$ 100$ billion in indirect and related costs. All of the world s countries in 2004 were impacted by sleep-disordered consequences (including unnecessary automobile accidents and deaths and spiraling health care
costs) from Belize (7\%) to China (8\%). The NIH s National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov/); National Heart, Lung and Blood Institute (www.nhlbi.nih.gov/ health/prof/sleep/); National Center on Sleep Disorders Research (www.nhlbi.nih.gov/about/ncsdr/ index.htm); National Sleep Foundation (www. sleepfoundation.org/); and Patient Education Institute (www.nlm.nih.gov/medlineplus/sleepdisorders.html) provide excellent resources about sleep disorders that explain the sleep apneas (complications from repeated, interrupted breathing during sleep that can be life threatening if untreated) and other sleep related disorders, such as restless leg syndrome (RLS), insomnia (inability to fall asleep or remain asleep), and narcolepsy (neurological disorder from failure to regulate sleep-wake cycles normally and characterized by excessive daytime sleepiness and dramatic decrease in muscle
tone and loss of reflexes or cateplexy). Sleep disorders also afflict between 80 and $90 \%$ of mostly middle-aged women diagnosed with fibromyalgia. Their sleep problems and chronic daytime fatigue occur in addition to pain and muscle and joint stiffness. A common characteristic of sleeping disorders includes loud and intermittent snoring. During these episodes, the blood s oxygen saturation can decrease to $80 \%$ or less. In severe cases, the individual spends more time not breathing than breathing-placing them at increased risk for death (common symptoms include daytime drowsiness and nighttime insomnia).

Treatments for sleep disorders include continuous positive airway pressure (CPAP, a mask system that regulates the amount and pressure of air sent into the nose to keep the nasal passages open during sleep), surgery (uvulopalatopharyngoplasty, or UPPP, removal of the back part of the soft palate and tissue at the back of the throat to open up more airspace to widen the passageway at the back of the throat), an oral appliance that repositions the jaw forward while sleeping to maintain a more open airway, pharmacologic interventions, and cognitive/behavioral strategies. The objective in all the procedures is to restore normal sleep patterns (without snoring), stabilization of blood oxygen
levels during sleep, and restoration of normal daily functions without sleepiness. The NIH has identified 30 research issues critical to understanding the effects of sleep disorders and sleep restriction related to cardiovascular and other disease treatment regiments (www.nhlbi.nih.gov/about/ncsdr/research/ research-a.htm); considerably more research is required to better understand all of the correlates among sleep disorders and their underlying mechanisms.
${ }^{a}$ Altin R, et al. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. J Clin Ultrasound 2005;33:80.
${ }^{b}$ Harsch IA, et al. Insulin resistance and other metabolic aspects of the Obstructive Sleep Apnea Syndrome. Med Sci Monit 2005 Feb 25;11(3):RA70 75.
${ }^{c}$ Kiely JL, McNicholas WT. Cardiovascular risk factors in patients with obstructive sleep apnea syndrome. Eur Respir J 2000; 16:128.
${ }^{d}$ Schafer H, et al. Sleep-related myocardial ischemia and sleep structure in patients with obstructive sleep apnea and coronary heart disease. Chest 1997;111:387.
${ }^{e}$ Wieber SJ. The cardiac consequences of the obstructive sleep apnea-hypopnea syndrome. Mt Sinai J Med 2005;72:10.

## Risk Factors in Children

The frequent occurrence of multiple CHD risk factors in young children emphasizes the need for early CHD initiatives to reduce atherosclerosis risk later in life. ${ }^{203,224}$ Risk factors assessed in childhood and adolescence associate with the thickness of the carotid artery later in life. As with adults, the association between body fat and serum lipid levels becomes readily apparent in overfat children; the fattest children usually have higher levels of serum cholesterol and triacylglycerols. General adiposity and visceral adipose tissue also relate to unfavorable hemostatic factors that increase CHD morbidity and mortality in adulthood. ${ }^{54}$ Of 62 overfat children ages 10 to 15 years, only one child had just one CHD risk factor. ${ }^{18}$ Of the remaining children, $14 \%$ had two risk factors, $30 \%$ three, $29 \%$ four, $18 \%$ had five, and the remaining five children, or $8 \%$, had six. A subsample then enrolled in a 20 -week program to evaluate the effects on the risk profile of either diet plus behavior therapy or regular exercise plus diet plus behavior therapy. No changes resulted in multiple-risk reduction in either the control group or those receiving diet plus behavior treatment. In contrast, children undergoing exercise plus diet plus behavior therapy dramatically reduced multiple risks (Fig. 31.29). These encouraging findings demonstrate that a supervised program of moderate food restriction and exercise with behavior modification reduces CHD risk factors in obese adolescents. Adding regular exercise augmented the effectiveness of risk-factor intervention.

Autopsy evidence and prevalence of CHD risk factors among preadolescents and adolescents indicate that heart disease begins in childhood. Usually, the most sedentary children (e.g., those who watch the most TV) have more body fat and a higher BMI than physically active peers. ${ }^{15}$ School-based programs that increase the level of daily physical activity, reduce risk factors, and increase students knowledge about risk factors and benefits of physical activity can produce a long-term positive effect on exercise habits and overall health. ${ }^{97,208}$ Because regular physical activity upgrades or stabilizes a poor risk factor profile, school curricula at all grade levels (especially kindergarten and elementary grades) should strongly encourage more physically active lifestyles. Not implementing required daily physical education in the school curriculum at all grade levels (especially elementary school) seems counterproductive from a public health policy standpoint.

## Calculating CHD Risk

Risk inventories assess an individual s susceptibility to CHD. Several different quantitative methods estimate CHD risk. The Framingham Risk Score derived from the Framingham Heart Study Cohort predicts 10-year risk of mortality from CHD and nonfatal myocardial infarction. ${ }^{43,198}$ The Framingham Risk Score considers age, gender, smoking status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and diabetes.


Figure 31.29 Multiple coronary heart disease risk factors for obese adolescents before and after treatment. $D B$, diet + behavior change group; EDB, exercise + diet + behavior change group. (From Becque DB, et al. Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. Pediatrics 1988;81:605.)

An alternative risk scoring method, the European SCORE, was developed in 2003 by the European Society of Cardiology (www.escardio.org/) to estimate 10-year risk of fatal cardiovascular disease in European nations in primary prevention. ${ }^{39}$ SCORE estimates total cardiovascular risk rather than risk of CHD alone by totaling calculated coronary and noncoronary components. The variables used for SCORE include age, gender, total cholesterol, systolic blood pressure, and smoking status.

Figure 31.30 presents a popular risk inventory developed by the AHA. To assess risk profile, determine the numerical value that best describes a person s status. Find the applicable box and circle the number in it. For example, a 19 -year-old person circles the number 1 in the box labeled 10 to 20 years. After checking all the rows, the circled numbers are totaled. The total number of points represents the risk score; see the table in the footnote for relative risk category.

## Summary

1. CHD represents the most prevalent cause of death in the Western world. Its pathogenesis involves degenerative changes in the inner lining of the arterial wall that progressively occlude blood vessels.
2. Major CHD risk factors include age and gender, blood lipid abnormalities, hypertension, cigarette smoking, obesity, physical inactivity, diet, family history, and ECG abnormalities during rest and exercise. Prudent treatment attempts to eliminate or reduce modifiable CHD risk factors.
3. A serum cholesterol level of $200 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ or lower is desirable, although experts recommend lower values to achieve the lowest CHD risk.
4. Treatment of elevated cholesterol should begin early in life because of a strong association between serum cholesterol level as a young adult and cardiovascular disease in middle age.
5. The distribution of HDL-C and LDL-C provides a more powerful predictor of heart disease risk than total serum cholesterol concentration alone.
6. LDL-C upon oxidation participates in atherosclerosis by stimulating monocyte macrophage infiltration and lipoprotein deposition.
7. HDL-C facilitates reverse cholesterol transport by removing surplus cholesterol from peripheral tissues (including arterial walls) for transport to the liver for bile synthesis and excretion via the small intestine.
8. Favorable alterations in HDL-C occur in sedentary men and women of all ages who regularly participate in moderate to intense aerobic exercise.
9. A high level of homocysteine exerts a powerful independent risk for vascular disease.
10. Dietary fiber exerts a dual role to prevent hyperinsulinemia by decreasing circulating insulin levels directly and thwarting obesity with its associated insulin resistance.
11. Cigarette smokers experience almost twice the risk of death from heart disease as nonsmokers. One mechanism for risk involves the adverse effects of smoking on lipoprotein levels.


Figure 31.30 American
Heart Associations checklist to evaluate coronary heart disease risk.
12. Sedentary men and women face approximately twice the risk of a fatal heart attack than more physically active counterparts. Maintenance of a physically active lifestyle throughout life lowers CHD risk factors and disease occurrence.
13. The interaction of CHD risk factors magnifies their individual effects on overall disease risk.
14. Nutrition, exercise, and weight control programs favorably alter CHD risk factors and usually improve an individual s health outlook.

## On the Internet

Centers for Disease Control and Prevention www.cdc.gov
U.S. Census Bureau

> www.census.gov

National Center for Health Statistics: Fast Stats A to Z: Life Expectancy
www.cdc.gov/nchs/fastats/lifexpec.htm
Northwestern Mutual Financial Network: The Longevity Game www.nmfn.com/tn/learnctr-lifeevents-longevity
World Health Organization: The World Health Report www.who.int/whr/

United States All-Round Weightlifting Association www.usawa.com
U.S.A. Powerlifting www.usapowerlifting.com/
U.S. Department of Health and Human Services www.hhs.gov
2008 Physical Activity Guidelines for Americans www.health.gov/paguidelines
National Center for Health Statistics: Fast Stats A to Z:
Deaths Leading Causes www.cdc.gov/nchs/FASTATS/lcod.htm
American Hospital Association www.aha.org
American Heart Association www.americanheart.org
Wrong Diagnosis.com: Statistics about Sleep Disorders www.wrongdiagnosis.com/s/sleep_disorders/stats.htm National Commission on Sleep Disorders Research www.nhlbi.nih.gov/health/prof/sleep/reschpln.htm

National Institute of Neurological Disorders and Stroke www.ninds.nih.gov/
National Heart, Lung and Blood Institute: Sleep Disorders Information
www.nhlbi.nih.gov/health/prof/sleep/
National Institutes of Health: National Center on Sleep Disorders Research www.nhlbi.nih.gov/about/ncsdr/index.htm
National Sleep Foundation www.sleepfoundation.org/
Medline Plus: Sleep Disorders www.nlm.nih.gov/medlineplus/sleepdisorders.html
National Center on Sleep Disorders Research www.nhlbi.nih.gov/about/ncsdr/research/research-a.htm
European Society of Cardiology www.escardio.org/

## CHAPTER 32



## Clinical Exercise Physiology for Cancer, Cardiovascular, and Pulmonary Rehabilitation

## CHAPTER OBJECTIVES

> Discuss the role of the exercise physiologist and health and fitness professional in the clinical setting
> Summarize the exercise benefits for cancer prevention and rehabilitation and make exercise recommendations for persons with cancer

- Review the potential benefits of aerobic exercise for moderate hypertension
- Discuss the role of regular physical activity in congestive heart failure
- Discuss the general components in the clinical assessment for cardiac disease
- Summarize noninvasive and invasive procedures to identify specific cardiac dysfunctions
> Describe three phases of cardiac rehabilitation, including objectives, required levels of supervision, and prudent physical activities
> Give three important reasons to include graded exercise stress testing for coronary heart disease screening
> Describe objective indicators of coronary heart disease during an exercise stress test
> List 10 reasons to stop a stress test
> Define the following terms for stress test results: true positive, false positive, true negative, and false negative
> Outline an approach to individualize an exercise prescription
- Discuss the heart transplant patients responses and adaptations to regular aerobic exercise and resistance training
> Categorize and describe five diseases that affect the pulmonary system
> Outline two proposed mechanisms for exerciseinduced bronchospasm and factors that modify its severity
> Describe the different neuromuscular diseases and the role that physical activity plays in their rehabilitation
> Describe the major classifications of cognitive/emotional diseases and the potential for exercise as adjunctive therapy


## THE EXERCISE PHYSIOLOGIST IN THE CLINICAL SETTING

Regular physical activity plays an increasingly important role in the global prevention of disease, in rehabilitation from injury, and as adjunctive therapy for medically related disorders. Attention now focuses on understanding the mechanisms by which physical activity improves health, physical fitness, and rehabilitation potential of patients challenged by chronic disease and disability. Table 32.1 lists several clinical applications of physical activity interventions for some of the medical/health conditions.

The clinical exercise physiologist has become an integral component in the team approach to health and total patient care. In the clinical setting, the exercise physiologist focuses primarily on restoring patient mobility and functional capacity while working closely with physical therapists, occupational therapists, and physicians. The exercise physiologist has an expanded role in clinical practice because of fundamental relationships among measures of functional capacity, physical fitness, and overall good health. The World Health Organization (WHO; www.who.int/) defines health as a state of complete physical, mental and social well-being, not merely the absence of disease and infirmity. This definition considers good health an ability to complete physical tasks successfully and maintain functional independence. Functional capacity measurement as depicted in the unnumbered figure (see p. 879) provides an objective assessment of a person $s$ current status and quantifies changes from diverse strategies to improve fitness, health, and well-being.

## Vital Link Between Sports Medicine and Exercise Physiology

One traditional view of sports medicine concerns rehabilitating athletes from sports-related injuries. In its broader
context, sports medicine relates to scientific and medical aspects of physical activity, physical fitness, health, and sports performance. Indeed, the WHO defines physical fitness as the ability to perform muscular work satisfactorily. This definition encompasses one s capacity to perform physical activity at work, at home, or on the athletic field. Sports medicine thus becomes closely linked to clinical exercise physiology because the sports medicine profession encompasses a broad spectrum of individuals. Patients with low functional capacity recovering from injury, disease, and medical interventions comprise one end of the continuum; the other extreme encompasses healthy, able-bodied and disabled athletes with welldeveloped levels of total body fitness. Carefully prescribed physical activity contributes to overall good health and quality of life (Table 32.2).

## TRAINING AND CERTIFICATION PROGRAMS FOR PROFESSIONAL EXERCISE PHYSIOLOGISTS

During the past 30 years, regular physical activity has gained widespread acceptance as an integral part of rehabilitative programs of care and health maintenance for a growing list of chronic diseases and disabling conditions. Likewise, expanding public interest in physical activity for health promotion has stimulated a parallel need to certify qualified professionals to provide sound advice and supervision regarding physical activities for preventive and rehabilitative purposes. About 35 years ago (1975), the American College of Sports Medicine (ACSM; www.acsm.org) initiated the first ACSM Clinical and Health/Fitness Certification program. The ACSM continues to be the preeminent organization to offer certification programs, newsletters, and continuing education credits (CEUs, or CECs) to support the professional growth of health

TABLE 32.1 Clinical Areas and Corresponding Diseases and Disorders Where Regular Physical Activity Applies

[^58]
## Diseases and Disorders

Ischemia; Chronic heart failure; Dyslipidemia; Cardiomyopathies; Cardiac valvular disease; Heart transplantation; Congenital
Chronic obstructive pulmonary disease; Cystic fibrosis; Asthma and exercise-induced asthma
Stroke; Multiple sclerosis; Parkinson s disease; Alzheimer s disease; Polio; Cerebral palsy
Obesity (adult and pediatric); Diabetes; Renal disease; Menstrual dysfunction Cancer; Breast cancer; Immune deficiency; Allergies; Sickle cell disease; HIV and and AIDS
Osteoporosis; Osteoarthritis and rheumatoid arthritis; Back pain; Sports injuries Sarcopenia
Anxiety and stress disorders; Mental retardation; Depression

## TABLE 32.2 Health Benefits of Regular Physical Activity ${ }^{a}$

| Physical Activity Benefit | Surety Rating | Physical Activity Benefit | Surety Rating |
| :---: | :---: | :---: | :---: |
| Fitness of Body |  | Cigarette Smoking |  |
| Improves heart and lung function | **** | Improves success in quitting | ** |
| Improves muscular strength/size | ** | Diabetes |  |
| Cardiovascular Disease |  | Prevention of type 2 | **** |
| Coronary heart disease prevention | **** | Treatment of type 2 | *** |
| Regression of atherosclerosis | ** | Treatment of type 1 |  |
| Treatment of heart disease | *** | Improvement in diabetic s life quality | *** |
| Prevention of stroke | ** | Infection and Immunity |  |
| Cancer |  | Prevention of the common cold | ** |
| Prevention of colon cancer | **** | Improves overall immunity | ** |
| Prevention of breast cancer | ** | Slows progression of HIV to AIDS | * |
| Prevention of uterine cancer | ** | Improves life quality of HIV-infected persons | *** |
| Prevention of prostate cancer | ** | Arthritis |  |
| Prevention of other cancer | * | Prevention of arthritis | * |
| Treatment of cancer | * | Treatment/cure of arthritis | * |
| Osteoporosis |  | Improvement life quality/fitness | **** |
| Helps increase bone mass and density | **** | High Blood Pressure |  |
| Prevention of osteoporosis | *** | Prevention of high blood pressure | **** |
| Treatment of osteoporosis | ** | Treatment of high blood pressure | **** |
| Blood Cholesterol/Lipoproteins |  | Asthma |  |
| Lowers blood total cholesterol | * | Prevention/treatment of asthma | * |
| Lowers LDL cholesterol | * | Improvement in asthmatic s life quality | *** |
| Lowers triacylglycerols | *** | Sleep |  |
| Raises HDL cholesterol | *** | Improvement in sleep quality | *** |
| Low Back Pain |  | Psychologic Well-Being |  |
| Prevention of low back pain | ** | Elevation in mood | **** |
| Treatment of low back pain | ** | Buffers effects of mental stress | *** |
| Nutrition and Diet Quality |  | Alleviates/prevents depression | **** |
| Improvement in diet quality | ** | Anxiety reduction | **** |
| Increase in total energy intake | *** | Improves self-esteem | **** |
| Weight Management |  | Special Issues for Women |  |
| Prevention of weight gain | **** | Improves total body fitness | *** |
| Treatment of obesity | ** | Improves fitness while pregnant | *** |
| Helps maintain weight loss | *** | Improves birthing experience | ** |
| Children and Youth |  | Improves health of fetus | ** |
| Prevention of obesity | *** | Improves health during menopause | *** |
| Controls disease risk factors | *** |  |  |
| Reduction of unhealthy habits | ** | **** Strong consensus with little or no conflicting data |  |
| Improves odds of adult activity | ** | *** Most data supportive, but more research required for |  |
| Elderly and the Aging Process |  | clarification |  |
| Improvement in physical fitness | **** | ** Some supportive data, but much more research needed |  |
| Counters loss in heart/lung fitness Counters loss of muscle | *** |  |  |
| Counters gain in fat | *** |  |  |
| Improvement in life expectancy | **** |  |  |
| Improvement in life quality | **** |  |  |

${ }^{a}$ Based on a total physical fitness program that includes physical activity to improve aerobic and musculoskeletal fitness. From Newman CC.
The human body. ACSM s Health Fitness J 1998;2(3):30.
and fitness professionals. The sports nutrition and body composition certifications offered by the International Society of Sports Nutrition (ISSN; www.sportsnutritionsociety.org) incorporate important concepts about physical activity, fitness, and health; natural historical and contemporary ties exist between sports nutrition and exercise physiology.

The ACSM certifications consist of two different tracks:

1. Health/Fitness Track for those who want to provide leadership in fitness assessment and exercise programming of a preventive nature for apparently
healthy individuals and for controlling diseases in corporate, commercial, and community settings.
2. Clinical Track for professionals who work with groups at high risk or with existing disease in addition to apparently healthy individuals.

The accompanying $F Y I$ on the facing page shows the different levels of certification within each track.

Competency-based certification at a given level requires a knowledge and skills base commensurate with that specific certification. Additionally, each level has a minimum experience


Exercise physiologists work in cooperation with local community groups to determine the effects of arm and leg strength training combined with static and dynamic balance and kinesthetic training in a large cohort of men and women older than age 65. The ongoing studies include force platform analysis and EMG with load and photo cells to quantify balance and kinesthetic awareness and dynamic strength assessments using isoinertial lifting tasks. (Photos courtesy of Hilde Ohne Seiler, Adger University College, Faculty of Health and Sport, Kristiansand, Norway.)
requirement, level of education, or other ACSM certifications. Certification programs continually undergo review and revision to ensure the highest level of professionalism. Over 400 groups and organizations offer different types of certifications, some without undergraduate degree requirements and some requiring a short examination or experience to replace core content. These so-called certifications, without approved standards and exclusions, confuse the public about the level of competence or care provided by a certified exercise professional. Table 32.3 lists nine organizations that offer related training and/or certification programs that deal with personal training.

Levels of Certification Within ACSMs Clinical and Health/Fitness Tracks

## Clinical Track

Program Director (PD)
Exercise Specialist (ES)
Health/Fitness Track
Health/Fitness Director (HFD)
Health/Fitness Instructor (HFI)
Exercise Leader (EL)

## CLINICAL APPLICATIONS OF EXERCISE PHYSIOLOGY TO DIVERSE DISEASES AND DISODERS

The following sections present clinical applications of exercise physiology for the major areas of oncology, cardiovascular diseases, pulmonary system disabilities, neuromuscular diseases and disorders, renal disease, and psychologic disorders. We focus on these disabilities because the clinical exercise physiologist routinely deals with these maladies.

## ONCOLOGY

Cancer represents a group of diseases collectively characterized by uncontrolled growth of abnormal cells. More than 100 different types of cancers exist, mostly in adults. Carcinomas develop from epithelial cells that line the surface of the body, glands, and internal organs. They account for 80 to $90 \%$ of all cancers that include prostate, colon, lung, cervical, and breast cancer. Cancers also can arise from cells of the blood (leukemias), the immune system (lymphomas), and connective tissues such as bones, tendons, cartilage, fat, and muscle (sarcomas).

## TABLE 32.3 Organizations that Offer Training/Certification Programs Related to Physical Activity

## Organization

Aerobics and Fitness Association of America (AFAA) www.afaa.com
American College of Sports Medicine (ACSM) www.acsm.org
American Council on Exercise (ACE) www.acefitness.com
Certified Personal Trainers Network
(CPTN) www.cptn.com
Canadian Society for Exercise Physiology www.csep.ca
Cooper Institute for Aerobics Research www.cooperinst.org

National Academy of Sports Medicine (NASM) www.nasm.org
National Strength \& Conditioning Association (NSCA) www.ncsa-lift.org
UCLA Certificate Program in Fitness Instruction www.uclaextension.edu/

## Areas of Specialization and Certification

Aerobics Fitness Practitioner, Primary Aerobics Instructor, Personal Trainer \& Fitness Counselor, Step Reebok Certification, Weight Room/Resistance Training Certification, Emergency Response Certification
Exercise Leader, Health/Fitness Instructor, Exercise Test Technologist, Health/Fitness Director, Exercise Specialist, Program Director
Group Fitness Instructor, Personal Trainer, Lifestyle and Weight Management Consultant
CPTN/OFC Certified Personal Trainer, CPTN Certified Specialty Personal Trainer, CPTN/OFC Assessor of Personal Trainers, CPTN/OFC Course Conductor for Personal Trainers
CFC-Certified Fitness Consultant, PFLC-Professional Fitness and Lifestyle Consultant, AFAC-Accredited Fitness Appraisal Center
Certifications in Physical Fitness Specialist, Master Fitness Specialist, Biomechanics of Resistance Training Specialty, Providing Dietary Guidance: Nutrition Specialty, Fitness Specialist for Older Adults Specialty, Special Populations Specialty, Martial Arts Specialist, Group Exercise Leadership, Indoor Cycling Specialty, Aquatics Specialty, Health Promotion Director, Developing Lifestyle Physical Activity Programs, Physical Fitness Specialist, Master Fitness Specialist
Certified Personal Trainer (NASM-CPT), Performance Enhancement Specialist (NASM-PES)
Certified Strength and Conditioning Specialist (CSCS), Certified Personal Trainer (NSCA-CPT)
Exercise and Fitness, Exercise Science and Nutrition, Continuing Education for Fitness Professionals

The current population of more than 13 million cancer survivors illustrates the ongoing need for rehabilitative and maintenance options in this expanding area of medicine. The most serious outcomes for current cancer patients and survivors include loss of body mass and functional status. Depressed functional status includes difficulty walking (even short distances) and serious fatigue that limits completion of simple household chores. Approximately 75\% of cancer survivors report extreme fatigue during and following radiotherapy or chemotherapy treatment. Weight loss, decreased muscular strength, and suboptimal cardiovascular endurance accompany these decrements. Maintaining and restoring functional capacity challenges the cancer survivor, even those considered cured. Sufficient rationale now justifies exercise intervention for cancer patients during and following different treatment modalities.

## Recent Cancer Statistics

Cancer has currently replaced heart disease as the top killer of Americans younger than age 85, and approximately one-third of the population have some form of cancer (www.cancer .gov/cancerinformation). New methodologies and increased surveillance and reporting techniques now allow the American Cancer Society to update cancer statistics yearly. Figure 32.1 represents the most recent statistics for cancer deaths for the U.S. population for 2008.

In 2005, the nation s leading cancer organizations reported that Americans risk of getting and dying from cancer
continued to decline (albeit slowly), and survival rates for many cancers continued to improve. Figure 32.2 shows the most recent analyses comparing U.S. death rates by cause between 1950 and 2005.

## Clinical Features

Clinical features of cancer relate to the effects of three primary cancer treatment modalities: surgery, radiation, and systemic (pharmacologic) therapy (this includes application of proteonomics that use proteins as biomarkers for clinical diagnosis).

1. Surgeries include operations to remove high-risk tissues to prevent cancer development, biopsies of abnormal tissue to diagnose cancer, excision of tumors with curative intent, insertion of central venous catheters to support chemotherapy infusions, reconstruction after definitive surgery, and palliative or symptom relief for incurable disease (e.g., partial bowel removal or resection).
2. Radiation involves photon penetration into a specific tissue to produce an ionized (electrically charged) particle that damages DNA to inhibit cell replication and produce cell death. Daily radiation treatment typically lasts between 5 and 8 weeks. Pharmacologic therapy is prescribed for many advanced solid tumors if cancer cells are suspected of metastasizing beyond the primary site and regional lymph nodes.


Figure 32.1 Estimated cancer deaths in United States, 2008. Source: Cancer Facts \& Figures 2008 (www.cancer.org).
3. Chemotherapy, endocrine therapy, and biologic therapy represent the three major types of systemic therapy.

Table 32.4 presents common clinical symptoms, effects, and outcome from surgery, radiation therapy, and systemic therapy interventions.

Cancer Rehabilitation and Physical Activity
Regular physical activity helps cancer patients recuperate and return to a normal lifestyle with greater independence and functional capacity. ${ }^{18,59,76}$ The most serious health outcomes for most cancer survivors include loss of body mass and decreased energy level and functional status. This is particularly prevalent


Figure 32.2 Change in U.S. death rates* by cause, 1950 and 2005. Rate per 100,000 population. Sources: 1950 mortality dataGDC/NCHS, Mortality Revised; 2005 mortality data甘.S. Mortality Data 2005, NCHS, Centers for Disease Control and Prevention, 2008. *Age-adjusted to 2000 U.S. standard population.
following surgery and during chemotherapy and radiation therapy. ${ }^{26,28,49}$ Loss of functional status includes difficulty walking more than one block and chronic fatigue that limits completion of routine household chores. Approximately 75\% of cancer survivors report extreme fatigue during radiation
therapy or chemotherapy, probably from weight loss and muscle atrophy and loss of cardiovascular endurance. Home-based exercise regimens reduce feelings of fatigue and enhance life quality and other biosocial outcomes following cancer diagnosis. ${ }^{23,138}$ Maintaining and restoring function present distinct challenges to the cancer survivor. Evidence justifies exercise intervention for breast cancer survivors, ${ }^{65,82,125,139}$ and nutrition intervention plus regular exercise reduces risk of contracting additional cancers. ${ }^{132,149,152}$

Table 32.5 lists 10 general preventive and intervention goals for patients who face sustained periods of inactivity, disuse, and bed rest. The overall goal of the health-care team is to rehabilitate the patient to a level of function that allows return to work and pursuit of normal recreational activities. Figure 32.3 shows the effects of a 6-week physical activity rehabilitation program of treadmill walking weekdays at $80 \%$ of peak heart rate during a stress test for five cancer patients suffering severe fatigue. During the first 3 weeks, each patient walked five intervals of 3 minutes with 3 minutes of active recovery. Exercise duration increased weekly, with the number of exercise intervals reduced until the patient could complete one continuous 30 - to 35 -minute bout during week 6 . Submaximal exercise heart rate and blood lactate concentration decreased during exercise (Fig. 32.3A), while walking speed and distance and maximal performance on the stress test increased (Fig. 32.3B). All subjects increased daily physical activity level without substantial limitations, and each reported increased daily vigor. This clinical investigation did not meet the rigors of experimental research design (e.g., no nonexercise control patients); nevertheless, the results highlight the positive potential of regular exercise for the rehabilitation of cancer patients.

## TABLE 32.4 Cancer Therapies and Their Complications

## Type of Treatment

Surgery Lung: reduced lung capacity, dyspnea, deconditioning
Neck: reduced range of motion, muscle weakness, occasional cranial nerve palsy
Pelvic region: urinary incontinence, erectile dysfunction, deconditioning
Abdomen: deconditioning, diarrhea
Limb amputation: chronic pain, deconditioning
Skin: redness, pain, dryness, peeling, sloughing, reduced elasticity
Brain: nausea, vomiting, fatigue, memory loss
Thorax: some degree of irreversible lung fibrosis, heart may receive radiation causing pericardial inflammation or fibrosis, premature atherosclerosis, cardiomyopathy
Abdomen: vomiting, diarrhea
Pelvis: diarrhea, pelvic pain, bladder scarring, occasional incontinence, sexual dysfunction
Joints: connective tissue and joint capsule fibrosis; possible decreased range of motion
Systemic Therapy

## Description and Effects/Outcome

Chemotherapies [Depending on type and amount]: extreme fatigue, anorexia, nausea, anemia, neutropenia, muscle pain, sensory and motor peripheral neuropathy, ataxia, anemia, vomiting, loss of muscle mass, deconditioning, infection
Endocrine Therapies [Depending on type and amount]: fat redistribution (truncal and facial obesity), proximal muscle weakness, osteoporosis, edema, infection, weight gain, extreme fatigue, hot flashes, loss of muscle mass
Biologic Therapies [Depending on type and amount]: Fevers or allergic reactions, chills, fever, headache, extreme fatigue, low blood pressure, skin rash, anemia

From Courneya KS, et al. In Myers J (Ed). ACSM s resources for clinical exercise physiology for special populations. 2nd ed. Baltimore: Lippincott Williams \& Wilkins, 2009.

TABLE 32.5 Ten General Treatment Goals of the Clinical Exercise Physiologist for Patients with Deconditioning, Immobility, or Disuse Syndromes

1. Improve overall functional status.
2. Improve active motion for nonrestrictive segments and joints.
3. Prevent loss of flexibility by active motion and passive movements.
4. Stimulate peripheral and central circulation through active motion exercise based on current functional level.
5. Increase ventilatory function with systematic breathing exercises.
6. Prevent thrombosis through physical activities.
7. Prevent loss of motor control and muscle strength and endurance with resistance exercises.
8. Reduce rate of bone loss through weight-bearing aerobic and muscle-strengthening exercises.
9. Through active aerobic and resistance exercise, slow the loss of fat-free body mass and subsequent reduction of BMR that accompanies deconditioning.
10. Monitor signs of increased fatigue or weakness, lethargy, dyspnea, pallor, dizziness, claudication, or cramping during or following exercise.

## Physical Activity: Protective Effects on Cancer Occurrence

Firm epidemiologic evidence confirms an inverse relation between amount of occupational or leisure-time physical activity and reduction in all-cause cancer risk. For example, one review concludes the magnitude of the protective effect of physical activity on estrogen-dependent cancer warrants including low-to-moderate exercise as a prudent preventive strategy. ${ }^{86}$ Other large-scale, community-based studies of colorectal, breast, and prostatic hyperplasia indicate that increased physical activity reduces cancer risk and mortality. ${ }^{31,70,97,122}$ A study of nearly 122,000 women found that exercising at least 1 hour daily reduced breast cancer risk by $20 \%$. ${ }^{132}$ The benefits may differ depending on menopausal status, with a greater risk reduction for postmenopausal women. ${ }^{47}$ The proportion of men at high risk for colon cancer would decrease considerably if men eliminated the modifiable risk factors of physical inactivity and excessive red meat consumption, obesity, alcohol consumption, cigarette smoking, and low folic acid intake. ${ }^{123}$

Regular physical activity exerts the following effects to thwart cancerous tumor formation:

Lowers circulating levels of blood glucose and insulin
Increases corticosteroid hormones
Increases antiinflammatory cytokines
Augments insulin-receptor expression in cancer-
fighting T cells
Promotes interferon production
Stimulates glycogen synthetase
Enhances leukocyte function


Figure 32.3 A. Reduction in heart rate and blood lactate concentration during submaximal walking at $5 \mathrm{~km} \cdot \mathrm{~h}^{1}$ following 6 weeks of exercise rehabilitation in five cancer patients suffering severe fatigue. B. Weekly changes in training speed (km $\cdot \mathrm{h}^{1}$ ) and daily distance walked (km) and pre- and posttraining maximal exercise performance. (From Dimeo F, et al. Aerobic exercise as therapy for cancer fatigue. Med Sci Sports Exerc 1998;30:475.)

Improves ascorbic acid metabolism Exerts beneficial effects on provirus or oncogene activation

## Physical Activity Prescription and Cancer

Limited research exists regarding the proper physical activity prescription for cancer patients and the proper timing of exercise relative to the various phases of cancer treatment. Thus, determining the best time to initiate exercise intervention in the recovery process remains problematic, but results have been encouraging. Thirty-five stomach cancer patients were placed in a physical activity or control group immediately following curative surgery. ${ }^{107}$ From postoperative day 2, patients performed arm and leg ergometer

## TABLE 32.6 Special Precautions for Testing the Functional Capacity of Cancer Patients

## Complication

```
Ataxia/dizziness/peripheral sensory neuropathy
Bone pain
Low blood count (hemoglobin \leq 5.0 g · dL ' 
    neutrophil count }\leq0.5\times1\mp@subsup{0}{}{9}\cdot\mp@subsup{\textrm{L}}{}{1}
Dyspnea
Fever \geq38 C
Mouth sores/ulcerations
Low functional status
Surgical wounds/tenderness
Severe nausea/vomiting
Ataxia/dizziness/peripheral sensory neuropathy
Bone pain
Low blood count (hemoglobin \(\leq 8.0 \mathrm{~g} \cdot \mathrm{dL}^{1}\); neutrophil count \(\leq 0.5 \times 10^{9} \cdot \mathrm{~L}^{1}\) )
Dyspnea
Fever \(\geq 38 \mathrm{C}\)
Mouth sores/ulcerations
Surgical wounds/tenderness
Severe nausea/vomiting
```


## Precaution

Avoid tests that require balance and coordination (treadmill; weights) Avoid high-impact tests that increase risk of fracture (treadmill; weights) Avoid tests that require high oxygen consumption or high impact (risk of bleeding); ensure proper sterilization of equipment
Avoid maximal tests
May indicate systemic infection; avoid exercise testing Avoid mouthpieces; use face masks
Avoid exercise testing
Avoid pressure/trauma to surgical site
Avoid/postpone exercise testing

Modified from Courneya KS, et al., Coping with cancer: can exercise help? Phys Sportsmed 2000;28(5):49.
exercise twice daily, 5 days weekly for 14 days at $60 \%$ of maximal heart rate. The early physical activity intervention increased natural killer cell cytotoxic activity in the exercise group compared with the control group. In light of limited information, exercise prescription recommendations for cancer rehabilitation generally include symptom-limited, progressive, and individualized physical activities. Ambulation of any kind as soon as practical becomes important for the most sedentary and deconditioned patients. Emphasis should focus on intervals of low-to-moderate aerobic activity performed several times daily rather than one relatively strenuous bout of continuous exercise. A dose response relationship seems to emerge between increased physical activity and improved health and functional capacity. ${ }^{69}$ Most sedentary patients derive clinically significant benefits by accumulating up to 30 minutes of daily walking (or equivalent energy expenditure in other activities). Health benefits accrue whether activity takes the form of structured exercise, home-based programs, or sport, household, occupational, or recreational activities.

Cancer patients initially receive a symptom-limited, graded exercise stress test (GXT) on a treadmill or cycle ergometer to form their exercise prescription. Testing procedures remain the same as for healthy individuals except the patient receives greater attention about sensations of fatigue. Generally, patients should not exercise to maximum. The exercise prescription initially aims to produce ambulation if no specific contraindications exist. The prescription also provides for range-of-motion movements and other exercises to improve muscular strength, augment fat-free body mass (FFM), and improve overall mobility (e.g., submaximal static exercises of the antigravity muscles, deep breathing exercises, and dynamic trunk rotation movements). Exercise progression and intensity are individualized, with initial work rest ratios of $1: 1$ increasing to $2: 1$. Eventually, continuous exercise for up to 15 minutes can replace intermittent exercise bouts. Table 32.6 presents special precautions to consider when testing the functional capacity of cancer patients. Table 32.7 presents general aerobic exercise guidelines for otherwise healthy cancer survivors.

## TABLE 32.7 General Aerobic Exercise Guidelines for Otherwise Healthy Cancer Survivors

Prescription
Variable

## Guidelines

Frequency

Intensity

Type (mode)

Time (duration)

Progression

Modified from Courneya KS, et al. Coping with cancer: can exercise help? Phys Sportsmed 2000;28(5):49.

## Breast Cancer Rehabilitation and Exercise

Carcinoma of the breast, the most common form of cancer in white females ages 40 years and older, causes the greatest number of deaths in women between the ages of 40 and 55 years. In 2001, 192,200 new invasive breast cancer cases were diagnosed and almost $22 \%$ of those women died. By age 30, the chance of being diagnosed with breast cancer remains just 1 in 2000; by age 40, the chances increase considerably to 1 in 233 , and by age 60,1 in 22 . Six risk factors for breast cancer include:

1. Family history
2. Personal history of cancer
3. First menstrual period at an early age
4. Menopause at a late age
5. First child born after age 30 or no childbirth
6. High-fat diet

Most studies of exercise for cancer patients have demonstrated physiologic and psychologic benefits. ${ }^{33,73,75,155}$ Unfortunately, most of this research remains limited because it did not involve randomized controlled trials and/or it used small sample sizes. Research with breast cancer patients has mainly used aerobic training rather than resistance exercise as the exercise modality.

Resistance exercise during cancer management can effectively counteract disease and treatment side effects. In a study from one of our laboratories, 28 patients recovering from breast cancer surgery enrolled in a 10 -week program of circuit-resistance training to evaluate the effects of exercise on depression, self-esteem, and anxiety. ${ }^{140}$ Patients performed hydraulic resistance exercises in a 14 -station aerobic exercise circuit 4 days a week with a self-paced, individualized program adjusted to their needs and fitness levels. Figure 32.4 shows that exercisers decreased depression by $38 \%$ compared with a $13 \%$ increase for nonexercising counterparts recovering from breast cancer surgery. The exercisers also decreased trait anxiety by $16 \%$ and state anxiety by $20 \%$, whereas nonexercising patients increased in both variables. These potent exercise effects on psychosocial variables during breast cancer rehabilitation bode well for advocating structured, comprehensive exercise programs.

## CARDIOVASCULAR DISEASE

This chapter examines the prevalence of different diseases of the cardiovascular system, possible causes and diagnosis of the disease, and specific applications of exercise for cardiovascular disease rehabilitation.

## Cardiovascular Disease and Exercise Capacity

Designing aerobic exercise programs for cardiac patients should consider three factors:

1. Specific pathophysiology of the disease
2. Mechanisms that may limit exercise performance
3. Individual differences in functional capacity

Table 32.8 lists three general categories of heart disease that cause functional impairment. Diseases of the myocardium predominate, particularly with advancing age. Any one of the following terms indicates myocardial disease: degenerative heart disease (DHD), atherosclerotic cardiovascular disease, arteriosclerotic cardiovascular disease, coronary artery disease (CAD), or coronary heart disease (CHD). In this text, we use CHD.

Hypertension represents a primary risk for CHD, so we first discuss blood pressure stratification and subsequent treatment recommendations. We then review the role of regular exercise in preventing and treating hypertension.




## Exercise $\square$ Control

Figure 32.4 Effects of 10 weeks of moderate aerobic exercise on depression (top), trait (middle), and state (bottom) anxiety in 28 women recovering from breast cancer surgery. (From Segar ML, et al. The effect of aerobic exercise on selfesteem and depressive and anxiety symptoms among breast cancer survivors. Oncol Nurs Forum 1998;25:107.)

TABLE 32.8 Cardiac Diseases That Cause Functional Impairment

| Diseases | Diseases | Diseases <br> Affecting <br> Affecting <br> the Heart <br> Muscle |
| :--- | :--- | :--- |
| Affecting <br> the Heart <br> Valves | Nervordiac <br> System |  |
| CHD | Rheumatic fever | Arrhythmias |
| Angina | Endocarditis | Tachycardia |
| Myocardial | Mitral valve | Bradycardia |
| infarction | prolapse <br> Pericarditis <br> Congestive heart <br> failure <br> Aneurysms | deformations |
|  |  |  |

## Blood Pressure: Classification and Risk Stratification

Hypertension (www.ash-us.org/) afflicts between 38 and $64 \%$ of men and 37 and $74 \%$ of women between ages 45 and 74 (see Fig. 15.9). Prevalence increases sharply with age, particularly so for blacks than whites. Figure 32.5 presents the prevalence of hypertension in black and white males and females. Note that total prevalence is only slightly higher in blacks than whites ( $28.1 \%$ vs. $23.2 \%$ ), yet in young adults, hypertension occurs more frequently in blacks, particularly black women. In the 35 to 44 age range, hypertension occurs in one-third as many white women (8.5\%) as black women (22.9\%).

Table 32.9 presents the standard classification of blood pressure for adults ages 18 years and older. Table 32.10 provides recommendations for initial screening and subsequent risk stratification and treatment for hypertensive patients. Chronic hypertension damages arterial vessels; it serves as a primary risk for arteriosclerosis, heart disease, stroke, and kidney failure. In many instances, regular exercise provides a prudent first line of defense to treat mild hypertension ( 140159 mm Hg systolic; 9099 mm Hg diastolic) and moderate hypertension (160 179 mm Hg systolic; 100109 mm Hg diastolic).

## Regular Exercise and Hypertension

Systolic and diastolic blood pressures decrease by 6 to 10 mm Hg with aerobic exercise training in previously sedentary men

TABLE 32.9 Classification of Blood Pressure for Adults Age 18 Years and Older

| Category | Systolic <br> $(\mathbf{M M ~ H g})$ |  | Diastolic <br> $(\mathbf{M M ~ H g})$ |
| :--- | :--- | :--- | :--- |
| Optimal | $<120$ | and | $<80$ |
| Normal | 120129 | and | 8084 |
| High normal | 130139 | or | 8589 |
| Hypertension | 140159 | or | 9099 |
| $\quad$ Stage 1 | 160179 | or | 100109 |
| Stage 2 | $\geq 180$ | or | $\geq 110$ |
| $\quad$ Stage 3 |  |  |  |

From the sixth report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNVI), Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, NIH Publ. no. 98 4080, Nov 1997. This classification should be used with individuals not taking antihypertensive medication and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be used to classify status. For example, $160 / 92 \mathrm{~mm} \mathrm{Hg}$ would be stage 2 and $174 / 120 \mathrm{~mm} \mathrm{Hg}$, stage 3.
and women regardless of age. Beneficial results occur with normotensive and hypertensive subjects during rest and exercise. ${ }^{27,44,85,158}$ Regular exercise as preventive therapy also controls the tendency for blood pressure to increase over time in individuals at risk for hypertension. ${ }^{119}$

Patients with mild hypertension respond favorably to exercise training, a response also noted among children


Figure 32.5 Prevalence of hypertension for blacks versus whites for both males and females or different age groupings. (From Wolz M, et al. Statement from the National High Blood Pressure Education Program: prevalence of hypertension. Am J Hypertens 2000;13:103.)

TABLE 32.10 Risk Stratification and Recommended Treatment for Hypertension

| Blood Pressure <br> Stages (MM Hg) ${ }^{a}$ | Risk Group A (No Risk Factors; No TOD ${ }^{b}$ or CCD ${ }^{c}$ ) | Risk Group B (One Risk Factor Not Including Diabetes; No TOD or CCD) | Risk Group C (TOD and/or CCD and/or Diabetes, with or Without Other Risk Factors |
| :---: | :---: | :---: | :---: |
| High-normal 130 139/85 89 | Lifestyle modification | Lifestyle modification | Drug therapy |
| Stage 1 $140 \quad 159 / 9099$ | Lifestyle modification | Lifestyle modification | Drug therapy |
| Stages 2 and 3 $\geq 160 / \geq 100$ | Drug therapy | Drug therapy | Drug therapy |
| ${ }^{\text {a }}$ See Table 32.9. |  |  |  |
| ${ }^{b}$ TOD, target organ disease. |  |  |  |
| ${ }^{\text {c }} \mathrm{CCD}$, clinical cardiovascular disease. |  |  |  |
| A person with diabetes, blood pressure of $142 / 94 \mathrm{~mm} \mathrm{Hg}$, and left ventricular hypertrophy classifies as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and another major risk factor (diabetes). This patient would be classified as stage 1 , risk group C , and recommended for immediate drug therapy. |  |  |  |
| From the sixth report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNVI), Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute, NIH Publication no. 98 4080, Nov, 1997. |  |  |  |

and adolescents (in the pediatric population). ${ }^{3,84,96,109}$ In fact, hypertension medication may be reduced by progressively increasing exercise intensity by walking faster each week. ${ }^{159}$

Table 32.11 shows that average resting systolic blood pressure decreased from 139 to 133 mm Hg in seven middleaged male patients following 4 to 6 weeks of interval training. During submaximal exercise, systolic pressure decreased from 173 to 155 mm Hg , while diastolic pressure decreased from 92 to 79 mm Hg . Consequently, training produced approximately a $14 \%$ decrease in mean arterial exercise blood pressure. Similar results occurred for an apparently healthy yet borderline hypertensive group of 37 middle-aged men following 6 months of regular aerobic exercise. ${ }^{17}$ For hypertensive older men and women, 9 months of low-intensity,
aerobic exercise lowered systolic blood pressure by 20 mm Hg and diastolic pressure by $12 \mathrm{~mm} \mathrm{Hg} .{ }^{56}$ Figure 32.6 shows changes in resting blood pressure with aerobic training and 1 month of detraining in elderly hypertensive men and women who trained at the lactate threshold three to six times a week for 36 weeks. Baseline values 3 months prior to training indicate subjects blood pressures with normal antihypertensive drug therapy. Regular exercise (with continued medication) produced decreases of 15 mm Hg in systolic blood pressure, 11 mm Hg in mean arterial pressure, and 9 mm Hg in diastolic blood pressure. Blood pressure returned to pretraining levels within 1 month for the five subjects who discontinued training. The ACSM s Position Stand on Physical Activity, Physical Fitness, and Hypertension can be accessed at www.acsm-msse.org/.

TABLE 32.11 Blood Pressure During Rest and Submaximal Exercise Before and After 4 to 6 Weeks of Training in Seven Middle-Aged CHD Patients

| Measure ${ }^{\text {a }}$ | Rest |  |  | Submaximal Exercise |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Average Value |  | Difference (\%) | Average Value |  | Difference (\%) |
|  | Before | After |  | Before | After |  |
| Systolic blood pressure ( mm Hg ) | 139 | 133 | -4.3 | 173 | 155 | -10.4 |
| Diastolic blood pressure ( mm Hg ) | 78 | 73 | -6.4 | 92 | 79 | -14.1 |
| Mean blood pressure ( mm Hg ) | 97 | 92 | -5.2 | 127 | 109 | -14.3 |

[^59]

Figure 32.6 Blood pressure changes in elderly subjects who received hypertensive medication following 9 months of exercise training at the lactate threshold and after 1 month of detraining (five subjects). Baseline values 3 months before training ( -3 ) indicate subjects blood pressures with their normal antihypertensive drug therapy only. SBP, systolic blood pressure; MBP, mean blood pressure; $D B P$, diastolic blood pressure; * statistically significant from baseline value. (From Motoyama M, et al. Blood pressure lowering effect of low intensity aerobic training in elderly hypertensive patients. Med Sci Sports Exerc 1998;30:818.)

The precise mechanism(s) for how regular physical activity lowers blood pressure remains unclear but two contributing factors include the following:

1. Reduced sympathetic nervous system activity with training and possible normalization of arteriole morphology decrease peripheral resistance to blood flow to lower blood pressure. ${ }^{2,117}$
2. Altered renal function facilitates the kidneys elimination of sodium, which subsequently reduces fluid volume and hence blood pressure.

Not all research supports physical activity as a way to treat hypertension. ${ }^{22,46}$ Even when research shows that regular physical activity lowers blood pressure, the studies often have methodologic shortcomings and inadequate design, particularly a lack of appropriate control subjects who have their blood pressure measured but do not exercise. Despite these limitations, it remains prudent to recommend regular aerobic exercise (and proper diet to induce weight loss when necessary) as a first-line strategy to manage borderline hypertension. ${ }^{3,79,144}$

Improved fitness often neutralizes increased mortality associated with elevated blood pressure. Even if regular exercise does not return elevated blood pressure to a normal level, aerobic training confers important independent health benefits. Aerobically fit individuals with hypertension achieved a $60 \%$ lower mortality rate than unfit normotensive peers. ${ }^{12}$ More severe elevations in blood pressure require pharmacologic intervention (more than 60 drugs and 30 pill combinations are available for treatment; see Fig. 15.10).

## Chronic Resistance Training Effects on Blood Pressure

Despite the relatively large rise in blood pressure during resistance exercise, long-term resistance training does not elevate resting blood pressure. ${ }^{21,37,57}$ Resistance training reduces the typical short-term blood pressure increases during this exercise mode. Trained bodybuilders, for example, show smaller increases in systolic and diastolic blood pressures with resistance exercise than novice bodybuilders and untrained individuals. ${ }^{37,135}$ The diminished blood pressure response posttraining becomes most evident when a person exercises at the same absolute load during pretraining and posttraining. ${ }^{99}$ Some resistance training protocols lower resting blood pressure, ${ }^{55,157}$ but aerobic exercise training (not standard resistance training) confers the greater blood pressure lowering benefits for hypertensives. ${ }^{79,80,116}$ As a general guideline, resistance training should not serve as the sole exercise mode to lower blood pressure in hypertensive individuals.

## Diseases of the Myocardium

Recent advances in molecular biology have isolated a possible genetic link to CHD. The gene, termed the atherosclerosis susceptibility (ATHS) gene (http://findarticles.com/ p/articles/mi_m1200/is_n6_v142/ai_12535765; www.ncbi.nlm. nih.gov/entrez/dispomim.cgi?id=108725), appears on chromosome 19 close to the gene that regulates the receptor that removes low-density lipoprotein cholesterol (LDL-C) from the blood. The ATHS gene accounts for nearly $50 \%$ of all cases of CHD in the United States. ${ }^{112}$ It apparently expresses a set of characteristics-abdominal obesity, low levels of high-density lipoprotein cholesterol (HDL-C), and high levels of LDL-C-that triple a person s risk of myocardial infarction (MI), or heart attack.

Symptoms rarely present in the early stages of CHD. As the disease progresses and coronary arteries narrow, clinical symptoms become evident and advance with increasing severity. The first sign of CHD is often slight angina pain accompanied by decreased functional capacity. This eventually leads to ischemia (reduced blood flow) and possible myocardial tissue necrosis. In severe cases, the person experiences persistent chest pain, anxiety, nausea, vomiting, and dyspnea. Chronic, untreated angina weakens the myocardium and eventually produces heart failure as cardiac output fails to meet metabolic demands. Pulmonary congestion (with a persistent cough) often accompanies heart failure. At this stage,
the patient becomes dyspneic even when sitting at rest and can suffer a sudden MI.

CHD pathogenesis progresses in five stages:

1. Injury to the endothelial cell wall of the coronary artery
2. Fibroblastic proliferation of the inner lining (intima) of the artery
3. Further obstruction of blood flow as fat accumulates at the junction of the arterial intima and middle lining
4. Cellular degeneration and subsequent formation of hyalin (a translucent, homogeneous substance produced in degeneration) within the arterial intima
5. Calcium deposition at the edges of hyalinated area

The major disorders caused by reduced myocardial blood supply in CHD include angina pectoris, MI, and congestive heart failure.

## Angina Pectoris

Chest-related pain, called angina pectoris, occurs in approximately $30 \%$ of initial manifestations of CHD. This temporary but painful condition indicates that coronary blood flow (and thus oxygen supply) momentarily reaches inadequate levels. Current theory suggests that metabolites within an ischemic segment of the heart muscle stimulate myocardial pain receptors. The sensation of angina pectoris includes squeezing, burning, and pressing or choking in the chest region, sensations that often mimic the discomforts of benign heartburn (Table 32.12). Anginal pain usually lasts 1 to 3 minutes. Approximately one-third of individuals who experience recurring anginal episodes die suddenly from an MI. Chronic stable angina (often called walk-through angina) occurs at a predictable level of physical exertion. Drugs that promote coronary artery vasodilation and reduce systemic peripheral vascular resistance (e.g., nitroglycerin) commonly treat this condition. Figure 32.7 illustrates the usual pain pattern with an acute episode of angina pectoris. Pain generally appears in the

TABLE 32.12 Comparison of Symptoms of Angina Pectoris and Heartburn

| Angina Pectoris | Heartburn |
| :--- | :--- |
| Gripping, viselike feelings <br> of pain or pressure behind <br> the breast bone | Frequent feeling of heartburn |
| Pain that radiates to the <br> neck, jaw, back, shoulders, <br> or arms (usually left) | Frequent use of antacids to <br> relieve pain |
| Toothache | Heartburn that wakes person <br> up at night |
| Burning indigestion | Acid or bitter taste in mouth <br> Shortness of breath |
| Burning chest sensation <br> Nausea |  |
| Frequent belching | Dood |
|  | Difficulty swallowing |



Figure 32.7 Locations for pain generally associated with angina pectoris.
left shoulder along the arm to the elbow or occasionally in the midback region near the left scapula along the spinal cord.

## Myocardial Infarction

A myocardial infarction (MI) can result from sudden insufficiency in myocardial blood flow, usually from coronary artery occlusion. A prior clot (thrombus) formed from plaque accumulation in one or more coronary vessels (see Chapter 31) can trigger sudden occlusion. Severe fatigue for several days without specific pain frequently precedes the onset of MI. Figure 32.8 shows the varied locations for pain and discomfort that represent early warning of an MI. During the infarction, severe, unrelenting chest pain can persist for more than 1 hour.

## Congestive Heart Failure

In congestive heart failure ( $\mathbf{C H F}$, chronic decompensation or heart failure), the heart fails to pump adequately to meet other organ needs. CHF results from one or all of the following seven factors:

1. Narrowed arteries from CHD that limit myocardial blood supply
2. Past MI with accompanying scar tissue (necrosis) that diminishes myocardial pumping efficiency
3. Chronic hypertension
4. Heart valve disease from past rheumatic fever or other pathology
5. Primary disease of the myocardium, called cardiomyopathy
6. Defects present in the heart at birth (congenital heart disease)
7. Infection of heart valves and/or myocardium (endocarditis or myocarditis)

A failing heart keeps pumping, but inefficiently. Heart failure produces shortness of breath and fatigue upon minimal exertion. As blood flowing from the heart slows, blood returning to the heart through the veins backs up, causing fluid to accumulate in the lungs and edema in legs and ankles. When


Figure 32.8 Anatomic locations for early warning signs of myocardial infarction. Note the diverse locations for pain.
fluid collects in the lungs, it interferes with breathing and causes shortness of breath, especially when lying supine. CHF also affects the kidneys disposal of sodium and water, further accentuating edema.

CHF is the most common cause for hospitalization of persons older than age 65 . It is responsible for more than 800,000 hospital stays, including many repeat visits. Figure 32.9 shows the consequences of CHF when the heart fails to pump adequately. For the most part, CHF patients contract the disease before age 60 and about $20 \%$ of patients die within 1 year of diagnosis, and nearly half die within 5 years.

CHF usually develops slowly as the heart gradually weakens and performs less effectively. Three primary causes of CHF include:

## 1. Chronic hypertension

2. Intrinsic myocardial disease
3. Structural defects (e.g., diseased heart valves)

These three conditions produce an oversized, misshapen heart with inadequate pump performance reflected by a low resting left ventricular ejection fraction (LVEF)a marker of life-threatening heart dysfunction-and failure to increase heart rate with exercise. ${ }^{40,77}$ Associated risk factors include diabetes, alcoholism, and chronic lung diseases such as emphysema. CHF symptoms produce extreme disability, but symptom intensity frequently bears little relation to disease severity. ${ }^{5,118}$ Patients with a low LVEF may not exhibit symptoms, while individuals whose hearts demonstrate normal pump function can experience severe disability. Heart disease and chronic hypertension contribute to disease progression. At the extreme stage, cardiac output from the left and/or right ventricles decreases to an extent that blood accumulates in the abdomen and lungs and sometimes in legs and feet. This stage of CHF produces fatigue, shortness of breath, and eventual flooding of the alveoli with blood, a condition termed pulmonary congestion.


Figure 32.9 Consequences of congestive heart failure (CHF) from impaired pumping ability of either the right or left heart or both. Although the prevalence of and deaths from CHF increase with age, nearly one-third ( 1.4 million) contract the disease before age 60 years. (Sources: National Center for Health Statistics and American Heart Association, 2000.)

Impaired blood flow may also damage other organs, particularly kidneys.

CHF Treatment and Rehabilitation. Before the 1980s, treatment for all stages of CHF advocated rest as the immediate treatment to reduce stress on the compromised cardiovascular system. Until recently, patients routinely received drugs aimed primarily at easing symptoms (e.g., digitalis to increase the heart s pumping function [inotropic effect]). Current recommendations promote a four-drug regimen with two traditional drugs, digitalis and a diuretic (to increase fluid excretion by kidneys), with newer angiotensin-converting enzyme (ACE) inhibitors and $\beta$-blockers.

Surgical treatment replaces damaged heart valves or repairs myocardial aneurysms-bulging areas that form on the myocardial wall. Cardiac transplantation represents the extreme treatment of progressive disability from CHF, although the shortage of donor organs persists. For patients awaiting a transplant, electrically powered pump implants placed in the abdomen below the heart mechanically assist ventricular function.

CHF and Exercise Training. Clinicians have reevaluated the role of regular exercise because many of the functional deteriorations in CHF duplicate those that accompany extreme physical deconditioning. Reduced physical fitness and intrinsic changes in skeletal muscle exacerbate the patient s physical incapacity. ${ }^{52}$ Current therapy advocates regular exercise as an effective adjunct in CHF rehabilitation. ${ }^{58,94,110}$

Clinical practice indicates that regular moderate exercise formulated from a symptom-limited GXT and prescribed medications benefits relatively low-risk, stable, compensated patients. ${ }^{30,104,130,147,160}$ Even intense endurance and resistanceexercise training is efficient in increasing cardiac function, exercise capacity, and peripheral muscle function and quality of life in CHF patients. ${ }^{35}$ These benefits include improvements in functional capacity, exercise tolerance, muscle metabolism, level for dyspnea and ventilatory response to exercise, risk for arrhythmias, quality of life, and shift toward greater dominance of vagal (parasympathetic) tone.

It remains controversial whether the benefits of exercise rehabilitation for CHF link directly to enhanced central circulatory function-either improved myocardial performance
per se or disease reversal reflected by reduced heart size. ${ }^{9,40,58}$ To a large extent, peripheral adaptations with regular exercise enhance function and symptomatic improvements.

The clinician supervises an exercise program (commencing with medical supervision) for compensated patients with controlled fluid volume status and absence of unstable or exercise-induced ventricular arrhythmias. The GXT provides the basis for the exercise prescription. For patients with marked exercise intolerance, relatively brief exercise intervals afford benefits ( 2 to 5 min of light exercise with 1 to 3 min of recovery). The prescription also includes multiple exercise sessions interspersed throughout the day. Because of the usually abnormal heart-rate response in CHF patients, exercising at between 40 and $60 \% \dot{\mathrm{VO}}_{2 \text { peak }}$ provides a more objective standard to establish initial exercise intensity. Alternatively, a rating of perceived exertion (RPE) on the Borg scale of light to somewhat hard (see Fig. 21.19) and/or 2 on the dyspnea scale ( mild, some difficulty; see Fig. 32.18) generally proves effective. Supervisory personnel should recognize the six warning symptoms of cardiac decompensation:

1. Dyspnea
2. Hypotension
3. Cough
4. Angina
5. Lightheadedness
6. Arrhythmias

After the patient begins to increase physical activity, exercise duration can increase to 20 to 40 minutes at least three times weekly. Following 6 to 12 weeks of supervised exercise, patients usually can undertake an unsupervised home exercise program.

## Aneurysm

Aneurysm describes an abnormal dilation in the wall of an artery, vein, or cardiac chamber. Vascular aneurysms develop when a vessel wall weakens from trauma, congenital vascular disease, infection, or atherosclerosis. Aneurysms are either arterial or venous according to their specific regions of origin (e.g., thoracic aneurysm). Most aneurysms develop without symptoms and often are discovered during a routine X-ray. The most common symptoms include chest pain with a specific palpable, pulsating mass in the chest, abdomen, or lower back.

## Heart Valve Diseases

Three medical conditions relate to heart valve abnormalities:

1. Stenosis: Narrowing or constriction that prevents heart valves from opening fully; may result from growths, scars, or abnormal calcified deposits
2. Insufficiency (also called regurgitation): Occurs when a heart valve closes improperly and blood moves back into a heart chamber
3. Prolapse: Occurs when enlarged valve leaflets in the mitral valve bulge backward into the left atrium during ventricular systole

Valvular abnormalities increase the heart s workload, causing it to pump harder to propel blood through a stenosed valve or to maintain cardiac output if blood seeps backward into one of its chambers during diastole. Rheumatic fever, a serious group A streptococcal bacterial infection, scars and deforms heart valves. The most common symptoms include fever and joint pain. Penicillin or other antibiotics treat this inflammatory condition, which typically occurs in children 5 to 15 years old.

## Cardiac Nervous System Diseases

Cardiac diseases that affect the heart s electrical conduction system include the following: dysrhythmias (arrhythmias) that cause the heart to beat too rapidly (tachycardia), too slowly (bradycardia), or with extra contractions (ectopic, extrasystole, or premature ventricular contractions [PVCs]) that possibly lead to fibrillation. Dysrhythmias can produce changes in circulatory dynamics that cause hypotension (extremely low blood pressure), heart failure, and shock. They often occur after a stroke induced by increased physical exertion or other stressful conditions.

Sinus tachycardia describes a resting heart rate above $100 \mathrm{~b} \cdot \mathrm{~min}^{-1}$; bradycardia describes a resting heart rate below $60 \mathrm{~b} \cdot \mathrm{~min}^{-1}$. Sinus bradycardia occurs frequently in endurance athletes and young adults and generally represents a benign dysrhythmia; it may benefit cardiac function by producing a longer ventricular filling time during the cardiac cycle.

## ASSESSING CARDIAC DISEASE

Before initiating an exercise intervention program, the healthcare team decides the extent of health screening. This may include a medical history, physical examination, laboratory assessments, and pertinent physiologic testing.

## Purpose of Health Screening and Risk Stratification

Assessment of specific risk factors and/or symptoms for chronic cardiovascular, pulmonary, and metabolic diseases optimizes safety during exercise testing and program participation. Proper preparticipation screening accomplishes the following:

Identifies and excludes persons with medical contraindications to exercise
Identifies persons who require in-depth medical evaluation because of age, symptoms, and/or risk factors Identifies persons with clinically significant disease who require medical supervision when exercising

Before beginning an exercise program, the ACSM recommends that age, health status, symptoms, and risk factor information classify individuals into one of three risk strata to ensure their safety (see ACSM Risk Stratification inset

## IN A PRACTICAL SENSE

## Par-Q to Assess Readiness for Physical Activity

## ORIGINAL PAR-Q

Common sense is your best guide in answering these questions. Please read each question carefully and check yes or no if it applies to you.

The Physical Activity Readiness Questionnaire (Par-Q) has been recommended as minimal screening for entry into moderateintensity exercise programs. Par-Q was designed to identify the small number of adults for whom physical activity might be inappropriate or those who should receive medical advice concerning the most suitable type of activity.
YES $\qquad$ NO - 1 . Has your doctor ever said that you have heart trouble?
YES __ NO __ 2. Do you frequently have pains in your heart and chest?
YES $\qquad$ _ 3. Do you often feel faint or have spells of severe dizziness?
YES __ NO __ 4. Has a doctor ever said your blood pressure was too high?
YES __ NO __ 5. Has your doctor told you that you have a bone or joint problem that has been aggravated by exercise or might be made worse with exercise?
YES $\qquad$ NO $\qquad$ 6. Is there a good physical reason not mentioned here why you should not follow an activity program even if you wanted to?
YES $\qquad$ NO $\qquad$ 7. Are you over age 65 and not accustomed to vigorous exercise?

## IF YOU ANSWERED YES TO ONE OR MORE QUESTIONS:

If you have not recently done so, consult with your personal physician by telephone or in person BEFORE increasing your physical activity and/or taking a fitness test. Show your doctor a copy of this quiz. After medical evaluation, seek advice from your physician as to your suitability for:

Unrestricted physical activity, probably on a gradually increasing basis
Restricted or supervised activity to meet your specific needs, at least on an initial basis; check in your community for special programs or services

## IF YOU ANSWERED NO TO ALL QUESTIONS:

If you answered no honestly to all Par-Q questions, you have reasonable assurance of your present suitability for:

A graduated exercise programa-gradual increase in proper exercise promotes good fitness development while minimizing or eliminating discomfort
An exercise test simple tests of fitness (such as the Canadian Home Fitness Test) or more complex types may be undertaken if you so desire
Postpone exercisingif you have a temporary minor illness, such as a common cold, postpone any exercise program

## PAR-Q (REVISED 1994)

One limitation of the original Par-Q was that about 20\% of potential exercisers failed the testmany of these exclusions were unnecessary because subsequent evaluations showed that the individuals were apparently healthy. The revised Par-Q (rPar-Q) was developed to reduce the number of unnecessary exclusions (false positives).

The revision can determine the exercise readiness of apparently healthy middle-aged adults with no more than one major risk factor for coronary heart disease.
YES __ NO __ 1. Has your doctor ever said that you have a heart condition and recommended only medically supervised activity?
YES __ NO __ 2. Do you have chest pain brought on by physical activity?
YES __ NO __ 3. Have you developed chest pain in the past month?
YES __ NO __ 4. Do you lose your balance because of dizziness, or do you ever lose consciousness?
YES __ NO ___ 5. Do you have a bone or joint problem that could be worsened by a change in your physical activity?
YES __ NO __ 6. Is your doctor currently prescribing drugs (for example, water pills) for high blood pressure or a heart condition?
YES __ NO __ 7. Do you know of any other reason why you should not do physical activity?
Note: Postpone testing if you have a temporary illness such as a common cold or are not feeling well.

## IF YOU ANSWERED YES TO ONE OR MORE QUESTIONS:

Talk with your doctor by phone or in person before you start becoming much more physically active or before you have a fitness appraisal. Tell your doctor about the rPar-Q and which questions you answered with yes.

You may be able to do any activity you wantas long as you start slowly and build up gradually. Or, you may need to restrict your activities to those that are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his or her advice.
Find out which community programs are safe and helpful for you.

## IF YOU ANSWERED NO TO ALL QUESTIONS:

If you answered no honestly to all rPar-Q questions, you can be reasonably sure that you can:

Start becoming much more physically activebegin slowly and build up gradually; this is the safest and easiest way to go
Take part in a fitness appraisalthis is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.
Delay becoming much more active:
If you are not feeling well because of a temporary cold or feverwait until you feel better, or If you are or may be pregnanttalk to your doctor before you start becoming more active.
Please note: If your health changes so that you then answer yes to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.
From Par-Q and You. Gloucester, Ontario: Canadian Society for Exercise Physiology, 1994.
below). ${ }^{4}$ Proper risk stratification provides a basis to recommend further testing, medical assessment, or diagnostic interventions before exercise participation. In a Practical Sense, page 893, provides the Physical Activity Readiness Questionnaire (Par-Q) commonly used as a minimal firstpass, preparticipation screening tool.

## ACSM Risk Stratification

## Low risk

Men $<45$ years; women $<55$ years, asymptomatic with $\leq 1$ risk factor ${ }^{a, b}$

## Moderate risk

Men $\geq 45$ years; women $\geq 55$ years, or with $\geq 2$ risk factors ${ }^{a, b}$

## High risk

Individuals with $\geq 1$ sign/symptom of cardiovascular or pulmonary disease ${ }^{c}$ or known cardiovascular (cardiac, peripheral vascular, or cerebrovascular), pulmonary (obstructive pulmonary disease, asthma, cystic fibrosis), or metabolic (diabetes, thyroid disorder, renal, or liver) disease.

From Franklin BA, et al. ACSM s guidelines for exercise testing and prescription. 8th ed. Baltimore, Lippincott Williams \& Wilkins, 2008.
${ }^{a}$ Risk factors: family history of heart disease, cigarette smoking, hypertension, hypercholesterolemia, impaired fasting glucose, obesity, sedentary lifestyle.
${ }^{b} \mathrm{HDL} \geq 60 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ (subtract 1 risk factor from the sum of other risk factors because high HDL decreases CHD risk). ${ }^{c}$ Signs/symptoms of cardiovascular and pulmonary disease: pain, discomfort in chest, neck, jaw, left arm; shortness of breath at rest or with mild exertion; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; ankle edema; tachycardia; intermittent claudication; heart murmur; unusual fatigue or shortness of breath with mild activity.

## Patient History

A thorough patient history, including past and current medical problems, documents the most common patient complaints and establishes the CHD risk profile. Most CHD symptoms include chest pain, so the differential diagnosis of this pain is a primary focus. Table 32.13 lists symptoms, possible causes, and related pathology of chest pain. A patient history typically includes the following entries:

Medical diagnosis of diseases<br>Previous physical examination findings to uncover abnormalities<br>Recent illnesses, hospitalizations, or surgical procedures<br>History of significant symptoms<br>Orthopedic problems<br>Medications<br>Work record<br>Family background<br>Psychologic record

## Physical Examination

The physical examination includes vital signs (body temperature, heart rate, breathing rate, and blood pressure) and possible indications of problems. Assessments encompass auscultation of lungs; palpation and inspection of lower extremities for edema; tests of neurologic function (reflexes and cognition); and inspection of the skin, especially of the lower extremities in diabetics. Resting cardiorespiratory variables sometimes provide indirect, noninvasive clues to cardiovascular dysfunction. For example, sinus tachycardia or abnormal bradycardia and increased breathing rate and systolic blood pressure can contraindicate exercise without further evaluation.

The clinical exercise physiologist assesses the patient s heart rate and blood pressure response to graded exercise in

## TABLE 32.13 Diagnosis of Chest Pain

| Pain/Complaint/Findings | Possible Causes | Stimuli | Possible Pathology |
| :--- | :--- | :--- | :--- |
| Pressure, ache, tightness or burning <br> in midsternum, left shoulder, arm; <br> sweating; nausea; vomiting; S-T <br> segment changes | MI | Exertion; cold; smoking; heavy <br> meal; fluid overload | CHD |
| Sharp pain worsens with inspiration, <br> improves with sitting | Inflammation | Acute MI | Pericarditis |
| Chest tightness with breathlessness; <br> low-grade fever | Infection | IV drug use; microbes | Myocarditis; |
| Sharp, stabbing pain; breathlessness; <br> cough; loss of consciousness | Pulmonary | Recent surgery | Pulmonary embolism |
| Burning pain; indigestion relieved by <br> antacids | Referred pain | Heavy meal, spicy food | Esophageal reflux |

order to prescribe exercise and identify potential warning signs. For example, a systolic blood pressure increase of 20 mm Hg or more with low-intensity exercise ( 2 to 4 METs) often reflects abnormal myocardial oxygen demand that often signals some form of cardiovascular impairment. Similarly, failure of systolic blood pressure to increase (hypotensive response) can indicate blunted ventricular function; a depressed response with high-intensity exercise (e.g., failure to achieve systolic blood pressures above 140 mm Hg ) frequently indicates the presence of dormant cardiac disease.

## Heart Auscultation

Listening to heart sounds (auscultation) during the cardiac cycle can assess cardiac performance. The exercise physiologist should become familiar with the different abnormal heart sounds and learn to identify associated murmurs (www.wilkes.med.ucla.edu/intro.html). Auscultation can uncover valvular conditions (e.g., MVP, diagnosed by click-murmur sounds) and congenital heart abnormalities (regurgitation sounds in ventricular septal defects; www.americanheart.org/ presenter.jhtml?identifier=11066).

## Laboratory Tests

Laboratory studies with chest X-ray, electrocardiogram (ECG), blood lipid and lipoprotein analyses, and serum enzyme testing help to assess the extent of CHD.

The chest X-ray reveals the size and shape of the heart and lungs, whereas resting and exercise ECGs assess myocardial electrical conductivity and degree of oxygenation. Clinical exercise physiologists require considerable experience reading and interpreting ECGs. Table 32.14 lists six different categories of ECG measurements and interpretations. Chapter 31 discusses various ECG abnormalities and atypical physiologic responses to exercise. Careful ECG monitoring during a GXT provides more extensive evaluation to target individuals with possible CHD. Table 32.15 presents common ECG changes during exercise and anomalies associated with CHD.

TABLE 32.14 ECG Interpretation Uses One of Six Different Criteria

1. Measurements

Heart rate (atrial and ventricular)
P R interval ( 0.120 .20 s )
QRS duration ( 0.060 .10 s )
Q T interval (HR dependent)
Frontal plane QRS axis (30 90)
2. Rhythm diagnosis
3. Conduction diagnosis
4. Wave form description
$P$ wave (atrial enlargement)
QRS complex (ventricular hypertrophy, infarction)
S T segment (elevated or depressed)
T wave (flattened or inverted)
U wave (prominent or inverted)
5. ECG diagnosis

Within normal limits
Borderline abnormal Abnormal
6. Comparison with previous ECG

From Fardy P, Yanowitz FG. Cardiac rehabilitation, adult fitness and exercise testing. Baltimore: Williams \& Wilkins, 1996.

Alterations in serum enzymes often confirm the existence of an acute MI. With myocardial cell death (necrosis) or prolonged ischemia, the following cardiac muscle enzymes leak into the blood from increased plasma membrane permeability: (1) creatine phosphokinase (CPK), (2) lactate dehydrogenase (LDH), and (3) serum glutamic oxaloacetic transaminase (SGOT). Elevated CPK levels reflect either skeletal or cardiac muscle fiber damage. To pinpoint the source of the enzyme leak, electrophoresis or radioimmunoassay analysis separates CPK into three different isoenzymes: MM-isoenzyme, unique to skeletal muscle; BB-isoenzyme, specific to brain tissue; and MB-isoenzyme, specific for cardiac muscle necrosis. LDH fractionates into different isoenzymes (as does CPK), one of which increases during an MI. An acute MI also raises SGOT. Additional blood tests for

## TABLE 32.15 Normal and Abnormal ECG Changes During Exercise

## Normal ECG Response in Healthy Individuals

## Abnormal ECG Response with CHD

1. Slight increase in P wave amplitude
2. Shortening of $P R$ interval
3. Shift to the right of QRS axis
4. S T segment depression $<1.0 \mathrm{~mm}$
5. Decreased T wave amplitude
6. Single or rare PVCs during exercise and recovery
7. Single or rare PVCs or PACs
8. Appearance of bundle branch block at a critical HR
9. Recurrent or multifocal PVCs during exercise and recovery
10. Ventricular tachycardia
11. Appearance of bradyarrhythmias, tachyarrhythmias
12. S T segment depression/elevation of $\geq 1.0 \mathrm{~mm} 0.08 \mathrm{~s}$ after J point
13. Exercise bradycardia
14. Submaximal exercise tachycardia
15. Increase in frequency or severity of any known arrhythmia

CHD diagnosis include serum homocysteine (see Chapter 31), lipoprotein (a), fibrinogen, tissue-type plasminogen activator (tPA), and C-reactive protein (CRP).

## Invasive Physiologic Tests

Invasive cardiovascular testing provides information unattainable through noninvasive procedures. This includes the extent, severity, and location of coronary atherosclerosis, degree of ventricular dysfunction, and specific cardiac abnormalities.

Radionuclide Studies. Radionuclide studies require injecting a radioactive isotope (e.g., mostly technetium-99) into the circulation during rest and exercise. Two examples include:

1. Thallium imaging: Evaluates areas of myocardial blood flow and tissue perfusion to differentiate between a true-positive and false-positive S T segment depression obtained by ECG evaluation during a GXT
2. Nuclear ventriculography: Radiographic imaging procedure that analyzes regional left ventricular contractility following injection of radioactive isotope contrast material

Pharmacologic Stress Testing. A pharmacologic stress test benefits individuals unable to undergo routine exercise stress testing because of extreme deconditioning, peripheral vascular disease, orthopedic disabilities, neurologic disease, or other health problems. This test involves systematic intravenous drug infusion (e.g., dobutamine, dipyridamole, or adenosine) every 3 minutes until the patient receives the appropriate dosage. Echocardiography and/or thallium scanning then monitor for changes in wall motion abnormalities or coronary perfusion limitations, respectively. Heart rate response, arrhythmias, angina symptoms, S T segment depression, and blood pressure dynamics also reflect myocardial viability during a pharmacologic stress test.

Cardiac Catheterization. A fine tube (catheter) inserted into a vein or artery passes into the heart s right or left side. The intracardiac catheter can sample blood, assess pressure differentials within the heart s chambers or vessels, and add contrast media to evaluate cardiac function.

Coronary Angiography. Radiography images the coronary circulation by injecting a contrast medium (essentially a dye) that flows into the coronary vasculature. The technique, highly effective to evaluate the extent of coronary atherosclerosis, serves as the gold standard to assess coronary blood flow and provides the baseline for other test comparisons. Unlike thallium imaging, angiography cannot determine how easily blood flows within portions of the myocardium and cannot be applied during exercise. The accompanying angiogram (Fig. 32.10) pinpoints impaired blood flow in the carotid artery (shown in red). Resectioning a vessel or removing its atherosclerotic plaques improves blood flow to reduce stroke occurrence.


Figure 32.10 Angiogram showing constriction and absence of blood flow through the right carotid artery (in red). (Courtesy of Dr. Barry Franklin, Beaumont Hospital, Birmingham, MI.)

## Noninvasive Physiologic Tests

Echocardiography. Pulses of reflected ultrasound (echo) assess the functional and structural characteristics of the myocardium. Ultrasound (high-frequency sound waves) identifies the heart s anatomic components during a cardiac cycle and measures their distances from the echo transducers to accurately estimate heart chamber and vessel size and myocardial wall thickness. Echocardiograms diagnose heart murmurs, evaluate valvular lesions, and quantify congenital defects and myopathies. The echocardiogram is preferred to the ECG for recognizing chamber enlargement, inefficient ventricular contractility, myocardial hypertrophy, and other structural abnormalities.

Ultrafast CT Scan. This 10-minute, noninvasive test uses a rapid (ultrafast) electron beam computed tomographic (EBCT) scan to assess calcium deposition within plaque in coronary artery linings. Test results determine how aggressively to treat blood lipid abnormalities (e.g., diet and exercise vs. drug therapy) and other CHD risk factors. Testing to detect coronary calcium deposition with EBCT is highly
sensitive in men and women with coronary disease validated by coronary angiography. ${ }^{53}$ Exclusion of coronary calcium buildup helps to characterize individuals with a low probability of significant stenosis.

Graded Exercise Stress Testing. The graded exercise stress test (GXT) evaluates the cardiac function under conditions that exceed resting requirements in defined, progressive increments to increase myocardial workload. The GXT also objectifies the functional capacity of patients with known disease and evaluates progress following surgery or other therapeutic interventions.

Table 32.16 presents subjective and objective information obtained during a GXT for designing an exercise prescription. The cardiologist and exercise physiologist supervise the exercise test, interpret the data, and prescribe the appropriate exercise intervention.

## Prudent Preexercise Evaluation

For a sedentary person with undetected CHD, a sudden burst of strenuous exercise can inordinately strain cardiovascular function. Medical evaluation before initiating an exercise program

## TABLE 32.16 Data from an Exercise Stress Test to Diagnose and Formulate the Exercise Prescription

## Subjective data

Angina pain
Dyspnea ratings
Fatigue and weakness
Leg discomfort
Dizziness
Rating of perceived exertion (RPE)

## Objective data

Physical examination data
Breathing sounds
Murmurs and gallops
Blood pressure
Pulmonary function tests (before or after exercise)
Heart rate response
Blood gas parameters
Rate-pressure product ( $\mathrm{RPP}=\mathrm{HR} \times$ systolic blood pressure )
Physical performance data
Time on treadmill/cycle ergometer
Maximum work or power output
Electrocardiogram data
S T segment changes
Rate responses
Dysrhythmias
Conduction abnormalities
Cardiorespiratory data
Lactate threshold
Carbon dioxide output
Minute ventilation
Oxygen consumption
Respiratory exchange ratio (R)
reduces this risk considerably. A GXT provides a crucial component of the medical evaluation.

The term GXT generally describes the systematic use of exercise for the following:

1. ECG observations
2. Evaluating patients with exertional discomfort
3. Assessing pharmacologic and therapeutic treatment strategies
4. Evaluating physiologic adjustments to increasing metabolic demands to objectify physical activity recommendations

Multistage bicycle and treadmill tests are the most common exercise stress testing modes. These tests, graded for exercise intensity, usually include several levels of 3 to 5 minutes of submaximal effort that bring the person to a self-imposed fatigue level or end point. The graded nature of testing allows exercise intensity to increase in small increments to pinpoint ischemic manifestations and rhythm disorders (e.g., anginal pain or ECG abnormalities). With heart disease, exercise testing provides a reliable, quantitative index of the person s functional impairment; this objectifies the diagnosis and subsequent exercise prescription. ${ }^{42}$ Testing generally does not require maximal effort, but the person should exercise to at least $85 \%$ of age-predicted maximum heart rate.

Exercise stress testing cannot show the extent of CHD or its specific location. Twenty-five to $40 \%$ of people with relatively advanced CHD (significant blockage in one or more coronary arteries) achieve a normal GXT evaluation. Interestingly, an abnormal heart rate recovery (i.e., failure of heart rate to decrease by more than $12 \mathrm{~b} \cdot \min { }^{1}$ in the first minute after peak exercise) predicts, independent of ECG assessment, subsequent mortality in patients referred specifically for exercise electrocardiography. ${ }^{111}$ This indicates that recovery heart rate provides additional prognostic information to complement interpretation of the exercise stress test.

## Reasons for Stress Testing

Stress testing serves the following six functions in a CHD evaluation:

## 1. Diagnoses overt heart disease and screens for silent coronary disease in seemingly healthy adults.

 Approximately $30 \%$ of persons with confirmed CHD have a normal resting ECG. Graded exercise testing generally uncovers $70 \%$ of the abnormalities.2. Assesses exercise-related chest symptoms. For individuals older than age 40 who suffer chest or related pain in the left shoulder or arm during physical exertion, ECG analysis identifies myocardial abnormalities and more precisely diagnoses exercise-induced pain.
3. Screens candidates for entry into preventive and cardiac rehabilitative exercise programs. Test results provide an objective framework to design a program based on current functional capacity and health status.

Repeat testing assesses progress and adaptations to regular exercise and provides for program modification
4. Uncovers abnormal blood pressure responses. Individuals with normal resting blood pressure sometimes show greater than normal increases in systolic blood pressure during mild-to-moderate exercise, which may signify developing cardiovascular complications.
5. Monitors effectiveness of therapeutic interventions (drug, surgical, dietary) to improve heart disease status and cardiovascular function. A patient s capacity to achieve a target heart rate without complications often confirms success of coronary bypass surgery.
6. Quantifies functional aerobic capacity $\left({V O_{2 p e a k}}\right)$ to evaluate its deviation from normal standards.

## INTEGRATIVE QUESTION

Give recommendations for a middle-aged man who experiences breathlessness and chest discomfort while walking the golf course yet wants to begin an aerobic exercise program.

## Who Requires Stress Testing?

Table 32.17 outlines screening and supervisory procedures for exercise testing that conform to policies and practices of the ACSM and the AMA.

## Informed Consent

All testing and exercise training must be performed on informed volunteers. Informed consent should raise the individual s awareness about all potential participation risks. It must include a written statement that the person had an opportunity to ask questions about the procedures, with sufficient information clearly stated so that consent occurs from a knowledgeable (informed) perspective. A legal guardian or parent must sign the consent form for minors. Individuals need assurance that test results remain confidential and that they can terminate testing or training at any time and for any reason. Table 32.18 presents a sample consent form to obtain before administering a health-related exercise test.

## Stress Testing Contraindications

## Absolute contraindications

A stress test should not take place without direct medical supervision if the following contraindications exist:

Resting ECG suggesting acute cardiac disease
Recent complicated MI
Unstable angina pectoris
Uncontrolled ventricular arrhythmias Uncontrolled atrial arrhythmias that compromise cardiac function
Third-degree AV heart block without pacemaker Acute CHF
Severe aortic stenosis
Active or suspected myocarditis or pericarditis

## TABLE 32.17 ACSM Recommendations for Current Medical Examination and Exercise Stress Testing (GXT) and Physician Supervision of GXT Prior to Participation in Exercise Program

| Risk Category | Medical Examination and GXT | MD Supervision |
| :---: | :---: | :---: |
| Low risk |  |  |
| Men $<45$ years | Moderate exercise; not necessary | Moderate exercise; not necessary |
| $\begin{aligned} & \text { Women }<55 \text { years; asymptomatic } \\ & \text { with } \leq 1 \text { risk factor }{ }^{a, b} \end{aligned}$ | Vigorous exercise; not necessary | Vigorous exercise; not necessary |
| Moderate risk |  |  |
| Men HDL-C $\leq 45 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ | Moderate exercise; not necessary | Moderate exercise; not necessary |
| $\begin{aligned} & \text { Women HDL-C } \leq 55 \mathrm{mg} \cdot \mathrm{dL}^{-1}, \\ & \text { with } \geq 2 \text { risk factors }{ }^{, a b} \end{aligned}$ | Vigorous exercise; recommended | Vigorous exercise; recommended |
| High risk |  |  |
| Individuals with $\geq 1$ sign/symptom of cardiovascular or pulmonary disease ${ }^{c}$ or known cardiovascular (cardiac, peripheral vascular, or cerebrovascular), pulmonary (obstructive pulmonary disease, asthma, cystic fibrosis), or metabolic (diabetes, thyroid disorder, renal or liver) disease | Moderate exercise; recommended <br> Vigorous exercise; recommended | Moderate exercise; recommended <br> Vigorous exercise; recommended |
| Modified from Franklin BA, et al. ACSM s guidelines for exercise testing and prescription. 8th ed. Baltimore: Lippincott Williams \& Wilkins, 2008. ${ }^{a}$ Risk factors: family history of heart disease; cigarette smoking; hypertension; hypercholesterolemia; impaired fasting glucose; obesity; sedentary lifestyle. ${ }^{b} \mathrm{HDL}>60 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ (subtract 1 risk factor from the sum of other risk factors because high HDL decreases CHD risk). <br> ${ }^{\text {c }}$ Signs and symptoms of cardiovascular and pulmonary disease: pain, discomfort in chest, neck, jaw, left arm; shortness of breath at rest or with mild exertion; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; ankle edema; tachycardia; intermittent claudication; heart murmur; unusual fatigue or shortness of breath with mild activity. |  |  |

[^60]
## TABLE 32.18 Sample Informed Consent for a Health-Related Exercise Stress Test

## Patient/Subject Name

1. Explanation of the exercise test

You will perform an exercise test on a cycle ergometer or a motor-driven treadmill. The exercise intensity begins at a level you can easily accomplish and will advance in stages depending on your fitness level. We may stop the test at any time because of signs of fatigue, or you may stop the test when you wish because of feelings of fatigue or discomfort.
2. Risks and discomforts

The possibility exists that certain abnormal physiologic changes can occur during the test. These include abnormal blood pressure, fainting, disorder of heart beat, and in rare instances heart attack, stroke, or death. Every effort will be made to minimize these risks by evaluating preliminary information related to your health and fitness and by observations during testing. Emergency equipment and available trained personnel can deal with unusual situations that may arise.
3. Responsibilities of the participant

Information you possess about your health status or previous experiences of unusual feelings with physical effort may affect the safety and value of your exercise test. Your prompt reporting of how you feel during the exercise test is also important. You are responsible for fully disclosing such information when requested to do so by the testing staff.
4. Expected benefits from the test

The results obtained from the exercise test may assist in diagnosing an illness or evaluating what type of physical activities you might do with low risk of harm.
5. Questions

We encourage you to ask any questions about the procedures used in the exercise test or in the estimation of functional capacity. If you have doubts or questions, please ask us for further explanations.
6. Freedom of consent

Your permission to perform this exercise test is voluntary. You are free to deny consent or stop the test at any point.
I have read this form and all procedures, risks, and potential benefits have been explained. I voluntarily consent to participate in this test.
Date:
Signature of Patient:
Signature of Witness:
Questions:
Responses:
Signature of Physician or Authorized Delegate: Date:

Recent systemic or pulmonary embolism Acute infections
Acute emotional distress

## Relative contraindications

A GXT can be administered with caution and with medical personnel in the test area under the following conditions:

Resting diastolic blood pressure $\leq 115 \mathrm{~mm} \mathrm{Hg}$ or systolic blood pressure $\leq 200 \mathrm{~mm} \mathrm{Hg}$
Moderate valvular disease
Electrolyte abnormalities
Frequent or complex ventricular ectopy
Ventricular aneurysm
Uncontrolled metabolic disease (diabetes, thyrotoxicosis)
Chronic infectious disease (hepatitis, mononucleosis, AIDS)
Neuromuscular or musculoskeletal disorders Pregnancy (complicated or in the last trimester)
Psychologic distress and/or apprehension about participating in the test

## GXT Termination

Graded exercise testing is generally safe when following recognized guidelines and taking proper precautions.

Table 32.19 lists reasons why test termination may be required before the person attains maximum volitional fatigue.

## TABLE 32.19 Criteria for Terminating a Graded Exercise Test by Apparently Healthy Adults

[^61]
## Stress Test Outcomes

The clinical success of the GXT depends on its predictive outcome; this means how effectively the test correctly diagnoses a person with heart disease.

Four possible GXT outcomes include:

1. True positive (successful test): The GXT correctly identifies a person with heart disease.
2. True negative (successful test): The GXT correctly identifies a person without heart disease.
3. False positive (unsuccessful test): The GXT incorrectly identifies a normal person as having heart disease.
4. False negative (unsuccessful test): The GXT incorrectly identifies a person with heart disease as normal.

A test s sensitivity refers to the percentage of persons for whom the test detects an abnormal (positive) response. This represents a true-positive condition that only subsequent follow-up can verify. False-negative results (unsuccessful test) occur $25 \%$ of the time, and false-positive (unsuccessful test) results approximately $15 \%$. Factors that contribute to falsenegative results include the patient s failure to reach an ischemic threshold, failure to recognize non-ECG signs and symptoms associated with underlying CHD, and technical or observer errors. Various drugs and conditions also increase the probability of false-negative results, particularly if the person takes $\beta$-blockers, nitrates, or calcium channel blocking agents.

Test specificity refers to the number of true-negative test results-correctly identifying someone without CHD. More false-positive results occur under the influence of the drug digitalis and hypokalemia (low blood potassium levels), mitral valve prolapse, pericardial disorders, and anemia.

## Stress Testing the Oldest-Old

The stress testing guidelines in Table 32.17 do not apply to individuals 75 years and older, those considered among the oldest-old. ${ }^{56}$ Only a small, highly select subgroup of these individuals participates in vigorous exercise or can successfully complete a stress test. For example, approximately $30 \%$ of persons ages 75 to 79 years can achieve a maximal exercise effort, $25 \%$ of those ages 80 to 84 years, and only $9 \%$ of those 85 years or older. ${ }^{70}$ The oldest-old differ markedly from younger ( $<70 \mathrm{y}$ ) persons in two key areas relative to stress testing: (1) high prevalence of asymptomatic CHD and (2) coexistence of other chronic conditions and physical limitations. Elderly, asymptomatic men and women exhibit increased ECG abnormalities, many of which diminish the diagnostic accuracy of the GXT. The prevalence of asymptomatic ischemic episodes uncovered by the exercise ECG increases dramatically among the elderly with no history of MI or ECG abnormalities. Given the large reservoir of asymptomatic CHD among older persons, routine exercise stress testing would likely initiate a cascade of requirements for follow-up invasive cardiac procedures. ${ }^{154}$ In the absence of strong evidence to support aggressive evaluation in the elderly, this
practice places many at unnecessary risk for complications from invasive assessment. For this reason, empirical screening for the elderly prescribes physical activity based on the person s previous exercise experiences and overall sense of well-being. This approach to exercise testing, training, and safety monitoring observes the widely accepted geriatric dictum start low and go slow.

## Exercise-Induced Indicators of CHD

Physical activity creates the greatest demand for coronary blood flow, thus making exercise testing an effective means of probing for CHD.

## Angina Pectoris

Myocardial ischemia-usually from restricted coronary circulation induced by atherosclerosis-stimulates sensory nerves in the walls of the coronary arteries and myocardium. Pain or discomfort generally manifests in the upper chest region, although it frequently presents as increased pressure or constriction in the left shoulder or arm, neck, or jaw (see Figs. 32.7 and 8). Impaired cardiac performance-reduced stroke volume and cardiac output and generally diminished left ventricular contractility—also accompanies angina. The pain usually subsides after a few minutes of inactivity, without permanent myocardial damage. Physical activity frequently precipitates an angina episode, yet angina also can occur at rest (called Prinzmetals angina or variant angina) with attacks usually occurring in the late evening or nighttime through early morning. Approximately two-thirds of people who have variant angina, caused by a coronary artery spasm, have severe blockage in at least one major coronary vessel. Stable angina indicates predictable chest pain on exertion or under mental or emotional stress.

## Electrocardiographic Abnormalities

Alterations in the heart s normal pattern of electrical activity often indicate insufficient myocardial oxygen supply. Such electrical clues rarely emerge unless myocardial metabolic and blood flow requirements exceed resting conditions.

Figure 32.11A shows a tracing of the dynamic electrical activity of the myocardium throughout the cardiac cycle. Standard ECG paper contains $1-\mathrm{mm}$ and $5-\mathrm{mm}$ squares. Horizontally, each small square represents 0.04 seconds (with normal paper speed of $25 \mathrm{~mm} \cdot \mathrm{~s}^{1}$ ); each large square represents 0.2 seconds. On the vertical axis, a small square indicates a $0.1-\mathrm{mV}$ deflection with a calibration of $10 \mathrm{~mm} \cdot \mathrm{mV}^{1}$. One normal heartbeat (cardiac cycle) consists of five major electrical waves labeled P, Q, R, S, and T. The P wave indicates the electrical impulse (wave of depolarization) before atrial contraction. The $\mathrm{Q}, \mathrm{R}$, and S waves, collectively known as the QRS complex, represent depolarization of the ventricles immediately before their contraction. Ventricular repolarization generates the T wave. The cause of $\mathbf{S} \mathbf{T}$ segment depression (Fig. 32.11B) remains unknown, yet this abnormal deviation


Figure 32.11 A. Normal ECG tracing with an upward-sloping S T segment. B. ECG tracing showing an abnormal horizontal S T segment depression (shaded area) of 2 mm , measured from a stable baseline. C. ECG tracing illustrating a premature ventricular contraction (PVC).
correlates with other CHD indicators that include coronary artery narrowing. Individuals with significant $S T$ segment depression usually have severe, extensive obstruction in one or more coronary arteries. The amount of S T segment depression relates directly to the chances of dying from CHD. Generally, persons with $1-$ to $2-\mathrm{mm} \mathrm{S}$ T segment depression during exercise exhibit a nearly fivefold increase in CHD mortality. The death risk increases approximately 20 -fold for those with more than 2-mm depression. Current opinion advocates including nonspecific ECG findings in the overall heart disease risk assessment. ${ }^{24}$ Even nonspecific minor S T segment
or T-wave abnormalities or both (termed ST T abnormalities) provide a disquieting hint of increased long-term risk of mortality from cardiovascular disease.

During a standard ECG-monitored treadmill test, special electrodes can identify extremely subtle electrical patterns to predict a patient s risk for ventricular fibrillation. The test, termed the alternans test, identifies electrical alternation of the heart. Specifically, it uses a device to analyze T-wave alternans, which represent beat-to-beat electrical fluctuations of just one-millionth of a volt. T-wave alternans reflect abnormalities in the way myocardial cells recover after transmitting
the heart s electrical impulse. Oscillation of the cells impulse can initiate a chain reaction that produces arrhythmias, fibrillation, and subsequent cardiac arrest in some 350,000 individuals in the United States. Predicting risk for sudden death via T-wave alternans gives high-risk patients medical protection that might include an implanted defibrillator (placed beneath the skin of the chest) to automatically correct abnormal cardiac electrical activity. The defibrillator activates a built-in pacemaker to restabilize the heart s rhythm if it detects minor arrhythmias. If that fails, the pacemaker delivers a small defibrillating electrical jolt that resets the rhythm.

## Cardiac Rhythm Abnormalities

Graded exercise testing uncovers abnormalities in the pattern of the heart s electrical activity. A PVC (Fig. 32.11C) during exercise often reflects abnormal alteration in cardiac rhythm or arrhythmia. In this case, the normal depolarization wave through the atrioventricular node does not stimulate the ventricles. Instead, portions of the ventricle spontaneously depolarize. This disorganized electrical activity produces an extra ventricular beat (QRS complex) without the P wave (atrial depolarization) that normally precedes it.

PVCs in exercise generally herald the presence of severe ischemic atherosclerotic heart disease that often involves two or more major coronary vessels. This specific myocardial electrical instability with exercise has greater predictive value than S T segment depression for CHD diagnosis. Patients with exercise-induced PVCs have a 6- to 10 -times greater risk of sudden death from abnormal course or fine rapid movements of the ventricles (ventricular fibrillation) than patients without this instability. Fibrillation risk becomes more prevalent for individuals with family history of this occurrence. With fibrillation, the ventricles do not contract in a unified manner, and cardiac output falls dramatically. Sudden death ensues unless normal ventricular rhythm returns. One way to reduce this risk requires implanting an electrical stimulator to correct the abnormal myocardial electrical conductance pattern.

## Other Exercise-Induced CHD Indicators

Blood pressure and heart rate responses to exercise provide three useful non-ECG indices of possible CHD:

1. Hypertensive exercise response: Normally, systolic blood pressure progressively increases during graded exercise from approximately 120 mm Hg at rest to 160 to 190 mm Hg during peak-intensity exercise. The change in diastolic pressure is generally less than 10 mm Hg . In exercise, systolic blood pressure can rise to well above 200 mm Hg , whereas the diastolic pressure can approach 150 mm Hg . This abnormal hypertensive response provides a significant clue to the presence of cardiovascular disease.
2. Hypotensive exercise response: Inability for blood pressure to increase during graded exercise reflects cardiovascular malfunction. For example, failure of
systolic blood pressure to increase by at least 20 or 30 mm Hg often results from diminished cardiac reserve.
3. Heart rate response: A rapid, large increase in heart rate (tachycardia) early in graded exercise often indicates cardiac dysfunction. Likewise, abnormally low exercise heart rates (bradycardia) in non endurance-trained individuals may reflect unhealthy function of the heart s SA node. Inability of heart rate to increase during graded exercise (chronotropic incompetence), particularly when accompanied by extreme fatigue indicates cardiac strain and CHD. An attenuated maximal exercise heart rate in apparently healthy men and women raises cardiovascular disease mortality risk. ${ }^{83,90}$ Specifically, failure to achieve at least $85 \%$ of age-predicted maximum heart rate during exercise predicts eventual all-cause mortality, independent of any exercise-induced myocardial perfusion defects. ${ }^{91}$

## STRESS TEST PROTOCOLS

A survey conducted in 2000, based on 75,828 exercise tests performed at Veterans Affairs Medical Centers with cardiology divisions, reported that $78 \%$ used the treadmill ( $82 \%$ preferred the Bruce or Modified Bruce protocol). Four major cardiac events occurred ( 3 MIs and one sustained ventricular tachycardia), representing an event rate of 1.2 per 10,000 exercise tests. ${ }^{106}$

## Bruce and Balke Treadmill Tests

Chapter 11 outlines protocols for the Bruce and Balke GXTs. Each test has distinct advantages and disadvantages. For example, the Bruce test provides more abrupt increases in exercise intensity between stages. This may improve sensitivity to detect ischemic ECG responses, but the patient must possess adequate fitness to tolerate increased exercise levels. Both protocols begin at relatively high levels of exercise for cardiac patients and older individuals and thus often require modification. The Bruce protocol incorporates lower initial exercise levels, whereas the Balke test includes a preliminary 2 - to 3 -minute initial stage at 2 mph and $0 \%$ grade.

Choice of a specific exercise test should consider overall health, age, and the person s fitness status. A stress test generally begins at a low level, with increments in exercise intensity every several minutes. A warm-up, either separately or incorporated within the test protocol, eases the patient into exercise. Total exercise duration should average at least 8 minutes. A test much longer than 15 minutes adds little additional information because the most meaningful cardiac and physiologic data emerge within this time interval.

## Bicycle Ergometer Tests

Bicycle ergometers have distinct advantages for exercise stress testing. In contrast to the treadmill, power output on the ergometer is readily computed and remains independent of the person $s$
body mass. Most bicycle ergometers are portable, safe, and relatively inexpensive. Generally, two types of ergometers have application for graded exercise testing: (1) electrically braked ergometers and (2) weight-loaded, friction-type ergometers. With electrically braked ergometers, the preselected power output remains fixed within a range of pedaling frequencies. With weight-loaded ergometers, power output, usually expressed in $\mathrm{kg}-\mathrm{m} \cdot \min ^{1}$ or watts $\left(1 \mathrm{~W}=6.12 \mathrm{~kg}-\mathrm{m} \cdot \mathrm{min}^{1}\right)$, relates directly to frictional resistance and pedaling rate.

The general guidelines for treadmill testing also apply to testing with the bicycle ergometer. Test protocols provide 2- to 4-minute stages of graded exercise with an initial resistance between 0 and 15 or 30 watts; power output generally increases in 15- to 30 -watt increments per stage. The subject usually pedals the weight-loaded ergometer at either 50 or 60 revolutions per minute.

## Arm-Crank Ergometer Tests

Arm cranking has application for graded exercise testing in special situations (e.g., cardiac assessment during upper-body effort) and for disabled individuals. Chapters 15 and 17 point out that arm exercise lowers $\mathrm{VO}_{2 \text { peak }}$ up to $30 \%$, and maximum heart rate generally averages 10 to $15 \mathrm{~b} \cdot \mathrm{~min}{ }^{1}$ lower than with
treadmill or bicycle exercise. Blood pressure is also difficult to measure during arm-crank exercise. Furthermore, submaximal arm cranking produces higher blood pressure, heart rate, and oxygen consumption values than the same power output with leg exercise. Nevertheless, graded exercise protocols similar to those developed for leg cycling tests apply to evaluating a patient s response to upper-body exercise. The initial frictional resistance remains lower in arm exercise, with smaller increments in power output adjusted accordingly.

INTEGRATIVE QUESTION
What type of exercise prescription most benefits a patient with CHD who experiences angina during upper-body work in his job as a plasterer or paperhanger?

## Stress Testing Safety

The safety of stress testing largely depends on knowing who not to test (prescreening health histories reveal noncandidates for testing), knowing when to terminate a test, and preparing for emergencies. Table 32.20 summarizes the results of

TABLE 32.20 Summary Reports of Incidence of Morbidity and/or Mortality During or Following a Graded Exercise Test (1969 1995)

| Study | GXT Tests | Type of <br> Subject | Morbidity Rate <br> (Per 10,000) | Mortality Rate <br> (Per 10,000) | Total Complications ${ }^{\boldsymbol{b}}$ <br> (Per 10,000) |
| :---: | :---: | :--- | :---: | :---: | :---: |
| 1 | $50,000^{a}$ | Variety | 5.2 | 0.4 | 5.6 |
| 2 | 18,707 | Variety | 3.8 | 0.9 | 4.7 |
| 3 |  |  | - | 2.5 | - |
| 4 | $>12,000$ | Variety | 2.1 | 0.3 | 2.4 |
| 5 | 58,047 | Variety | 0.7 | 0.1 | 0.8 |
| 6 | $71,914^{a}$ | Variety | Variety | 3.2 | 0 |
| 7 | 28,133 | 0.3 | 0 | 0.2 |  |
| 8 | 4,050 | Variety | 2.4 | 1.0 | 3.4 |
| 9 | $170,000^{a}$ | Variety | 0 | 0 | 0 |
| 10 | $353,638^{a}$ | Athlete | 1.4 | 0.2 | 1.6 |
|  | $712,285^{a}$ | CHD patients | 8.4 | 0.5 | 8.9 |
| 11 | $518,448^{a}$ | Variety | 232 | 232 |  |

[^62]12 reports about exercise stress testing complications (morbidity and mortality during and after the test) involving 2 million exercise tests with different supervision levels. ${ }^{16,43,77,145}$

Only 16 high-risk but apparently healthy patients suffered coronary episodes in approximately 170,000 submaximal and maximal stress tests. This represents about one person per 10,000 , or approximately $0.01 \%$ of the total group. For more than 9000 stress tests, no cardiovascular episodes occurred for subjects with increased heart disease risk. In other reports, risk of coronary episodes for healthy, middleaged adults during a maximum stress test equaled about 1 in $3000 .{ }^{44}$ Test risk in most middle-aged men and women generally increases to about 6 to 12 times more than for young adults. For patients with documented CHD (including previous myocardial infarction or episodes of angina), risk of cardiovascular incident in stress testing increases 30 to 60 times above normal. Based on total risk analyses, many experts believe that a lower overall risk exists for those who take a GXT and then initiate a regular exercise program than for those who take no GXT and remain sedentary.

Despite differences in testing techniques, purposes, safety precautions, type, and mode of testing, three conclusions about risk during or immediately following a GXT appear warranted:

1. Low risk of death $(\leq 0.01 \%)$
2. Low risk of an acute MI $(\leq 0.04 \%)$
3. Low risk of complications that require hospitalization, including acute MI or serious arrhythmias $(\leq 0.2 \%)$

Clearly, the risk benefit ratio favors GXT testing as part of the medical evaluation process.

## PRESCRIBING PHYSICAL ACTIVITY AND EXERCISE

An exercise prescription should improve fitness, promote overall health by reducing risk factors, and ensure a safe and enjoyable exercise experience. Prescribing physical activity involves successful integration of exercise science with behavioral objectives to enhance patient compliance and goal attainment.

Heart rate and oxygen consumption (or exercise intensity) measured during the stress test provide the basis for the exercise prescription. The prescription individualizes exercise based on current fitness and health status, with emphasis on intensity, frequency, duration, and exercise type.

Initiating a physical activity program at the proper level takes on added importance for CHD patients because beginners do not often recognize their limitations.

## Practical Illustration

Figure 32.12 illustrates a practical approach that permits functional translation of treadmill or bicycle exercise test responses to the exercise prescription. The figure depicts data for a male cardiac patient generated from an algorithm of responses from the Bruce treadmill protocol for level-ground ambulation.

Heart rate (A) was plotted as a function of time, with a mathematical line of best fit $(B)$ applied to the data points. A target zone for heart rate (shaded portion, $C$ ) represented approximately 75 to $85 \%$ of the maximum heart rate of $170 \mathrm{~b} \cdot \min { }^{1}$. The individualized prescription is then detailed for pace (13.8 to $\left.15.4 \mathrm{mi} \cdot \mathrm{min}^{1}, D\right)$ and/or METs ( 4.1 to $5.9, E$ ). The acceptable exercise intensity range in area $C$, based on heart rate response during the exercise test, includes the following recreational activities: aerobics, bicycling, canoeing, light-tomoderate volleyball, skating, skiing, tennis and badminton, swimming, skating, touch football, and waterskiing. This practical approach to prescribing exercise may improve the prescription s effectiveness and adherence for healthy, previously sedentary individuals and CHD patients.

## Improvements in CHD Patients

A properly prescribed and monitored exercise program safely improves a cardiac patient s functional capacity. Clinical symptoms (e.g., ECG abnormalities) often improve or disappear. This occurs partly from structural and functional changes in the myocardium. Cardiac patients and healthy individuals respond to exercise training with physiologic adjustments that reduce cardiac work at any given external exercise load. For example, reduced exercise heart rate and blood pressure (two major determinants of myocardial workload and oxygen consumption) reduce myocardial effort. The reduced rate pressure product ( $\mathrm{HR} \times \mathrm{SBP}$ ) delays the onset of anginal pain and allows exercise of greater intensity and duration. For individuals whose occupations predominantly require arm exercise, training (and testing) should emphasize this musculature because physical conditioning benefits are highly specific and generally not transferable among muscle groups.

## The Program

The Web site http://circ.ahajournals.org/cgi/reprint/ CIRCULATIONAHA.107.185649 provides joint recommendations of the ACSM and AHA for cardiovascular screening of children, adolescents, and adults before enrollment or participation in activities at health/fitness facilities. The recommendations also discuss staff qualifications and emergency policies related to cardiovascular safety.

The most effective preventive and rehabilitative exercise programs focus on individual needs. Low- to moderateintensity exercise regimens evoke greater adherence than intense physical activity. Prescribed exercises usually include rhythmic big-muscle movements that stimulate cardiovascular improvement; examples include walking, jogging, cycling, rope skipping, swimming, stair-climbing and cross-country ski simulation, dynamic calisthenics, and higher intensity interval training, even among the elderly and patients with congestive heart failure. ${ }^{1,102,103}$ On an outpatient basis, less restricted activities such as mountain biking serve as a recreational adjunct to rehabilitate regularly exercising MI patients with stable CHD. ${ }^{72}$

Chapter 21 discussed guidelines for decision making concerning training frequency, duration, and intensity.


Figure 32.12 Exercise prescription based on functional translation algorithm for level-ground ambulation. Letters in figure identified in text. (Used with permission of Dr. Carl Foster, University of Wisconsin-LaCrosse, LaCrosse, WI.)

Ideally, the personalized exercise prescription should include a recommendation for weight loss and dietary modification (if necessary), warm-up and cool-down exercises, and a developmental flexibility and strength program. Some heart disease patients exhibit a reduced exercise heart rate response with correspondingly reduced maximum heart rate. In such cases, target heart rates based on age-predicted maximum for the general, healthy population grossly overestimate the appropriate training intensity. This supports the wisdom of exercise stress testing each patient to symptom-limited maximum and
then formulating the exercise prescription from the test s heart rate data.

## Supervision Level

The ACSM has categorized several types of exercise programs with specific criteria for entry and supervision (Table 32.21). These programs are either unsupervised or supervised, with four subdivisions in the supervised category. Unsupervised programs meet the needs of asymptomatic

## TABLE 32.21 ACSM Categories for Exercise Programs Related to Patient Symptoms

| Type | Participants | Entry MET Level | Supervision |
| :---: | :---: | :---: | :---: |
| A. Unsupervised | Asymptomatic | 8+ | None |
| B. Supervised |  |  |  |
| 1. Inpatient | All symptomatics-post myocardial infarction, postoperative, pulmonary disease | 3 | Supervised ambulatory therapy |
| 2. Outpatient | All symptomatics-post-myocardial infarction, postoperative, pulmonary disease | $3+$ | Exercise specialist, physician on call |
| 3. In home | Symptomatic + asymptomatic | >3 5 | Unsupervised; periodic hospital reevaluation |
| 4. Community | Symptomatic + asymptomatic, 68 weeks postinfarct, 48 weeks postoperative | $>5$ | Exercise program director + exercise specialist |

participants of any age with functional capacities of at least 8 METs and without known major risk factors. The supervised exercise programs focus on patients with specific needs. These include asymptomatic physically active or inactive persons of any age with CHD risk factors but no known disease (B4) and symptomatic individuals, including individuals with recent onset of CHD and those with a changed disease status (B1 to B3).

## Resistance Exercise Provides Benefits

Resistance exercises added to a cardiac rehabilitation program restore muscular strength, promote preservation of FFM, improve psychologic status and quality of life, and increase glucose tolerance and insulin sensitivity. ${ }^{45,99,100}$ Combining resistance training and aerobic training yields more pronounced physiologic adaptations (improved aerobic capacity, muscle strength, and lean body mass) in patients with coronary artery disease than aerobic training alone. ${ }^{98}$ For patients with advanced heart disease, no adverse effects occur while performing weightlifting arm exercise at 50,65 , and $85 \%$ of $1-$ RM. ${ }^{81}$ In comparisons of resting and exercise responses, no changes occurred in pulmonary wedge pressures, S T segment of the ECG, or incidence of dysrhythmias. Contraindications to resistance training for cardiac patients parallel those for aerobic training. ${ }^{124}$ The following six conditions preclude cardiac patients from participating in resistance training:

1. Unstable angina
2. Uncontrolled arrhythmias
3. Left ventricular outflow obstruction (e.g., hypertrophic cardiomyopathy with obstruction)
4. Recent history of CHF without follow-up and treatment
5. Severe valvular disease, hypertension (systolic blood pressure $>160 \mathrm{~mm} \mathrm{Hg}$ and/or diastolic blood pressure $>105 \mathrm{~mm} \mathrm{Hg}$ )
6. Poor left ventricular function and exercise capacity below 5 METs with anginal symptoms or ischemic S T segment depression

Resistance Training Prescription. Cardiac patients should exercise with light resistance (range of 30 to $50 \%$ of

1-RM) because of exaggerated blood pressure responses with straining-type exercise. In the absence of contraindications, elastic bands, light ( 15 lb ) cuff and hand weights, light free weights, and wall pulleys can be applied at entrance to an outpatient program. Do not initiate low-level resistance training until 2 to 3 weeks post-MI. Introduce barbells and/or weight machines after 4 to 6 weeks of convalescence.

Most cardiac patients begin range-of-motion exercises using relatively light weights for the lower and upper extremities. In accordance with AHA recommendations, they should perform one set of 10 to 15 repetitions to moderate fatigue, using 8 to 10 different exercises (e.g., chest press, shoulder press, triceps extension, biceps curl, lat pull-down, lower back extension, abdominal crunch/curl-up, quadriceps extension or leg press, leg curl, calf raise). Exercises performed 2 to 3 days a week produce favorable adaptations. ${ }^{124}$ The RPE should range from 11 to 14 on the Borg scale ( fairly light to somewhat hard ). To minimize dramatic blood pressure fluctuations during lifting, patients should be warned to avoid straining, performing the Valsalva maneuver, and gripping weight handles or bars tightly.

## Cardiac Medications and Exercise Response

Knowledge of the physiologic effects of drug intervention allows the clinical exercise physiologist to properly assess patient response during physical activity. Table 32.22 presents six classifications of common cardiac drugs along with trade names, side effects, and possible effects on exercise responses.

## INTEGRATIVE QUESTION

Why would participating in a weightlifting competition pose a risk to a person with advanced CHD?

## CARDIAC REHABILITATION

A comprehensive cardiac rehabilitation program focuses on improving longevity and quality of life, in addition to risk factor modification. ${ }^{32,115}$ After diagnosis and intervention

TABLE 32.22 Cardiac Medications: Their Use, Side Effects, and Effects on Exercise Response

| Type/Trade Name | Use | Side Effects | Effects on Exercise Response |
| :---: | :---: | :---: | :---: |
| I. Antianginal agents <br> A. Nitroglycerin compounds <br> [Amyl nitrate; Isordil; <br> Nitrostat] | Smooth muscle relaxation; decrease cardiac output | Headache, dizziness, hypotension | Hypotension; increase exercise capacity |
| B. $\beta$-Blockers [Inderal; propranolol; Lopressor; Corgard; Biocadren] | Block $\beta$ receptors; decrease sympathetic tone; decrease HR, myocardial contractility, BP | Bradycardia, heart block, insomnia, weakness, nausea, fatigue, increased cholesterol and blood sugar | Decrease HR; <br> hypotension; decrease cardiac contractility |
| C. Calcium antagonists [Verapamil; nifedipine; Procardia] | Block influx of calcium; dilate coronary arteries; suppress dysrhythmias | Dizziness, syncope, flushing, hypotension, headache, fluid retention | Hypotension |
| II. Antihypertensive agents <br> A. Diuretics <br> [Thiazides, Lasix, <br> Aldactone] | Inhibit $\mathrm{Na}^{+}$and $\mathrm{Cl}^{-}$in kidney; increase excretion of sodium and water, and control high BP and fluid retention | Drowsiness, dehydration, electrolyte imbalance; gout, nausea, pain, hearing loss, elevated cholesterol and lipoproteins | Hypotension |
| B. Vasodilators <br> [Hydralazine, Captopril, Apresoline, Loniten, Minoxidil] | Dilate peripheral blood vessels; used in conjunction with diuretics; decrease BP | Increase HR and contractility; headache, drowsiness, nausea, vomiting, diarrhea |  |
| C. Drugs interfering with sympathetic nervous system [Reserpine, propranolol, Aldomet, Catapres, Minipress] | Decrease BP, HR, and cardiac output by dilating blood vessels | Drowsiness, depression, sexual dysfunction, fatigue, dry mouth, stuffy nose, fever, upset stomach, fluid retention, weight gain | Hypotension |
| III. Digitalis glycosides, derivatives |  |  |  |
| [Digoxin, Lonoxin, digitoxin] | Strengthen heart s pumping force and decrease electrical conduction | Arrhythmias, heart block, altered ECG, fatigue, weakness, headache, nausea, vomiting | Increase exercise capacity; increase myocardial contractility |
| IV. Anticoagulant agents [Coumadin, sodium heparin, aspirin, Persantine] | Prevent blood clot formation | Easy bruising, stomach irritation, joint or abdominal pain, difficulty swallowing, unexplained swelling, uncontrolled bleeding |  |
| V. Antilipidemic agents [Cholestyramine, Lopid, niacin, Atromid-S, Mevacor, Questran, Zocor, Lipitor] | Interfere with lipid metabolism and lower cholesterol and low-density lipoproteins | Nausea, vomiting, diarrhea, constipation, flatulence, abdominal discomfort, glucose intolerance, myalgia, liver dysfunction, muscle fatigue |  |
| VI. Antiarrhythmic agents [Cardioquin, procaine, quinidine, lidocaine, Dilantin, propranolol, bretylium tosylate, verapamil] | Alter conduction patterns throughout the myocardium | Nausea, palpitations, vomiting, rash, insomnia, dizziness, shortness of breath, swollen ankles, coughing up blood, fever, psychosis, impotence | Hypotension; decrease HR; decrease cardiac contractility |

(e.g., aggressive risk factor reduction, bypass surgery, angioplasty), the exercise physiologist evaluates the cardiac patient for functional capacity and ensuing classification and rehabilitation. ${ }^{34}$ Table 32.23 outlines functional and therapeutic classifications of heart disease from the New York Heart Association and guidelines for risk stratification from the AHA (www.americanheart.org) to categorize patients for subsequent rehabilitation. Patients differ greatly
in symptoms, functional capacities, and rehabilitation strategies. The rehabilitation program incorporates stringent guidelines to promote low-risk treatment. ${ }^{38,61,150} \mathrm{CHD}$ patients with mild ischemia tolerate steady-rate exercise at intensities consistent for aerobic training, without progressive deterioration in left ventricular function. For patients without ischemia, left ventricular function in prolonged exercise remains similar to healthy controls. ${ }^{39}$ Five important

TABLE 32.23 A. Functional and Therapeutic Classifications of Heart Disease from the New York Heart Association. B. Guidelines for Risk Stratification from the AHA When Considering an Exercise Program

## A. New York Heart Association

## Functional Capacity Classification

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain
Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain
Class IV: Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest; any physical activity increases discomfort

## Therapeutic Classification

Class A: Physical activity need not be restricted
Class B: Ordinary physical activity need not be restricted, but unusually severe or competitive efforts should be avoided
Class C: Ordinary physical activity should be moderately restricted, and more strenous efforts should be discontinued
Class D: Ordinary physical activity should be markedly restricted
Class E: Patient should be at complete rest and confined to bed or chair
B. American Heart Association
$\left.\begin{array}{lllll}\hline & \begin{array}{l}\text { NYHA } \\ \text { AHA Classification } \\ \text { Class }\end{array} & \begin{array}{c}\text { Exercise } \\ \text { Capacity }\end{array} & \begin{array}{c}\text { Angina/Ischemia and } \\ \text { Clinical Characteristics }\end{array} & \begin{array}{c}\text { ECG } \\ \text { Monitoring }\end{array} \\ \hline \text { A. Apparently healthy } & & \begin{array}{c}\text { Less than } 40 \text { years of age; } \\ \text { without symptoms, no } \\ \text { major risk factors, and } \\ \text { normal GXT }\end{array} & \begin{array}{c}\text { No supervision or monitoring } \\ \text { required }\end{array} \\ \begin{array}{lll}\text { B. Known stable CHD, low risk } \\ \text { for vigorous exercise }\end{array} & \text { I or II } & 56 \mathrm{METs} & \begin{array}{c}\text { Free of ischemia or angina at } \\ \text { rest or on the GXT; EF }= \\ 40 \text { to } 60 \%\end{array} & \begin{array}{c}\text { Monitored and supervised } \\ \text { only during prescribed } \\ \text { sessions (6 12 sessions); } \\ \text { light resistance training may }\end{array} \\ \text { be included in comprehensive } \\ \text { rehabilitation programs }\end{array}\right]$

Adapted from American College of Sports Medicine. Guidelines for exercise testing and prescription. 8th ed. Baltimore: Williams \& Wilkins, 2008. ${ }^{a}$ NYHA, New York Heart Association; EF, ejection fraction; CHD, coronary heart disease; GXT, graded exercise test.
aspects of a successful cardiac rehabilitation program include:

1. Appropriate patient selection
2. Concurrent medical, surgical, and pharmacologic therapies
3. Comprehensive patient education
4. Appropriate exercise prescription
5. Careful patient monitoring during rehabilitation

Traditional cardiac rehabilitation programs consist of three distinct phases with different objectives, physical activities,
and required supervision. More contemporary programs have changed on the basis of new theories of risk stratification, exercise safety data, and changes in the health-care industry. Current programs recognize individual differences in rehabilitation when determining program length, degree of supervision, and required ECG monitoring.

Contemporary cardiac rehabilitation includes inpatient and outpatient programs and services, with emphasis on outcome measures. Almost all postsurgery patients benefit from inpatient exercise intervention, risk factor assessment, lifestyle activity and dietary counseling, and patient and
family education. Patients stay at the hospital an average of 3 to 5 days postsurgery before release.

## Inpatient Programs

Inpatient cardiac rehabilitation focuses on the following four objectives:

1. Medical surveillance
2. Identification of patients with significant impairments before discharge
3. Rapid patient return to daily activities
4. Preparation of patient and family to optimize recovery upon discharge
In-hospital physical activity during the first 48 hours following an MI and/or cardiac surgery is restricted to self-care movements, including arm and leg range of motion and intermittent sitting and standing to maintain cardiovascular reflexes. After several days, patients usually sit and stand without assistance, perform self-care activities, and walk independently up to six times daily, provided none of the following contraindications exist:

> Unstable angina
> Elevated resting blood pressure
> Orthostatic systolic blood pressure above 200 mm Hg with symptoms
> Critical aortic stenosis
> Acute systemic illness or fever
> Uncontrolled atrial or ventricular arrhythmias
> Uncontrolled sinus tachycardia above $120 \mathrm{~b} \cdot \mathrm{~min}^{1}$
> Uncompensated CHF
> Active pericarditis or myocarditis
> Recent embolism or thrombophlebitis
> Resting S T segment displacement of 2 mm or more
> Severe orthopedic conditions

## Outpatient Programs

Upon discharge, the patient should know appropriate and inappropriate physical activities and dietary guidelines and have a prudent and progressive plan of risk reduction with specific exercise prescription. Enrollment in an outpatient exercise program is the ideal. Four goals for outpatient cardiac rehabilitation include:

1. Monitoring and supervising patient to detect changes in clinical status
2. Returning patient to premorbid/vocational/recreational activities
3. Assisting patient to implement at-home, unsupervised exercise program
4. Providing family support and education

Most outpatient program sites encourage multiple physical activities that include resistance exercise and walking, cycling, and swimming. Supervision should include personnel trained in CPR and advanced life support, and in some cases, home defibrilators.

## PULMONARY DISEASES

The clinical exercise physiologist s involvement in treating patients with pulmonary disease focuses on improving ventilatory capacity, decreasing the energy cost of breathing, and increasing overall level of physiologic function. The personal history, physical examination, pertinent laboratory data, and imaging studies provide important background information. Cardiovascular system disorders almost always affect pulmonary function, which eventually leads to varying degrees of pulmonary disability. Conversely, pulmonary disease intimately relates to cardiovascular complications. Patients with pulmonary disease and disabilities often benefit from exercise rehabilitation. Pulmonary abnormalities classify as either obstructive (normal airflow impeded) or restrictive (lung volume dimensions reduced). Despite the convenience of this classification system, pulmonary disorders often reflect both restrictive and obstructive impairment.

## Restrictive Lung Dysfunction

Abnormal reduction in pulmonary ventilation, along with diminished lung expansion, decreased tidal volume, and loss of functioning alveolar capillary units, characterize a large and diverse group of pulmonary disorders collectively termed restrictive lung disease, or RLD.

The genesis of RLD involves pathophysiology of three aspects of pulmonary ventilation:

## 1. Lung compliance

2. Lung volumes and capacities
3. Physiologic work of breathing

In RLD, the chest and lung tissues stiffen and resist expansion under the normal pressure differentials of breathing. The additional resistance to lung expansion requires greater pulmonary force to maintain adequate alveolar ventilation. This increases the energy cost of normal ventilation and accounts for up to $50 \%$ of the total oxygen requirement during physical activity. ${ }^{69}$ Eventually, the progression of RLD negatively affects all lung volumes and capacities. Figure 32.13 provides examples of typical lung volumes in different conditions associated with RLD. Diminished inspiratory and expiratory reserve volumes occur consistently under all conditions.

Table 32.24 lists major RLD conditions, along with their causes, signs and symptoms, and suggested treatments. Known causes of RLD include rheumatoid arthritis, immunologic pathology, massive obesity, diabetes mellitus, trauma from injury, penetrating wounds, radiation, burns, other inhalation injuries, poisoning, and complications from drug therapy (including reactions to antibiotics and antiinflammatory drugs).

## Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), also termed chronic airflow limitations (CAL), comprises several respiratory tract diseases that obstruct airflow (e.g., emphysema, asthma, and chronic bronchitis). The disease destroys lung parenchyma, causing a mismatch between regional alveolar air and blood


Figure 32.13 Values for lung volumes in different conditions that cause restrictive lung disease. ALS, amyotrophic lateral sclerosis.

TABLE 32.24 Restrictive Lung Diseases ${ }^{a}$
Causes/Type
I. Maturational
a. Abnormal fetal lung development
b. Respiratory distress syndrome (hyaline membrane disease)
c. Aging
II. Pulmonary
a. Idiopathic pulmonary fibrosis
b. Coal workers pneumoconiosis
c. Asbestosis
d. Pneumonia
e. Adult respiratory distress syndrome

## Etiology

Premature birth (hypoplasiareduced lung tissue)
Insufficient maturation of lungs due to premature birth

Aging and cumulative effects of pollution, noxious gas, inhaled drug use, and cigarette smoking

Unknown origin (perhaps viral or genetic)

Repeated inhalation of coal dust over 1012 years

Long-term exposure to asbestos

Inflammatory process caused by various bacteria microbes, viruses

Acute lung injury (fat emboli, drowning, druginduced, shock, blood transfusion, pneumonia)

Asymptomatic; pulmonary insufficiency
$\uparrow$ Respiration rate; $\downarrow$ lung volumes; $\downarrow \mathrm{PAO}_{2}$; acidemia; rapid and labored respiration pressure
$\uparrow$ Residual volume; $\downarrow$ vital capacity; repetitive periodic apnea
$\downarrow$ Lung volumes; pulmonary hypertension; dyspnea; cough; weight loss, fatigue
$\downarrow$ TLC, VC, FRC; $\downarrow$ lung compliance; dyspnea; $\downarrow$ $\mathrm{PAO}_{2}$; pulmonary hypertension; cough
$\downarrow$ Lung volumes; abnormal x-ray; $\downarrow \mathrm{PAO}_{2}$; dyspnea on exertion, shortness of breath
$\downarrow$ Lung volumes; abnormal x-ray; tachypneic dyspnea; high fever, chills, cough; pleuritic pain
Abnormal lung function tests; $\mathrm{PAO}_{2}<60 \mathrm{~mm} \mathrm{Hg}$; extreme dyspnea; cyanotic; headache; anxiety

No specific treatment
Treat mother prior to birth (corticosteroids); hyperalimentation; continuous positive airway
No specific treatment; increase physical activity

Corticosteroids; maintain adequate nutrition and ventilation
Nonreversible, no known cure

Nonreversible, no known cure

Drug therapy (antibiotic)

Intubation and mechanical ventilation

## TABLE 32.24 Continued

| Causes/Type | Etiology | Signs and Symptoms | Treatment |
| :---: | :---: | :---: | :---: |
| f. Bronchogenic carcinoma | Tobacco use | Variable, depending on type and location of growth | Surgery, radiation, chemotherapy; specific drainage |
| g. Pleural effusions | Accumulation of fluid within pleural space; heart failure; cirrhosis | Shortness of breath; pleuritic chest pain; $\downarrow \mathrm{PAO}_{2}$ |  |
| III. Cardiovascular <br> a. Pulmonary edema | $\uparrow$ Pulmonary capillary hydrostatic pressure secondary to left ventricular failure | $\uparrow$ Respiration rate; $\downarrow$ lung volumes; $\downarrow \mathrm{PAO}_{2}$; arrhythmias; report feelings of suffocation, shortness of breath, cyanotic, cough | Drug therapy, diuretics; supplemental oxygen |
| b. Pulmonary emboli | Complications of venous thrombosis | $\downarrow$ Lung volumes; $\downarrow \mathrm{PAO}_{2}$; tachycardia; acute dyspnea, shortness of breath; syncope | Heparin therapy; mechanical ventilation |
| IV. Neuromuscular <br> a. Spinal cord injury | Trauma paralysis of respiratory muscle | $\downarrow$ Lung volumes; hypoxemia; fatigue; shortness of breath; inability to cough; $\downarrow$ voice volume | Active and passive chest wall stretching |
| b. Amyotrophic lateral sclerosis | Degenerative disease of nervous system | $\downarrow$ Lung volumes; $\downarrow$ maximum voluntary volume | No treatment except supportive therapy |
| c. Poliomyelitis | Viral infectious disease that attacks motor nerves | Paralysis of diaphragm; shortness of breath | No treatment except supportive therapy |
| d. Guillain-Barr syndrome | Demyelinating disease of motor neurons | Profound muscular weakness; <br> $\downarrow$ lung volumes | Passive range-ofmotion exercises; active exercise |
| e. Neuromuscular diseases (myasthenia gravis, tetanus, muscular dystrophy) | Diseases of neuromuscular system, genetic or other cause resulting in chronic muscular weakness and wasting | Weakness, fatigue, loss of muscle function and strength, paralysis affects pulmonary system with eventual loss of function | Drugs; passive and active exercise; supportive therapy |
| V. Musculoskeletal <br> a. Diaphragmatic paralysis | Loss or impairment of motor function of diaphragm muscle due to specific lesion | $\downarrow$ Lung volumes; dyspnea, shortness of breath | Not needed |
| b. Kyphoscoliosis | Excessive anteroposterior and lateral curvature of thoracic spine (cause unknown) | $\downarrow$ Lung volumes; exertional dyspnea | Use of orthotic devices; active exercise |
| c. Ankylosing spondylitis | Chronic inflammatory disease of spine (inherited) | Exertional dyspnea | No treatment |

${ }^{a_{\text {Www.nlm.nih.gov/medlineplus/; www.cvm.msu.edu/RESEARCH/PULMON/site/respiratory_diseases/diseases/Heaves/mainFrame.html }} \text { (Hent }}$
flow. This ultimately affects the lung s mechanical function to compromise gas exchange (ventilation perfusion ratio) at the alveolar level. A dramatic decrease in exercise tolerance almost always accompanies COPD. The natural history of COPD spans 20 to 50 years and closely parallels a history of chronic cigarette smoking. The Heart, Lung, and Blood Institute (NHLBI; www.nhlbi.nih.gov/) projects that COPD will be the third leading cause of death by the year 2020.

Changes in pulmonary function measures, most notably decreased expiratory flow rate and increased residual lung
volume, usually form the diagnosis of COPD. The classic disease symptoms include spontaneous spasms of bronchial smooth muscle that produce chronic cough, increased mucus production, inflammation and thickening of the mucosal lining of the bronchi and bronchioles, wheezing, and dyspnea upon exertion. Table 32.25 summarizes differences in anatomic location and pathology among major COPD conditions. Factors predisposing to COPD include chronic cigarette smoking (greater effect in women than men; particularly on the increase among college students), ${ }^{131}$ air pollution, occupational

TABLE 32.25 Differences Among Major COPD Diseases
$\begin{array}{lll}\text { Name } & \text { Area Affected } & \text { Result } \\
\hline \text { Bronchitis } & \text { Membrane lining bronchial tubes } & \text { Inflammation of bronchial lining } \\
\text { Bronchiectasis } & \begin{array}{l}\text { Bronchial tubes (bronchi or air passages) } \\
\text { Emphysema } \\
\text { Asthma }\end{array} & \text { Air spaces beyond terminal bronchioles (alveoli) }\end{array} \begin{array}{l}\text { Breakdown of alveolar walls; air spaces enlarged } \\
\text { Bronchial dilation with inflammation } \\
\text { Cystic fibrosis }\end{array}$ Bronchioles (small airways) \(\left.\quad \begin{array}{l}Bronchioles obstructed by muscle spasm; swelling of <br>

mucosa; thick secretions\end{array}\right\}\)| Bronchioles become obstructed and obliterated; |
| :--- |
| plugs of mucus cling to airway walls, leading to |
| bronchitis, atelectasis, pneumonia, or pulmonary |
| abscess |

exposure to irritating dusts or gases, heredity, infection, allergies, aging, and drugs. COPD rarely occurs in nonsmokers. The airways narrow to obstruct pulmonary airflow in all forms of COPD. Airway narrowing hinders ventilation by trapping air in the bronchioles and alveoli; in essence, the disease increases pulmonary physiologic dead space. The obstruction also increases resistance to airflow (chiefly in expiration), hinders normal gas exchange, and reduces exercise performance by increasing the energy cost of breathing. The latter reduces ventilatory capacity to hinder full arterial oxygen saturation and carbon dioxide elimination. Patients with severe COPD exhibit decreased whole-body mechanical efficiency during physical activity. ${ }^{129}$ This suggests that factors associated with the respiratory effort also magnify the energy requirements of wholebody exercise to further negatively impact exercise capacity. Exercise intervention can sometimes reverse peripheral abnormalities associated with COPD. ${ }^{156}$

The following sections focus on four major COPD diseases:

1. Chronic bronchitis
2. Emphysema
3. Cystic fibrosis
4. Asthma and exercise-induced bronchospasm

## Chronic Bronchitis

Acute bronchitis, an inflammation of the trachea and bronchi, usually is self-limiting and of short duration. In contrast, prolonged exposure to nonspecific irritants produces chronic bronchitis. Over time, the swollen mucous membranes and increased mucus production obstruct airways, causing wheezing and chronic coughing. Partial or complete airway blockage from mucus secretion produces inadequate arterial oxygen saturation, diminished carbon dioxide elimination, and pulmonary edema. Eventually, the patient develops the characteristic look of a blue bloater (Fig. 32.14). Chronic bronchitis develops slowly and worsens over time. Patients usually have a history of cigarette smoking for decades. Functional capacity decreases considerably, and fatigue occurs readily with mild exercise. If left untreated, this disease leads to premature death.

## Emphysema

An abnormal, permanent enlargement of air spaces distal to the terminal bronchioles characterizes emphysema. The disease occurs most frequently among chronic cigarette smokers. It develops as a consequence of chronic bronchitis; its symptoms include dyspnea, hypercapnea, persistent cough, cyanosis, and digital clubbing (evidence of chronic hypoxemia; Fig. 32.15). Emphysemic patients consistently demonstrate low exercise capacity and extreme dyspnea with exertion; patients appear thin and often lean forward with arms braced on the knees to support the shoulders and chest to ease breathing. The chronic effects of trapped air and alveolar distension change the size and shape of the chest, causing the characteristic emphysemic barrel chest appearance (Fig. 32.16). Regular exercise does not improve pulmonary function of individuals with emphysema, but it enhances cardiovascular fitness, strengthens both respiratory and nonrespiratory musculature, and improves psychologic status. ${ }^{10}$ In selected patients with severe emphysema, lung-volume reduction surgery has improved pulmonary function, exercise capacity, and quality of life. Its effects on longevity remain uncertain. ${ }^{50}$

## Cystic Fibrosis

The term cystic fibrosis (CF; www.cff.org) originates from the diagnosis of cysts and scar tissue observed on the pancreas during autopsy. Pancreatic cysts and scar tissue often exist but do not reflect the primary characteristics of the disease. Table 32.26 lists clinical signs and symptoms of this inherited and always fatal disease characterized by thickening secretions of all exocrine glands (e.g., pancreatic, pulmonic, gastrointestinal). Glandular secretions ultimately lead to pulmonary obstruction, mainly in lung tissue. CF, the most common inherited disease (both parents must carry the recessive trait) in whites, afflicts approximately 1 in 2000 infants in the United States. Approximately 5\% (12 million) of Americans carry the gene for CF located on chromosome 7, first identified in 1985 by research scientists John R. Riordan, Mayo Clinic Scottsdale, Arizona, and Lap-Chee Tsui, Department of Genetics at the Research Institute of The Hospital for Sick


Figure 32.14 A person with chronic bronchitis usually develops cyanosis and pulmonary edema with the characteristic appearance known as the blue bloater. Insert. Effects of chronic bronchitis: misshapen or large alveolar sacs with reduced surface for oxygen and carbon dioxide exchange.

(A)

©
Figure 32.15 Normal digit configuration (A) and digital clubbing (B). Club fingers and toes indicate chronic tissue hypoxia, a common diagnosis in emphysema.


Figure 32.16 Emphysema traps air in the lungs, making exhalation difficult. With time, changes occur in the physical features of the patient, hence the name pink puffer.

TABLE 32.26 Clinical Signs and Symptoms of Cystic Fibrosis and Related Pulmonary Involvement

Early stage clinical signs and symptoms of cystic fibrosis
Persistent cough and wheezing
Recurrent pneumonia
Excessive appetite but poor weight gain
Salty skin or sweat
Bulky, foul-smelling stools (undigested lipids)
Late stage clinical signs and symptoms of cystic fibrosis with pulmonary involvement

Tachypnea (rapid breathing)
Sustained chronic cough with mucus production on vomiting Barrel chest
Cyanosis and digital clubbing
Exertional dyspnea with decreased exercise capacity
Pneumothorax
Right heart failure secondary to pulmonary hypertension

Children, Toronto. The unnumbered figure below shows the approximate gene location on the Chromosome 7 map.

A positive sweat electrolyte (chloride) test result diagnoses CF. Patients possess a faulty copy of the gene that allows cells to construct a channel for the passage of chloride ions. Consequently, salt accumulates in the cells that line the lungs and digestive tissues, making the surrounding mucus thicker and salty. These mucous secretions, the critical feature of CF , obstruct ducts and passages in the pancreas, liver, and lungs.


CFTR, cystic fibrosis transmembrane conductance regulator. Photo courtesy of NCBI Entrez.

Pulmonary impairment represents the most common and severe manifestation of CF. Airway obstruction leads to chronic lung hyperinflation. Over time, RLD superimposes on the obstructive disease that leads to chronic hypoxia, hypercapnea, and acidosis. These three maladies increase the risk of arterial desaturation during exercise. The disease progresses to pneumothorax and pulmonary hypertension and eventually death.

Treatment of CF includes antibiotics, the FDA-approved mucus-thinning drug Pulmozyme, TOBI (tobramycin) solution for inhalation, high dosages of ibuprofen, enzyme supplements, nutritional intervention, and frequent mucous secretion removal. Assessments of physical capacity of children with CF suggest a positive role for regular physical activity. For example, aerobic fitness correlates inversely with 8 -year mortality. ${ }^{113}$ The anaerobic power of children with CF is lower than healthy counterparts, although CF patients rely more on anaerobic pathways during strenuous exercise. ${ }^{13,14}$ The kinetics of oxygen uptake slow in cystic fibrosis patients. ${ }^{63}$ Increased minute ventilation with aerobic exercise helps to clear airways of excessive secretions. ${ }^{136,161}$ For example, 20 to 30 minutes of aerobic exercise replaces one session of secretion removal for some children. Thus, increasing physical fitness can delay CF s crippling effects. An abnormally high NaCl loss in the sweat increases the likelihood of plasma hypoosmolality with a concomitant reduction in thirst drive. A flavored drink with relatively high salt content (e.g., $50 \mathrm{mmol} \cdot \mathrm{L}^{1}$ ) enhances drinking and reduces exercise dehydration risk in CF patients. ${ }^{87}$

## Pulmonary Assessments

Exercise physiologists do not diagnose pulmonary disease, but understanding the different tests and their results assists in planning and implementing exercise interventions. Pulmonary disease diagnosis involves several different objective measures that include chest imaging, flow and volume tests, blood gas analyses, and cytologic and hematologic evaluations.

## X-Ray

Chest and lung imaging are the most popular pulmonary assessment techniques. These include the conventional X-ray in which roentgen rays (named after German physicist and 1901 Nobel Laureate in physics Wilhelm Konrad R ntgen [1845 1923]) penetrate the body to provide an image of the chest s anatomy on film (radiograph or roentgenogram). This standard diagnostic tool screens for abnormalities, provides a baseline for subsequent assessments, and monitors disease progression. A chest radiograph shows body fat, water, tissue, bone, and air space. The low density of air in the lungs allows greater roentgen ray penetration, which produces a dark image. Relatively dense bone represents the other extreme; it allows fewer roentgen rays to penetrate its tissue, thus producing a white image. The top of Figure 32.17 illustrates a normal chest radiograph taken in the posteroanterior (PA) position. The bottom of the figure shows the same radiograph


Figure 32.17 Chest $X$-ray. The top radiograph shows a normal chest X-ray in the posteroanterior (PA) view. The bottom radiograph shows labeling of the normal anatomic structures. 1, trachea; 2, right mainstem bronchus; 3, left mainstem bronchus; 4, left pulmonary artery; 5, pulmonary vein to the right upper lobe; 6, right interlobular artery; 7, aortic knob; 8 , superior vena cava; 9 , ascending aorta.
with the normal anatomic structures labeled. Abnormal radiographic densities identify specific lung lesions.

## Computed Tomography

Most clinical radiologists consider computed tomography (CT) scanning, invented in 1972, the single greatest advance in radiography of anatomic structures since the discovery of roentgen rays ( 1979 Nobel Prizes were awarded in Physiology or Medicine to Godfrey N. Hounsfield [1919 2004] and Allan M. Cormack [1924 1998]). CT uses a narrow X-ray beam that moves across the body to define adjacent cross-sectional columns of tissue known as a translation. Another pass of the beam progresses at a different angle or
rotation. Repeated translations and rotations in different directions in a given plane with subsequent digitization produce a clear computer-summated image of X-ray transmission data for diagnostic interpretation.

## Other Measures

Chapter 12 discussed static and dynamic lung function tests with simple spirometry. Carefully collected spirometric forced vital capacity (FVC), forced expiratory volume in 1 second ( $\mathrm{FEV}_{1.0}$ ), maximum voluntary ventilation (MVV), peak expiratory flow (PEF), and lung compliance provide crucial diagnostic information. To measure compliance, the patient swallows a balloon catheter. The technician positions the catheter in the lower third of the esophagus and connects it to a manometer to measure esophageal pressure. The relation of lung volume change to any change in pressure within the catheter then establishes the curve for lung compliance.

Other useful functional tests include pulmonary diffusing capacity (DL or DLCO, expressed in $\mathrm{mL} \cdot \mathrm{min}^{1} \cdot \mathrm{~mm} \mathrm{Hg}{ }^{1}$ ), which measures how much gas enters pulmonary blood per unit time per unit pressure differential across the alveolar capillary membrane. Flow-volume loops provide graphic representations of events occurring during forced inspiration and expiration. Recording the flow versus volume in an X Y presentation diagnoses central or peripheral airway obstructions.

Blood gas analyses provide important information to assess problems related to acid base balance, alveolar ventilation, and level of arterial oxygen saturation and carbon dioxide elimination. Cytologic and hematologic tests identify microorganisms that cause pulmonary disease.

## Pulmonary Rehabilitation and Physical Activity Prescription

Pulmonary rehabilitation programs receive considerably less attention than programs for cardiovascular and musculoskeletal diseases. The lack of emphasis on pulmonary rehabilitation stems from a failure of rehabilitation to improve pulmonary function significantly or cure these potentially deadly diseases. Nevertheless, successful pulmonary rehabilitation places central focus on increased physical activity because of its positive impact on exercise capacity, respiratory and nonrespiratory muscle functions, ventilatory equivalents for oxygen, psychologic status, quality-of-life variables (e.g., selfesteem and self-efficacy), frequency of hospitalization, and disease progression. ${ }^{10,20}$ The spiral of progressive physical deconditioning from a sedentary lifestyle (as patients attempt to avoid dyspnea) is not just the direct effect of COPD. ${ }^{126,142}$ Peripheral and respiratory muscle weakness frequently contribute to the COPD patients poor exercise performance and physiologic incapacity. ${ }^{62,141}$ Within this framework, the major goals for pulmonary rehabilitation include:

Improving health status
Improving respiratory symptoms (shortness of breath and cough)

Recognizing early signs that require medical intervention
Decreasing frequency and severity of respiratory problems
Maximizing arterial oxygen saturation and carbon dioxide elimination
Enhancing daily functional capacity through improved muscular strength, joint flexibility, and cardiorespiratory endurance
Modifying body composition to enhance functional capacity
Optimizing nutritional status
The overall pulmonary rehabilitation program emphasizes general patient care, pulmonary respiratory care, exercise and functional training, education about the disease, and psychosocial management. Table 32.27 outlines the important components of an exercise prescription for COPD patients. The training aspects of rehabilitation take on

TABLE 32.27 Components of the COPD Exercise Prescription

## Evaluation

Assess cardiac risk
Assess exercise capacity with Naughton-type protocol (see
Fig. 11.10) using a treadmill or stationary cycle, starting at a
low workload and increasing slowly, and monitoring desaturation with pulse oximeter
Determine appropriate exercise levels to prevent arrhythmias or hypoxia in cardiac-impaired patients
Determine amount of supplemental oxygen needed during exercise
Determine need for bronchodilators during exercise Assess side effects of agonist inhalers or aminophylline derivatives during exercise
Supervised exercise
Direct patient to supervised rehabilitation if disease is significant
Set goal of eventually graduating to independent exercise (many patients can do this in about 6 weeks)

## Independent exercise

Suggest appropriate training mode: stationary cycling,
bicycling, treadmill walking, outdoor walking, stair climbing, or arm ergometry
Set goal of 60 to $80 \%$ of $\mathrm{HR}_{\text {max }}$ for 20 to 30 minutes, 3 days per week (build on individual ability)
Expect 70 to $80 \%$ increase over initial work capacity within 6 weeks
Provide active encouragement and reassurance (especially at first) to overcome anxiety associated with dyspnea

## Exercise aids

Supplemental oxygen
Bronchodilators (adrenergic agonists and/or aminophylline derivatives)
Mucolytics
Corticosteroids (inhaled or oral)
Monitoring

From Mink BD. Exercise and chronic obstructive pulmonary disease: modest fitness gains pay big dividends. Phys Sportsmed 1997;25(11):43.


Figure 32.18 Dyspnea scale. Subjective ratings of dyspnea on a scale of 1 to 4 during graded exercise testing. Dyspnea usually accompanies poor exercise capacity and an impaired systolic blood pressure response.
importance for patients with weakness, fatigue, and severe dyspnea that profoundly limit physical activity. Physiologic monitoring during exercise rehabilitation includes measurement of heart rate, blood pressure, respiratory rate, arterial oxygen saturation by pulse oximetry, and dyspnea. Dyspnea monitoring as a target for exercise training involves a perceived dyspnea scale (Fig. 32.18) similar to the ratings of perceived exertion scale. ${ }^{41,68}$ The dyspnea scale emphasizes symptoms of breathing difficulty rather than perceptions of whole-body physical distress, which the RPE measures. Selfmonitoring exercise intensity in this manner has two inherent advantages because (1) respiratory disease usually impairs exercise pulmonary function rather than cardiovascular response and (2) target heart rate for training healthy individuals usually exceeds the peak heart rate achieved when stress testing pulmonary patients. The most common reasons for stopping exercise include extreme shortness of breath, fatigue, palpitations, chest discomfort, and a 3 to $5 \%$ decrease in pulse oximetry.

The pretraining GXT and spirometric analyses form the basis for the exercise prescription. ${ }^{25}$ Interpretation of the exercise stress test includes determining the following:

1. Whether the test terminated because of cardiovascular or ventilatory end points
2. The difference between pre- and postexercise pulmonary function (e.g., a decrease of $10 \%$ in $\mathrm{FEV}_{1.0}$ indicates the need for bronchodilator therapy before exercise)
3. Need for supplemental oxygen during exercise (e.g., a pre- to posttest decrease in $\mathrm{PaO}_{2}$ of more than 20 mm Hg or a $\mathrm{PaO}_{2}$ below 55 mm Hg )

Exercise prescription (cycling, walking, treadmill exercise, and stair climbing) for patients with mild lung disease-shortness of breath with intense exercise-remains similar to requirements for healthy subjects. Exercise for patients with moderate lung disease-shortness of breath with normal daily activities or clinical symptoms of RLD or COPD-typically achieves an intensity no greater than $75 \%$ of the ventilatory reserve, or the point where the patient becomes noticeably dyspneic. For most patients, this exercise intensity usually falls in the middle of the calculated training heart rate range- 50 to $70 \%$ of age-predicted maximum with a goal of 60 to $80 \%$ of maximum-and corresponds to 40 to $85 \%$ of maximum MET level on the GXT. In this case, exercise duration averages 20 minutes, 3 times weekly. If the patient can exercise only for a shorter duration (e.g., 5 to 15 min per session), exercise frequency can increase to 5 to 7 days weekly.

Patients with severe lung disease-shortness of breath during most daily activities and FVC and $\mathrm{FEV}_{1.0}$ below $55 \%$ of predicted values-require a modified approach to exercise testing and prescription. Low-level, discontinuous testing usually begins at 2 to 3 METs with increments every 2 to 3 minutes. Exercise prescription relies on symptom-limited walking speeds and distances. Brief bouts of interval exercise also provide an option. The low level of the initial training prescription means that patients should exercise a minimum of once daily. Even small gains in exercise tolerance add to improving daily function and quality of life.

General exercise and specific expiratory muscle training effectively improve respiratory muscle function and reduce sensations of respiratory effort during exercise in nearly all patients with pulmonary disease. ${ }^{19,89,146}$ Two approaches achieve this goal:

1. Resistance training of the ventilatory musculature with a continuous positive airway pressure (CPAP) device; this specifically overloads the respiratory muscles similarly to progressive resistance exercise for nonrespiratory skeletal muscles
2. Increasing respiratory muscle force and endurance capacity through regular aerobic exercise training

INTEGRATIVE QUESTION
Why might regular exercise prove more effective for coronary heart disease patients than patients with pulmonary disease?

## Pulmonary Medications

Pulmonary medications include bronchodilators, antiinflammatory agents, decongestants, antihistamines, mucokinetic agents, respiratory stimulants, depressants, and paralyzing and antimicrobial agents. The drugs promote bronchodilation, facilitate removal of lung secretions, improve alveolar ventilation and arterial oxygenation, and optimize breathing patterns. Table 32.28 lists the most commonly administered pulmonary drugs.

## EXERCISE AND ASTHMA

## Asthma Statistics

The latest available statistics indicate that asthma has increased in severity and scope (www.aaaai.org/media/ resources/media_kit/asthma_statistics.stm). Hyperirritability of the pulmonary airways followed by bronchial spasm,

## TABLE 32.28 Major Pulmonary Bronchodilator Drugs: Their Uses and Side Effects

| Drug/Name | Action and Clinical Uses | Side Effects |
| :---: | :---: | :---: |
| Sympathomimetics Isoproterenol, ephedrine, Bronkosol, Alupent, Brethine, Proventil, Ventolin (Albuterol inhaler) | Decrease intracellular calcium; smooth muscle relaxation; bronchodilation | Tachycardia, palpitations, GI distress, nervousness, headache, dizzines |
| Methylxanthines Amnodur, Elixophyllin, Theo-dur, Choladril | Increase cAMP; block cAMP decrease | Agitation, hypotension, chest pain, nausea, tachycardia, palpitations, GI distress, nervousness, headache, dizziness |
| $\boldsymbol{\alpha}$-Sympatholytics | Block cAMP decrease; bronchodilation | Agitation, hypotension, chest pain, nausea, tachycardia, palpitations, GI distress, nervousness, headache, dizziness |
| Parasympatholytics Atrovent, atropine sulfate | Block parasympathetic stimulation and prevents increases in cGMP; prevents bronchoconstriction | Central nervous system stimulation with low doses and depression with high doses; delirium, hallucinations, decreased GI activity |
| Glucocorticoids <br> Prednisone, Cortisol, Azmacort, Vanceril | Decrease inflammatory response; bronchodilation | Obesity, growth suppression, hyperglycemia and diabetes, mood changes, irritability or depression, thinning of skin, muscle wasting |
| Cromolyn sodium Intal, Fivent | Prevents influx of calcium ions, thus blocking mast cell release of mediators responsible for bronchoconstriction; bronchodilation | Throat irritation, hoarseness, dry mouth, cough, chest tightness, bronchospasm |



Figure $32.19 \quad$ A. Typical response to an asthma attack. B. Pattern of dynamic lung function ( $\mathrm{FEV}_{1.0} / \mathrm{FVC}$ ) during an episode of exercise-induced bronchospasm. C. Interaction between exercise intensity (walking, jogging, running) and environmental characteristics. Note that maximal obstruction occurs when inhaling dry air at low temperature (e.g., winter) and minimal obstruction occurs when breathing warm, humid air (e.g., summer). (C. modified from McFadden ER Jr, Gilbert IA. Exercise-induced asthma. N Engl J Med 1994;330:1362.)
edema, and mucus secretion characterize this obstructive pulmonary disease (Fig. 32.19). Common asthma symptoms include chest tightness, coughing, wheezing, and/or shortness of breath.

A high level of physical fitness does not confer immunity from asthma. ${ }^{36,93,114,120,151}$ The recreational road runner is more likely to report symptoms of allergy and/or asthma but less likely to have prescription medication than the Olympic athlete. ${ }^{127}$ U.S.
women s basketball player Tamika Catchings, an asthma sufferer, won a gold medal in the 2004 Olympic games, and $21 \%$ of British athletes in these games were confirmed asthmatics. Studies of Finnish elite track and field athletes report physician-diagnosed asthma in $17 \%$ of long-distance runners, $8 \%$ of power athletes, and $3 \%$ of nonathletic controls, while $35 \%$ of figure skaters showed a significant increase in airway resistance following skating routines. ${ }^{64,95}$

For nearly $90 \%$ of persons with asthma and 30 to $50 \%$ of those suffering from allergic rhinitis and hay fever, exercise provides a potent stimulus for bronchoconstriction termed exercise-induced bronchospasm. Reduced vagal tone and increased catecholamine release from the sympathetic nervous system during exercise normally relax pulmonary airway smooth muscle. ${ }^{8}$ Figure 32.19A shows that initial bronchodilation with exercise occurs in healthy persons and asthmatics. For the asthmatic, bronchospasm accompanied by excessive mucus secretion follow initial bronchodilation. An acute episode of airway obstruction often occurs within 5 to 15 minutes postexercise (Fig. 32.19B); recovery usually occurs spontaneously within 30 to 90 minutes. One useful technique to detect an exercise-induced asthmatic response applies progressive exercise increments. A spirometric evaluation of FVC and $\mathrm{FEV}_{1.0}$ takes place after each exercise period and during 10 to 20 minutes of recovery. A 10 to $15 \%$ reduction in preexercise $F E V_{1.0} / F V C$ confirms the diagnosis of exerciseinduced bronchospasm. ${ }^{67,88,101}$ For elite athletes who perform in cold-weather sports (e.g., biathlon, canoeing/kayaking, cross-country skiing, ice hockey, Nordic combined, and speed skating), combining pulmonary function testing with nearmaximal sport-specific exercise testing, preferably in a cold, dry environment, provides greater sensitivity for screening than laboratory-based (warm air environment) challenges or self-reported symptoms. ${ }^{69,133,134}$

## Sensitivity to Thermal Gradients and Fluid Loss

Several mechanisms help to explain bronchospastic responses to exercise. An attractive theory relates to how ventilation in exercise and recovery alters the rate and magnitude of heat and water exchange in the tracheobronchial tree. As the incoming breath of air moves down the respiratory tract, heat and water move away from the airway lining as the air warms and humidifies. The conditioning of inspired air ultimately cools and dries the respiratory mucosa. Drying increases mucosal lining osmolality, with accompanying mast cell degranulation. This in turn releases powerful proinflammatory mediators that trigger bronchoconstriction (e.g., leukotrienes, histamine, and prostaglandins). Rewarming the airways following exercise dilates the bronchial microcirculation to increase blood flow. Bronchial vasculature engorgement precipitates edema that constricts the airway, independent of any constrictive action of bronchial smooth muscle. Bronchial cooling during exercise and rewarming in recovery also stimulate chemical mediator release that induces bronchoconstriction.

Regardless of the precise mechanism, the large volume of incompletely conditioned inspired air taxes the tracheobronchial tree s smaller airways, causing mucosal temperature to decrease. Heat loss from the airways during exercise relates directly to the degree of bronchoconstriction. In susceptible individuals, the thermal gradient generated by the combination of airway cooling during exercise and subsequent rewarming in recovery intensifies bronchospastic processes.

## Environmental Impact

Figure 32.19 C shows that a warm humid (summer) environment suppresses the magnitude of exercise-induced bronchospasm regardless of air temperature. Inhaling ambient air fully saturated with water vapor often abolishes an asthmatic s bronchospastic exercise response. This explains why persons with asthma tolerate walking or jogging on a warm, humid day or swimming in an indoor pool, in contrast to outdoor winter sports that typically trigger an asthmatic attack. ${ }^{74,137}$

## Benefits of Warm-Up and Medication

Fifteen to 30 minutes of a light-to-moderate, continuous warm-up or repeat several-minute warm-up intervals initiate a refractory period where subsequent intense exercise does not trigger as severe a bronchoconstrictive response. ${ }^{8,11,128}$ The warm-up benefit continues for up to 2 hours, perhaps from prostaglandin release. Prolonging the cool-down period also reduces the severity of postexercise bronchoconstriction; this could occur by slowing airway rewarming and subsequent bronchiole vascular dilation and edema.

Effective preexercise medications limit bronchoconstriction for those desiring to exercise regularly without adversely affecting exercise performance. Medications include (1) bronchodilators such as theophylline or the leukotriene-receptor antagonist montelukast or $\beta_{2}$-agonists (salmeterol) and (2) inhaled heparin therapy or antiinflammatory corticosteroids or cromolyn sodium. ${ }^{15,29,108}$

Exercise training does not eliminate or cure an asthmatic condition; instead, it increases pulmonary airflow reserve and reduces ventilatory work by potentiating exercise bronchodilation. This lets asthmatics maintain higher airflow and sustain relatively intense exercise despite impaired pulmonary function. For asthmatic children, aerobic exercise training (swimming and cycle ergometry) improves $\dot{\mathrm{V}} \mathrm{O}_{2 \max }$ and suppresses asthmatic symptoms.

## NEUROMUSCULAR DISEASES, DISABILITIES, AND DISORDERS

Neuromuscular diseases and disabilities affect the brain in specific ways. Progressive degeneration or trauma to specific brain neurons induces distinct impairment that ranges from simple to complex.

## Stroke

Stroke refers to a potentially fatal reduction in the brain s blood flow from restricted blood flow (ischemia) or bleeding (hemorrhage). The resulting brain injury affects multiple systems depending on injury site and amount of damage sustained. Effects include motor and sensory impairment and language, perception, and affective and cognitive dysfunction. Strokes cause severe limitations in mobility and cognition or can be less severe with short-term, nonpermanent consequences (www. strokeassociation.org/presenter.jhtml?identifier=1200037).

## Clinical Features

Clinical features of stroke depend on location and severity of injury. Signs of a hemorrhagic stroke include altered levels of consciousness, severe headache, and elevated blood pressure. Cerebellar hemorrhage usually occurs unilaterally and associates with disequilibrium, nausea, and vomiting. Table 32.29 presents the typical physical and psychologic conditions and comorbidities associated with a stroke.

Cerebral blood flow (CBF) represents the primary marker to assess ischemic strokes. When CBF drops below $10 \mathrm{~mL} \cdot 100 \mathrm{~g} \cdot \min ^{1}$ of brain tissue (normal CBF $=5055$ $\mathrm{mL} \cdot 100 \mathrm{~g} \cdot \min { }^{1}$ ), synaptic transmission failure occurs; cell death results at a CBF of $\leq 8 \mathrm{~mL} \cdot 100 \mathrm{~g} \cdot \mathrm{~min}{ }^{1}$.

Stroke produces physical and cognitive damage. Lefthemisphere lesions typically associate with expressive and receptive language deficits compared with right-hemisphere lesions. Motor impairment from a stroke usually triggers hemiplegia (paralysis) or hemiparesis (weakness). Damage to descending neural pathways produces abnormal regulation of spinal motor neurons. This adversely changes postural and stretch reflexes and produces difficulty with voluntary movement. Deficits in motor control involve muscle weakness, abnormal synergistic organization of movement, impaired regulation of force, decreased reaction times, abnormal muscle tone, and loss of active range of joint motion.

## Exercise Prescription

The emphasis for stroke survivors centers on rehabilitation of movement (passive and active-assisted flexibility and muscle strength) during the first 6 months of recovery. The few exercise training studies with stroke patients support exercise to improve mobility and functional independence and

TABLE 32.29 Physical and Psychologic Conditions and Comorbidities in Stroke Patients

| Physical <br> Conditions | Psychologic <br> Conditions | Comorbidities |
| :--- | :--- | :--- |
| Aphasia | Cognitive impairment | Coronary heart |
| Balance | Emotional instability | disease |
| problems | Cognitive impairment | Diabetes mellitus |
| Falls | Depression | Hypertension |
| Fatigue | Memory loss | Hyperlipidemia |
| Muscle | Low self esteem | Obesity |
| $\quad$ weakness | Social isolation | Peripheral |
| Obesity |  | vascular |
| Paralysis |  | disease |
| Paresis |  |  |
| Spasticity |  |  |
| Visual |  |  |
| impairments |  |  |
|  |  |  |

prevent or reduce further disease and functional impairment. ${ }^{7,92,153}$

Stroke survivors vary widely in age, degree of disability, motivational level, and number and severity of comorbidities, secondary conditions, and associated circumstances. The specific exercise prescription focuses on reducing these conditions and improving functional capacity.

## Multiple Sclerosis

Multiple sclerosis (MS) represents a chronic, often disabling disease characterized by destruction of the myelin sheath (demyelination) that surrounds CNS nerve fibers. Lesions of inflammatory demyelination can be present in any part of the brain and spinal cord.

## Clinical Features

Two or more areas of demyelination confirm the diagnosis of MS. This disease usually develops between ages 20 and 40. Frequently a history emerges of transient neurologic deficits that include extremity numbness, weakness, blurred vision, and diplopia (double vision) in childhood or adolescence prior to more persistent neurologic deficits that lead to the definitive diagnosis. Fatigue is the most common symptom of MS. MS occurs worldwide at a higher frequency in latitudes further from the equator (40 ). For unknown reasons, MS prevalence in the United States below the 37th parallel is 57 to 78 cases per 100,000, whereas the prevalence rate above the 37th parallel averages 140 cases per 100,000. Patients with a definite MS diagnosis often have a variety of other autoimmune illnesses such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and myasthenia gravis. A first-degree relative with MS has a 12- to 20-fold increased chance of developing MS.

## Exercise Prescription

MS patients benefit from a comprehensive health prescription that involves aerobic, strength, balance, coordination, and flexibility exercises. About $80 \%$ of MS patients report adverse effects to heat exposure. This occurs whether generated environmentally by outside climatic changes or internally via fever or exercise-induced thermogenesis. This effect makes continuous exercise training difficult and not well tolerated. Nevertheless, MS patients still can improve cardiovascular function. Stationary cycling, walking, and low-impact chair or water aerobics provide excellent training choices depending on personal interest and level and nature of physical impairment. Ideal exercise consists of walking in a climate-controlled area that provides stable temperatures, a level surface, and opportunity to rest frequently. Controlling body temperature is a primary consideration in the exercise prescription. A realistic and achievable goal for structured exercise provides training three times a week for a minimum of 30 minutes each session divided into three 10 -minute periods.

## Parkinsons Disease

Parkinsons disease (PD) belongs to a group of conditions called motor system disorders, that are the result of the loss of dopamine-producing brain cells (www.parkinson.org).

## Clinical Features

Clinical symptoms of PD include (1) varying degrees of tremor, (2) decrease in spontaneity and movement (bradykinesia), (3) rigidity, and (4) impaired postural reflexes. These conditions produce extreme gait and postural instability that increases falling episodes and difficulty walking. Some patients exhibit a complete lack of movement (akinesia). Functional problems hinder getting out of bed or a car and rising from a chair. Other problems include difficulties dressing, writing, talking, and swallowing. A person with PD generally experiences difficulty with more than one task at a time. As the disease progresses, these problems become more pronounced, and the person eventually loses ability to perform activities of daily living. In the last stage of the disease, the person becomes wheelchair and/or bed bound.

## Exercise Prescription

Most exercise prescriptions for PD patients are individualized and directed toward interventions that affect associated motor control problems. They emphasize slow, controlled movements for specific tasks through various ranges of motion while lying, sitting, standing, and walking. Treatment protocols include range-of-motion exercises that emphasize slow static stretches for all major muscle joint areas, balance and gait training, mobility, and/or coordination exercises.

## RENAL DISEASE

Treatment modalities for the major metabolic diseases of obesity, diabetes, and renal dysfunction use regular exercise as adjunctive therapy. Diabetes and obesity are discussed in Chapters 20 and 30, respectively, of this text. This section reviews aspects of renal disease related to exercise physiology.

Chronic renal disease occurs when kidneys no longer adequately carry out their filtering functions. Acute renal failure occurs from a toxin (e.g., drug allergy or poison) or severe blood loss or trauma. Diabetes is the primary cause of kidney disease, responsible for about $40 \%$ of all kidney failures; hypertension is the second cause, responsible for about $25 \%$. Genetic diseases, autoimmune diseases, and birth defects most commonly cause kidney ailments.

## Clinical Features

Common symptoms of chronic kidney disease, sometimes referred to as uremia (retention in the blood of waste
products normally excreted in urine), include the following characteristics:

Changes in urination: These include making more or less urine than usual, feeling pressure when urinating, changes in the color of urine, foamy or bubbly urine, or having to get up frequently at night to urinate. Swelling of the feet, ankles, hands, or face: Fluid the kidneys are unable to remove stays in the tissues.
Fatigue or weakness: Build-up of wastes or a shortage of red blood cells (anemia) causes these problems as the kidneys begin to fail.
Shortness of breath: Kidney failure is sometimes confused with asthma or heart failure because fluid builds up in the lungs.
Ammonia breath or an ammonia or metal taste in the mouth: Waste build-up causes bad breath, changes in taste, or an aversion to protein foods such as meat.
Back or flank pain: The kidneys are located on either side of the spine in the back.
Itching: Waste accumulation causes severe itching, especially of the legs.
Loss of appetite
Nausea and vomiting
Increased hypoglycemic episodes, if diabetic
Chronic uremia eventually progresses to end-stage renal disease (ESRD) that requires life-long dialysis or kidney transplant. The number of renal transplants has increased steadily worldwide in the last decade and generally offers a more normal lifestyle and full rehabilitation. Nearly $80 \%$ of transplant patients function at near normal levels compared with 40 to $60 \%$ of those treated with dialysis. Almost $75 \%$ of transplant patients resume work compared with 50 to $60 \%$ of patients who receive dialysis.

## Exercise Prescription

Regular exercise is important in rehabilitating dialysis and transplant patients to better adapt to their illness. The rehabilitation program should begin prior to the start of dialysis to optimize beneficial effects. Normal low-level endurance training (following ACSM guidelines) reduces muscle protein degradation in moderate renal insufficiency, reduces resting blood pressure in some hemodialysis patients, and modestly improves aerobic capacity in patients who undergo hemodialysis.

No longitudinal data exist about aerobic training effects or more physically active lifestyle on patient survival with chronic uremia or kidney transplants. Uremic patients who maintain diverse physical activity report enhanced quality of life. Despite lack of quantitative, long-term quality of life and survival data, 30 years have passed since initiation of the first U.S. Transplant Games in 1990 (www.kidney.org/recips/ athletics/tgames/index.cfm). Participants in these games, open to recipients of a currently functioning solid organ or tissue transplant, train daily and perform at near world record levels.

## COGNITIVE/EMOTIONAL DISEASES AND DISORDERS

The National Institutes of Mental Health (www.nimh.nih .gov/) estimates that about $26 \%$ of Americans ages 18 and older-about 1 in 4 adults-suffer from a diagnosable mental disorder in a given year. In addition, 4 of the 10 leading causes of disability in the United States and other developed countries are mental disorders-major depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Suicide, closely linked to depression, represents the third leading cause of death among 10- to 24-year-olds. Also, 6 to $8 \%$ of all outpatients in primary care settings suffer major depression. Despite the large numbers of depressed patients, mental disorders remain underdiagnosed; only about onethird of those diagnosed receive treatment.

The five major classifications of cognitive/emotional diseases include:

1. Major depressive disorder-commonly referred to as depression
2. Dysthymia-mildly depressed on most days over a period of at least 2 years
3. Seasonal affective disorder-recurrence of the depressive symptoms during certain seasons (e.g., winter)
4. Postpartum depression-in women who have recently given birth; typically occurs in the first few months after delivery, but can happen within the first year after giving birth
5. Bipolar disorder (previously known as manicdepressive illness)—characterized by extremes in mood and behavior that last for at least 2 weeks

## Clinical Features

Depression has no single cause but often results from a combination of factors or events. Whatever its cause, depression is not just a state of mind. Depression relates to physical changes in the brain and a chemical imbalance of neurotransmitters.

Women are almost twice as likely to become depressed as men, partly because of hormonal changes from puberty, menstruation, menopause, and pregnancy. Although the risk for depression is lower, men more likely go undiagnosed and are less likely to seek help. Men may show the typical symptoms of depression but tend to be angry and hostile or mask their condition with alcohol or drug abuse. Suicide remains a serious risk for depressed men, who are four times more likely than women to kill themselves. Depression among the elderly poses a unique situation. Older persons often lose loved ones and have to adjust to living alone. Physical illness depresses normal levels of physical activity. Such changes all contribute to depression. Loved ones may attribute signs of depression to normal aging, and many older persons are reluctant to talk about their symptoms. As such, older persons may not receive proper treatment for depression. Table 32.30 presents common signs and symptoms of depression.

## TABLE 32.30 Common Signs and

 Symptoms of DepressionLoss of enjoyment from things that were once pleasurable Loss of energy
Feelings of hopelessness or worthlessness
Difficulty concentrating
Difficulty making decisions
Insomnia or excessive sleep
Stomachache and digestive problems
Decreased sex drive
Aches and pains (e.g., recurrent headaches)
Change in appetite causing weight loss or gain
Thoughts of death or suicide
Attempting suicide

Four common factors in depression include:

1. Family situation-trauma and stress from financial problems, breakup of a relationship, death of a loved one, other major life changes
2. Pessimistic personality-higher risk for individuals who have low self-esteem and a negative outlook
3. Health status-medical conditions such as heart disease, cancer, and HIV that contribute to depression
4. Other psychologic disorders-anxiety disorders, eating disorders, schizophrenia, and substance abuse that often appear with depression

## Exercise Prescription

Exercise studies in clinically depressed populations include both hospitalized and ambulatory patients. Overall, the data support the positive effects of regular physical activity on depressive symptoms. ${ }^{6}$ In most cases, exercising patients had significantly decreased depression scores.

No one kind of exercise has the greatest impact on depression, yet most studies have used running or other aerobictype activities. Interestingly, positive psychologic outcomes do not depend on achieving physical fitness, although such fitness-related indicators as lower blood pressure and increased aerobic capacity frequently do improve.

The exercise prescription for patients with depression considers the following eight factors:

1. Anticipate barriers. Common symptoms of depression-fatigue, lack of energy, and psychomotor retardation-pose formidable barriers to physical activity. Feelings of hopelessness and worthlessness also interfere with motivation to exercise.
2. Keep expectations realistic. Make exercise recommendations with caution. Depressed patients often self-blame and may view exercise as another occasion for failure. Do not raise false expectations that can arouse anxiety and guilt. Explain that exercise provides an adjunct to, not a substitute for, primary treatment.

## FOCUS ON RESEARCH

## Physical Fitness Protects Against Death


#### Abstract

Blair S, et al. Physical fitness and all-cause mortality: a prospective study of healthy men and women. JAMA 1989;262:2395.


> A 1998 report by the Centers for Disease Control and Prevention stated that physical inactivity is one of the major underlying causes of premature mortality in the United States (Centers for Disease Control and Prevention. Self-reported physical inactivity by degree of urbanization-United States. MMWR 1998;47:1097.) This assertion confirmed that sedentary living causes about one-third of deaths from coronary heart disease, colon cancer, and type 2 diabetes. Increasing the nation s collective level of regular physical activity would therefore reduce the rate of premature deaths from these diseases by two-thirds.

The 1989 study by Blair and associates was the first to reveal the striking relationship between all-cause mortality and physical fitness in a healthy group of 10,224 men and 3120 women. Measurements included maximal treadmill testing for aerobic capacity, including extensive follow-up of large enough samples of both men and women to permit meaningful statistical analyses. The research focused on physical fitness-a biologic attribute as an objective marker for habitual physical activity-rather than physical activity, a behavior subject to measurement and interpretation difficulties. The dependent variable comprised all-cause and cause-specific mortality followed for up to 110,482 person-years, or an average of more than 8 years. This research and subsequent studies by the same investigators formed the basis for renewed interest and research support about the role of regular physical activity in overall health and disease prevention.

Participants underwent baseline measurements that included personal and family history, physical examination, a questionnaire on demographic characteristics and health habits (including cigarette smoking), anthropometry, resting ECG, blood chemistry, blood pressure, and a maximal treadmill exercise test. Subjects had no known heart problems, hypertension, stroke, diabetes, and resting or exercise ECG abnormalities. Total treadmill test time quantified physical fitness level; treadmill time correlated highly ( $r \geq 0.92$ ) with $\dot{\mathrm{VO}} 2_{\text {max }}$ in men and women. Initial test results placed subjects into one of five aerobic fitness categories (1: low fitness; 5: high fitness) based on gender and age to assess the link between physical fitness and allcause and cause-specific mortality.

Figure 1 shows age-specific, all-cause death rates for men (top) and women (bottom) categorized by fitness level.


Figure 1 Age-specific, all-cause death rates per 10,000 person-years of follow-up in 10,224 men and 3120 women by physical fitness quintiles as determined by maximal treadmill exercise testing.

For both groups, the decline in death rate with higher fitness became more pronounced with aging. Table 1 shows the age-adjusted all-cause death rates per 10,000 personyears of follow-up (1970 1985) by fitness grouping. Clearly, less fit women and men experienced higher death risk than more fit counterparts. Significantly higher relative risk for all-cause mortality emerged for the least fit quintile of men and for the two least fit quintiles of women.

Figure 2 shows age-adjusted mortality per 10,000 per-son-years as a function of metabolic equivalents (METs) and estimated $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ from maximal treadmill testing. The lower limit for mortality risk for men (orange bars) and women (yellow bars) asymptotes at about the same point for each age grouping-9 METs $\left(\dot{\mathrm{VO}}_{2 \text { max }}=31.5 \mathrm{~mL} \cdot \mathrm{~kg}{ }^{1}\right.$. $\left.\min { }^{1}\right)$ for women and $10 \mathrm{METs}\left(\dot{\mathrm{VO}}_{2 \max }=35.0 \mathrm{~mL} \cdot \mathrm{~kg}^{1}\right.$. $\min { }^{1}$ ) for men. These MET values and corresponding $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ values objectify a lower-limit aerobic fitness cutoff

## FOCUS ON RESEARCH

TABLE 1 Age-Adjusted, All-Cause Death Rates Per 10,000 Person-Years of Follow-up (1970 1985) by Aerobic Fitness Categories in Women and Men

| Fitness <br> Group | Person-Years of <br> Follow-Up | Number <br> of Deaths | Age-Adjusted Rates per <br> $\mathbf{1 0 , 0 0 0}$ Person-Years | Relative <br> Risk |
| :--- | :---: | :---: | :---: | :---: |
| Men |  |  |  |  |
| 1 (low) | 14,515 | 75 | 64.0 | 3.44 |
| 2 | 16,898 | 40 | 25.5 | 1.37 |
| 3 | 17,287 | 47 | 27.1 | 1.46 |
| 4 (high) | 18,792 | 43 | 18.7 | 1.17 |
| Women | 17,557 |  |  | 1.00 |
| 1 (low) | 4916 | 18 | 39.5 | 4.65 |
| 2 | 5329 | 6 | 20.5 | 2.42 |
| 3 | 5053 | 4 | 12.2 | 1.43 |
| 4 | 5522 |  | 6.5 | 0.76 |
| 5 (high) | 4613 |  | 8.5 | 1.00 |

below which health risk increases. Individuals who regularly engage in moderate exercise generally achieve a fitness level above that associated with increased death risk. Brisk walking for 30 to 60 minutes daily provides sufficient exercise overload to sustain a threshold aerobic fitness standard of 9 METs for women and 10 METs for men.

The data showed a clear, strong, and graded inverse relationship between aerobic fitness and mortality from
all causes. The finding remained consistent for men and women, even after adjustment for age, serum cholesterol level, blood pressure, smoking habit, fasting blood glucose level, family history of CHD, and length of followup. The strength of the associations and the high prevalence of sedentary habits and low fitness levels produce high attributable risk estimates for the general population.


Figure 2 Age-adjusted, allcause death rates per 10,000 person-years of follow-up by aerobic fitness categories in 3120 women and 10,224 men. Fitness categories expressed as maximal metabolic equivalents (METs) achieved during the maximal treadmill test. Estimated $\dot{\mathrm{V}}{ }_{2 \text { max }}$ ( $\mathrm{mL} \cdot \mathrm{kg}^{1} \cdot \min { }^{1}$ ) for each category is presented along the bottom axis.
3. Design a feasible plan. Make the exercise prescription realistic and practical, not an additional burden to compound the patient s sense of futility. Consider the individual s background and history. For severely depressed patients, postpone exercise until medication and psychotherapy alleviate symptoms. Previously sedentary patients should start with a light exercise schedule; for example, just a few minutes of walking each day.
4. Accentuate pleasurable aspects. Guide the choice of exercise by the patient s preferences and circumstances. Use pleasurable activities that are easily added to the patient s schedule.
5. Include group activities. Depressed, isolated, and withdrawn patients are most likely to benefit from increased social involvement. The stimulation of being outdoors in a pleasant setting may enhance mood; exposure to light exerts therapeutic effects for seasonal depression.
6. State specifics. Walking is almost universally acceptable, carries minimal risk of injury, and benefits mood enhancement. In keeping with recent ACSM recommendations for healthy adults, a goal of 20 to 60 minutes of walking or other aerobic exercise, three to five times a week, remains reasonable. The ACSM also recommends resistance and flexibility training 2 to 3 days per week.
7. Encourage compliance. Improved fitness may be a valuable consequence of exercise participation but is not necessary to produce an antidepressant effect. Compliance increases with less physically demanding exercise programs.
8. Integrate exercise with other treatments. The primary treatments for depression should not present exercise obstacles. Antidepressant medication is frequently prescribed when depression impairs a patient s ability to function.

## Summary

1. In the clinical setting, the exercise physiologist focuses on total patient care and restoring patient mobility and functional capacity.
2. Disability refers to diminished functional capacity compounded by an inactive lifestyle. Handicapped denotes a physical performance frame of reference defined by society.
3. Exercise plays an important role in cancer risk reduction, perhaps by increasing levels of antiinflammatory cytokines. These augment insulin receptor expression in T cells or positively affect provirus and oncogene activation.
4. The exercise prescription for cancer patients is symptom-limited, progressive, and individualized, with improved ambulation the primary goal.
5. A carefully planned, circuit resistance-exercise program decreases depression and state and trait
anxieties for women recovering from breast cancer surgery.
6. Cardiovascular disease affects the heart muscle directly, the heart valves, or neural regulation of cardiac function. Each disorder has its specific pathogenesis and intervention strategy.
7. Myocardial pathologies include angina pectoris, myocardial infarction, pericarditis, congestive heart failure (CHF), and aneurysm. Moderate-intensity exercise and prescribed medications provide benefits with relatively low risk for stable, compensated CHF patients.
8. Heart valve diseases include stenosis, insufficiency (regurgitation), prolapse, and endocarditis. Congenital malformations include ventricular or atrial septal defects and patent ductus arteriosus. Dysrhythmias (bradycardia, tachycardia, and premature ventricular contractions) are diseases of the heart s nervous system.
9. Cardiac patient assessment includes medical history, physical examination, heart auscultation to uncover murmurs and valvular problems, and laboratory tests (chest X-ray, ECG, blood lipid analyses, serum enzyme testing).
10. Physiologic assessments for CHD include noninvasive tests (echocardiography, exercise stress testing, and ECG analysis). Invasive testing includes radionuclide (thallium) imaging, cardiac catheterization, and coronary angiography.
11. Resistance exercise in cardiac rehabilitation restores and maintains muscular strength, promotes preservation of FFM, improves psychologic status and quality of life, and increases glucose tolerance and insulin sensitivity.
12. Graded exercise stress testing provides low-risk screening for CHD preventive and rehabilitative exercise programs. Stress-test results provide the objective framework to design an exercise program within a person s current functional capacity and health status.
13. Multistage bicycle and treadmill tests usually include several levels of 3 to 5 minutes of submaximal exercise to a self-imposed fatigue level.
14. Alterations in the heart s normal electrical activity pattern often indicate insufficient myocardial oxygen supply. Significant $S$ T segment depression heralds severe, extensive obstruction in one or more coronary arteries.
15. PVCs in exercise generally indicate severe atherosclerotic heart disease, often involving two or more major coronary vessels. Sudden death from ventricular fibrillation averages 6 to 10 times higher in patients with frequent PVCs.
16. Significant deviations from normal blood pressure and heart rate responses during graded exercise testing often indicate underlying cardiovascular pathology.
17. Stress tests have four possible outcomes: true positive (test successful); false negative (person with CHD misdiagnosed); true negative (test successful); false positive (healthy person misdiagnosed).
18. With a properly prescribed and monitored exercise program, cardiac patients improve functional capacity to the same extent as healthy counterparts.
19. RLD and COPD are the two major categories of pulmonary disease. RLD increases chest lung resistance to inflation. COPD affects expiratory flow capacity and ultimately impedes aeration of alveolar blood.
20. Regular exercise can effectively manage various pulmonary diseases, providing that exercise intensity, patient monitoring, and exercise progression receive close attention.
21. Exercise-induced bronchospasm is associated with ambient temperature and humidity and their drying effects on the respiratory mucosa. Drying increases mucosal lining osmolality, which stimulates release of powerful mediators that trigger bronchoconstriction.
22. Exercise training does not cure asthma; instead, it increases airflow reserve and reduces breathing work during exercise.
23. The few exercise-training studies with stroke patients support the use of exercise to improve mobility and functional independence and reduce further disease and functional impairment.
24. Fatigue is the most common symptom of MS; other symptoms include muscle weakness in the extremities, clumsiness, and numbness and tingling. Patients benefit from a comprehensive health prescription that involves aerobic, strength, balance, and flexibility exercises.
25. Clinical symptoms of Parkinsons disease (PD) include varying degrees of tremor, decreased spontaneity and movement (bradykinesia), rigidity, and impaired postural reflexes.
26. Exercise prescriptions for PD are individualized and directed toward interventions that affect associated motor control problems. They emphasize slow, controlled movements for specific tasks through various ranges of motion while lying, sitting, standing, and walking.

References are available online at http://thepoint.lww.com/mkk7e.

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National Institute of Mental Health www.nimh.nih.gov/


## On the Horizon

# Interview with Dr. Frank W. Booth 



Education: BS (Denison University, Granville, OH); PhD (Exercise Physiology, University of Iowa, Ames, IA); postgraduate studies (School of Aerospace Medicine, Brooks Air Force Base, San Antonio, TX. Department of Preventive Medicine, Washington University School of Medicine, St. Louis, MO).

Current Affiliation: Professor, Department of Veterinary Biomedical Sciences, College of Veterinary Medicine; Department of Physiology, and Dalton Cardiovascular Research Institute, University of Missouri, Columbia, MO.

Honors and Awards: See Appendix E, available online at http://thepoint.lww.com/mkk7e.
Research Focus: Molecular basis of how physical inactivity increases the risk of unhealthy syndromes and diseases in humans and companion animals.

Memorable Publication: Booth FW. Perspectives on molecular and cellular exercise physiology. J Appl Physiol 1988;65:1461.

## STATEMENT OF CONTRIBUTIONS: ACSM Citation Award

In recognition of outstanding contributions in the basic and applied sciences related to exercise physiology and biochemistry.

Dr. Booth is recognized for his innovation and quantitative and integrative investigations on the cellular and molecular mechanisms in skeletal muscles associated with
the conditions of immobilization, simulated microgravity, acute exercise, and training. His findings have given new meaning and interpretation for the adaptive response of muscle.

Dr. Booth is also deserving of citation for his dedicated leadership and his outstanding example in bringing the discipline of exercise physiology into the realm of molecular biology.

## What influence did your undergraduate education have on your final career choice?

> The courses I took as part of my biology program, along with Dr. Haubrichs encouragement, were the primary influences. I loved my comparative anatomy class, where we did animal dissections. This caused me to think about how things worked in humans. My favorite course was philosophy of religion, a course that really made me think.

## Who were the most influential people in your career, and why?

> Four individuals exerted a profound effect on my thinking about my career. First, Dr. Haubrich made me think critically about the science of exercise, although I didnt think of it as a real science back then. On team bus trips, or when I would speak with
him in his office, we would discuss science in general. I always wondered what was happening to my body during all those hours in the pool. I recall writing a paper for one of my classes about metabolic pathways that really turned me on about the topic.

## What first inspired you to enter the exercise science field? What made you decide to pursue your advanced degree and/or line of research?

My biology advisor at Denison University, Dr. Robert Haubrich, also was the assistant swim coach. Because I was on the swim team, he and I had many talks together, not only about swimming but science in general, including discussions about exercise and training methods. Dr. Haubrich knew of my interest in biology and sports, and one day after practice gave me a flyer
advertising a new graduate program in exercise physiology at the University of Iowa. As soon as I finished reading it, I knew graduate school was what I wanted to pursue, so I applied to the program.

Second, Dr. Charles Tipton (see Interview in the front matter) at the University of Iowa taught me to explore mechanisms of exercise adaptations. He stressed honesty, as he was a real straight shooter. Dr. Tipton encouraged me to convey what was on my mind and not simply to tell people what they wanted to hear. He was instrumental in getting me to communicate precisely what I thought and to be human yet honest in doing so. From a physiological metabolic perspective, Dr. Tipton consistently tried to uncover why something occurred. Ive never lost that burning desire to seek out basic explanations.

The third person was Dr. James Barnard, a fellow graduate student and now a professor at UCLA. Jim was an exemplary student (perhaps the smartest Ive met), always getting As in the hardest courses. His ability and enthusiasm for knowledge motivated me to push myself intellectually, both in coursework and in the laboratory. Jim was a great role model for me.

The fourth person, Dr. John Holloszy (see Interview in Section 2), mentored my postdoctoral work and taught me to think more critically. As I was continually around other postdocs and scientists who were trying to devise creative ways to explain biologic phenomena, there was no way to hide from contributing. More than any person I know, Dr. Holloszy possessed the most amazing intuitive feel for which experimental procedures would work and which would not. He taught me the basic tenets about how to do science. My interactions with Dr. Holloszy and the other postdoctoral students in conducting various experiments and writing up the results of our work were invaluable in shaping my career in science.

## What has been the most interesting/enjoyable aspect of your involvement in science? What was the least interesting/enjoyable aspect?

> I cherish the camaraderie of exercise science colleagues, particularly those with whom I have in-depth discussions about various science topics. The individuals who open up and share the truth about their research are the ones I truly enjoy knowing and relating to. The ideal and most enjoyable environment enables one to speak freely, to really express truthful opinions about a topic. I do not enjoy people who tell you what they want you to hear or know for purposes of personal gain (i.e., to build their own ego or self-promote) instead of communicating with respect for the purity of scientific discovery.

## What is your most meaningful contribution to the field of exercise science, and why is it so important?

> This is a very difficult question for which I have no answer. I suspect that the answer will emanate from the judgments of others. However, I do love applying cutting-edge technology to try to answer mechanistic questions concerning exercise. It is important to try to get to the bottom of things, and using new techniques often provides the key to unlocking the required information. Sometimes, it takes months to perfect the procedure you need for an experiment, and then months more to finally get it to work properly.

## What advice would you give to students who express an interest in pursuing a career in exercise science research?

- It is important for the student to be excited by a course or topic in a course. Sometimes, undergraduate students have difficulty making a decision about their future. I encourage students with an interest in discovering new insights about any exercise-related topic to become involved with a professors research projects. Even in graduate school, there is a wide range of true desire to continue to pursue research interests. However, those students who experience joyous feelings when searching for the unknown will know deep down they have found a suitable path to follow. If a student can find a mentor, then by all means take advantage of the situation, and do whatever it takes to become deeply involved in the intellectual pursuit.


## What interests have you pursued outside your professional career?

- I am basically a big-time workaholic. Except for evening runs with my dog Swim, I pretty much start in the lab early and end late. I love vigorous exercise and try to do as much as I can when time permits.


## Where do you see the exercise science field (particularly your area of greatest interest) heading in the next 20 years?

$>$ Our field needs to produce the very best science to counter the cultural trends that have created a sedentary society with all of its ailments and diseases. Discovering the benefits of exercise and conveying those benefits to the public, from the broadest possible topic areas to the molecular basis of disease, remains our best chance to prevent many diseases and upgrade the nations health. The field needs to cooperate with multiple partners in a major public health effort to convince

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the world about the long-term health benefits of regular exercise. We as scientists must systematically provide the medical evidence and cross-disciplinary connections to show that exercise, not drugs, exerts the greatest impact on disease to improve health. All of us must become strong advocates, using education and laboratory-based research to convince people everywhere to pursue a healthy lifestyle.

## You have the opportunity to give a last lecture. Describe its primary focus.

> The basis of my talk would involve how regular exercise affects daily living. I would focus not just on the physiologic function and performance aspects, but on exercises effects on chronic ills like diabetes, pulmonary and kidney diseases, heart disease, and cancer. For the ever-increasing number of American citizens living in nursing homes, I would discuss the profound effect of sedentary living on muscular atrophy
and reduced strength, two factors that limit these individuals ability to carry out even the simplest tasks of daily living. I would emphasize that relying on pills to tackle disease contributes relatively little to a happy and healthy life. I would also hope to convince the audience that the exercise biologists role is not simply to study the effects of physical activity or enhance sport performance. The new exercise physiologist must reintroduce regular physical activity into an unhealthy, overweight, and sedentary population that is genetically programmed to expect physical activity. I refer to this unhealthy state as SeDS, an abbreviation for sedentary death syndrome.

Achievement of a future, healthy world must involve cooperative effort among diverse public and private organizations that invest enough money in fundamental research to make a real difference. Talking a good game simply will not do it; putting sufficient resources to work will create newer and better opportunities for success through proper research.


## Molecular Biology A New Vista for Exercise Physiology

The most sensible way to prepare for the challenges and opportunities arising from progress in the identification of the genetic and molecular basis of health and disease is to become familiar with this field and to learn its tools.

Claude Bouchard, Robert Malina, and Louis P russe. Genetics of Fitness and Physical Performance. Champaign, IL: Human Kinetics, 1997.

Gene: segment of DNA with an ordered nucleotide sequence for encoding a specific functional substance (i.e., a protein or RNA molecule)
Molecular biology: study of the molecular basis of life
Molecular genetics: study of the structure and sequence of the molecules that carry genetic information
Pharmacogenetics: genetic engineering to design specific drugs to target specific disease conditions of an individuals genetic code; this field investigates how genetic diversity affects the efficacy and side effects of targeted drugs
Pharmacogenomics: application of genomic methods and perspectives to study drug-responsive genes
Bioinformatics: understanding the underlying chemical codes of organisms by interpreting gene sequences, converting primary linear code into complex 3-dimensional structures, managing automated screens, and running combinatorial chemistry syntheses
Metagenomics: the study of a mixture of genetic material from different organisms contained in an environmental sample
Protein: relatively large molecule composed of one or more chains of amino acids in a specific order (determined by the base sequence of nucleotides in the gene coding for the protein); proteins (perhaps up to 140,000 different structures in the body) provide for unique structure, function, and regulation of cells, tissues, and organs; examples include hormones, enzymes, and antibodies

Proteomics: systematic analysis of the protein expression of healthy and unhealthy genomes at the molecular level by identifying, characterizing, and quantifying proteins
Genome: an organisms complete genetic information (DNA and RNA)

The early 1950s ushered in the dawn of the modern age of molecular biology, and the past 5 years of exercise physiology research has, fortunately, embraced this opportune field. And so it should. Techniques now available to study how genetic characteristics shape human behavior will revolutionize almost every facet of human physical activity and sports medicine. The new generation of exercise physiologists has a fantastic opportunity to study the molecular world of genes and their role in human exercise performance and health and disease. Todays exercise physiology students often cooperate in research projects from basic science, clinical and environmental medicine, chemistry, molecular biology and molecular genetics, pharmacogenetics, pharmacogenomics, bioinformatics, metagenomics, and other newly emerging disciplines in the physical and life sciences.

Many exercise physiology laboratories have well-funded research programs to study the genetic basis of increased physical activity (and inactivity) related to diseases and dysfunctions. This spans the gamut from the role of genetics in training and exercise performance to skeletal muscle, neural, and visual adaptations to prolonged microgravity exposure. Occupational, physical, and rehabilitation medicine can apply gene therapy as a way to transfer genetic material to enhance the patients production of growth factors (e.g., www.ncmrr.org/Sites/ChildrensNationalMedicalCenter/tabid/182/Default.aspx). These small protein molecules stimulate cell proliferation, migration, and differentiation; and they promote matrix synthesis to facilitate healing of injured or surgically repaired tissues with limited blood supply and slowed cell growth that impairs normal processes of tissue repair. ${ }^{79}$ In addition to delivering therapeutic proteins to injured tissues, molecular biology provides a way to engineer new tissues. These biologic substitutesewogenous structures and/or tissue scaffoldingean link gene therapy procedures to support tissue regeneration and healing from athletic trauma. Molecular biology also focuses on how short-term and chronic physical activity act and interact to induce structural and functional adaptations that enhance exercise performance and produce desirable health outcomes.

Booth and colleagues ${ }^{16,17}$ assert that future exercise physiology research should emphasize primary disease prevention, with focus on uncovering environmental roots of modern chronic diseases such as type 2 diabetes, almost entirely preventable with increased physical activity. ${ }^{72}$ These maladies annually cause in excess of 250,000 premature deaths and play a role in $\$ 1$ to 2 trillion dollars in health care costs for conditions associated with sedentary living, not to mention the toll on human suffering. Dr. Frank Booth, whose contributions we chronicled on pages 930 to 932 , coined the term SeDS (sedentary death syndrome) to characterize the effects of a sedentary lifestyle on unhealthy outcomes. ${ }^{14,15,18}$

Studying the basic biology of organisms at the molecular level offers novel ways to illuminate disease mechanisms and strategies that best combat them. Research challenges also emerge in the exercise biology sciences. Eighteen years ago, Baldwin made a compelling case that the membership of the American College of Sports Medicine should exploit new fields and technologies involved with molecular exercise sciences. ${ }^{7}$ The contemporary views of Booth and Baldwin, not unlike our own, maintain that exercise physiology and sports medicine have progressed over the past decade from an exercise biochemistry focus at the organ level to a current emphasis on molecular dynamics at the cellular level. These scientists posit that our field has already shifted to the molecular age, as evidenced by research emphasis in integrative biology and proteomics. In the 5th edition of this text, a literature search on PubMed (www.ncbi.nlm.nih.gov:80/entrez) reinforced their point. For the 3-month period between January 1, 2001, and April 1, 2001, almost one-fourth of the citations to the term muscle were linked to the term gene ( 502 citations), and 72 articles concerned genes and human muscle. Not surprisingly, a search for the term genome yielded 64,112 entries through March 2001, most occurring from 1998 to 2001. Compared with the 2001 citation search, a tremendous proliferation has occurred in molecular biology research through 2008 related to the exercise sciences as illustrated in Figure 1. As of January 30, 2009, 659,683 articles were tagged to genome (a $59.3 \%$ increase from 2005 compared to 2001, with a further sixfold increase through 2008), while citations with the terms muscle and genes increased from 502 in 2001 to 16,184 in 2005, with a further increase to 58,741 on January 30,2009 ! Not unexpectedly, the number of citations for gene exceeded 1.3 million, a $142 \%$ increase since May 2005! We have included other combinations of terms to use as a frame of comparison in future editions of the text.


Figure 1 Comparison of citations from 2001 to 2009 (as of Jan 30, 2009) for molecular biology terms with exercise science entries.

Funding for research in the genomics area has also increased dramatically. Figure 2 shows that in 1988, the Department of Energy (DOE) and the National Institutes of Health (NIH) spent a combined $\$ 27.9$ million for their human genomic programs; in 2000, that amount increased nearly 13 -fold to $\$ 360.6$ million and continued to climb steadily, reaching 437 million in 2003 2004. We were unable, despite repeated requests to the DOE, to obtain current funding information.

Figure 2 Department of Energy (DOE) and National Institutes of Health (NIH) budget from 1988 to 2004.
 No similar data exists for 20052009.

In this chapter, we introduce molecular biology in general, with specific emphasis on gene expression and protein synthesis. Where possible, we link applications to human exercise performance, exercise testing, and sports medicine. Our tour begins with background information about Watson and Cricks pioneering 1953 achievement in deciphering the 3-dimensional molecular structure of the deoxyribonucleic acid (DNA) molecule. ${ }^{127}$ Their seminal publication, included with the reference materials on the Web site for this textbook (http://thepoint.lww.com/mkk7e), immediately thrust research in molecular biology to the

Gene expression: converting a genes coded information by transcription and translation into cellular structures; expressed genes include those transcribed (copied) from DNA nucleotide sequences into mRNA and then translated by ribosomes into specific nucleotide sequences to form protein
Protein synthesis: process of creating a protein from amino acid subunits
Deoxyribose nucleic acid (DNA): double-helix molecule (two complementary chains of nucleotides) containing an organisms total hereditary information

Genetics: branch of science that studies patterns of inheritance of specific traits in successive generations
Human Genome Project: government-sponsored project (Department of Energy and National Institutes of Health) to (1) create an ordered set of DNA segments from known chromosomal locations, (2) develop new computational methods to analyze genetic maps and DNA sequence data, and (3) develop new techniques and instruments for detecting and analyzing DNA (i.e., deciphering the complete sequence of genetic instructions in humans). Hundreds of robotic sequencing machines work around the clock to analyze nucleotide sequences using the Sanger-Coulson dideoxy DNA sequencing method to map different genomes
Nucleus: structure that contains the cells genetic material (chromosomal DNA)

Natural selection: Darwins basic idea that species survive because more favorable phenotypic traits pass down through successive generations
forefront of scientific exploration worldwide. Their solving the puzzle of the DNA structure led to new techniques and models of how organisms transmit genetic information from parent to offspring and ultimately to successive generations. The spectacular growth of molecular biology worldwide affects almost every facet of biomedical research and has forever changed the face of hereditary science. Research in molecular biology within kinesiology and the exercise sciences has fundamentally impacted the study of human exercise performance and topics related to health-related fitness, activities of daily living, and disease. ${ }^{21,41,76}$

In all likelihood, future limits to athletic performance will be determined less by an athletes innate physiology and anatomy (and commitment to training) and more by surgical enhancement (e.g., more flexible tendons) and genetic interventions engineered for fasteracting, more powerful muscles, greater oxygen transport, and more rapid circulation. The continuing use of banned substances made public at the 2000 Sydney Olympic Games, 27th Athens Olympiad in 2004, and 2008 Beijing Olympics highlights challenges facing the new, independent drug-testing agency to confront the consequences of continuing illegal drug use in future winter and summer Olympic Games. It would not surprise us if breakthroughs in gene therapy techniques in the coming years infiltrate the athletes arsenal of tricks in time for a future Olympiad or other world-class competitions. This will cause both students and an educated general public to confront specialists in exercise physiology concerning the implications of the molecular biology of gene therapy and genetic ergogenics, as increasing numbers of amateur and professional athletes in many sport disciplines cheat with advanced molecular techniques to gain a competitive edge.

A new feature of this chapter includes supplementary material on the Web page dedicated to this textbook (http://thepoint.lww.com/mkk7e). This Web site includes (1) readings related to molecular biology and genetics, twins, and human performance; (2) reference to excellent texts that devote hundreds of pages to the intricacies of the molecular biology of gene transcription and protein synthesis; (3) articles from Scientific American that concern molecular biology; (4) useful molecular biology Internet sites; (5) microscope technologies germane to molecular biology (light microscope, fluorescence microscope, electron microscope, and positron emission tomography [PET]), (6) a reprint of Watson and Cricks onepage classic paper in Nature about their deduction of DNAs structure, which nearly six decades later unraveled the pieces to the primordial jigsaw puzzle of the Human Genome Project; and (7) a timeline of events about genetics before Mendel, followed by notable events in genetics and molecular biology to 2005.

## BRIEF HISTORY TOUR OF MOLECULAR BIOLOGY

The road to uncovering DNAs 3-dimensional structure began with an innocent discovery by Swiss physiologist Friedrich Miescher (1844 1895), Professor of Physiology at the University of Basel, Switzerland, and charter member of the 1889 First International Congress of Physiologists. In 1869, Miescher identified what he considered a new biologic substance. Cells from fish sperm and human tissue cells obtained from pus in discarded surgical bandages contained unusual proportions of nitrogen and phosphorus in their nucleus. Miescher called the substance nuclein, which one of his students, Richard Altman, in 1899 termed nucleic acid because of its slightly acidic properties.

As late as the second half of the 19th century, chemists and biologists did not know what role if any genes played in transmitting hereditary information in plants or animals. But this


Charles Darwin would change when English naturalist, geologist, and biologist, Charles Robert Darwin (1809 1882) (www.public.coe.edu/ departments/Biology/darwin_bio.html) proposed a theory of evolution based on natural selection of random variation. ${ }^{33}$ Darwin developed his theory gradually after many years of geologic and biologic observations on native lands, particularly along the western coast of South America including the Galapagos Islands (www.gct.org/darwin.html). Darwins insightful observations about the distribution and continuation of animal and plant phenotypic traits were first published on November 26, 1859, 10 years before Miescher discovered nuclein.

Researchers at Brandeis University, Waltham, Massachusetts, have used Darwins basic ideas about natural selection to create the GOLEM project (Genetically Organized Lifelike Electro Mechanics; http://demo.cs.brandeis.edu/golem/). They successfully created artificial locomoting machines that mimicked biologic life forms (e.g., robots that design and build other robots without human assistance). The simulations demonstrated the feasibility of creating successively more complex entities from proceeding generations to solve more difficult simulation tasks. The implications of such biologic simulations may have a bearing on the role of natural selection on intelligence and memory.

The English naturalist and explorer, evolutionist, and anthropologist (and prolific writer and essayist) Alfred Russel Wallace (1823 1913; www.wku.edu/~smithch/index1.htm), had independently formed his own views regarding natural selection at about the same time Darwin completed his work dealing with evolution theory. Except for sharing his thoughts with selected colleagues in various disciplines, Darwin had not yet made them widely known in formal publications. Darwins reading of Wallaces 1855 paper about natural selection, On the Tendency of Varieties to Depart Indefinitely From the Original Type (reprinted in reference ${ }^{124}$ ) no doubt accelerated his pace to publish the single-volume discourse on evolutionary theory that remains an enduring scientific legacy, forever changing our view about human evolutionary progression through the ages. It was Wallace who encouraged Darwin to use the phrase survival of the fittest (coined by British sociologist and philosopher Herbert Spencer [1820 1903]), to convey the basic idea about natural selection to the general public.


Alfred Russel Wallace, age 25

Darwins carefully crafted, thought-provoking treatise On the Origin of the Species, by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life ${ }^{32}$ indirectly provided empirical data on how environmental pressures selected for the survival of a species observable characteristics (traits) from one generation to the next. His ideas about evolution emerged mainly from insightful observations of subtle differences among plant and animal species during his 4-year, 9-month, and 2-day voyage around the world (www.aboutdarwin.com/voyage/voyage03. html), begun in 1831 aboard the survey ship HMS Beagle. ${ }^{31}$ Darwins theory explained how adaptive modifications to environmental stressors impacted the common descent of current animal and plant species and how natural selection preserved a species survival.

Interestingly, Mieschers discovery of nuclein came 4 years after Austrian monk Gregor Johann Mendels (1822 1884) elegant 25 -year breeding experiments with 10,000 varieties of edible pea plants Pisum sativum. Mendel vigilantly tracked the peas inherited characteristics and in 1865 submitted his findings, Versuche ber Pflanzen-


The HMS Beagle ( 235 ton, 27 m length, 7 m breadth, 6 canons) engaged in three survey missions from 1826 to 1843, with Charles Darwin the naturalist on the second survey. On the morning of 27 December 1831, HMS Beagle, with a crew of seventy-three men, sailed out of Plymouth harbor under a calm easterly wind and drizzly rain. Darwin became seasick almost immediately and started to have second thoughts about the voyage. ( www.aboutdarwin.com/ voyage/voyage03.html). HMS Beagle courtesy of marine artist Ron Scobie, ASMA (www.ronscobie-marineartist.com).

Ribonucleic acid (RNA): nucleic acid that contains the sugar ribose; usually single stranded Nucleotide: segment of a nucleic acid containing a 5-carbon sugar, phosphate group, and nitrogencontaining base

Transgenic: transforming genes from one species into another

Polymerase chain reaction (PCR): technique for artificially amplifying the number of copies of a target DNA sequence, usually by 106 - to 109 -fold, during repeated cycles of denaturation, annealing with primer, and extension with DNA polymerase


Gregor Johann Mendel

Hybriden, to an obscure natural history society journal. The work appeared in 1866 and in 1950 was translated into English by William Bateson (1861 1926). ${ }^{10}$ Darwins unifying evolution theory and Mendels experiments on heredity formed scientific pillars of insights embraced by a relatively new field of studymolecular biologythat would subsequently dominate fundamental discoveries in biology, chemistry, genetics, nutrition, and medicine to this date and surely beyond. The importance of Darwins contributions and worldwide impact is reflected in a Google search on Charles Darwin (February 1, 2009) that references $4,570,000$ Web sites (compared to only $3,470,000$ in May 2005)! Interestingly, British scientists using molecular biology methods in 2005 unraveled the cause of Darwins 40 years of suffering from long bouts of vomiting, gut pain, headaches, severe tiredness, skin problems, and depression. ${ }^{23}$ Darwins family history revealed a major inherited component of predisposed hypolactasia (aversion to milk and cream). The authors concluded that Darwins multifold symptoms and illness highlights a missed observationthe importance of lactose in mammalian and human evolution.

Mendels meticulous scientific insights remained relatively obscure for nearly three decades until three scientists (German botanist Carl Correns [using maize and peas], Dutch botanist Hugo De Vries [working with flowering plants], and Austrian agronomist Erich van Tschermak-Seysenegg [using peas]) rediscovered his research in about 1900. It would take nearly 65 years after Mendels initial publication (and enormous progress in biochemical techniques) to unravel further secrets highlighting the mysteries of hereditary transmission in human cells. In 1929, Phoebus A. T. Levene (1869 1940) discovered that the essential components of the nucleic acids DNA and ribonucleic acid (RNA) were long chains of repeating nucleotides. It remained unclear to Levene and others how these molecules assembled. If the genes indeed contained the hereditary information, scientists needed to know the process involved. Twenty-five years later, a major breakthrough occurred (discussed in the next section) that delivered the biggest biologic thunderbolt since Darwin stirred a revolution in scientific thinking concerning evolutionary theory. This breakthrough impacted at least eight other crucial scientific milestones through 2008:

1. 1966eracking the DNA genetic code
2. 1972 to 1973start of tremendous advances in biotechnology by splicing pieces of DNA together to form genes (called recombinant molecules) that were inserted into bacteria to produce human proteins
3. 1977elucidating the complete genetic information of a microorganism, paving the way for the Human Genome Project
4. 1981ereating the first transgenic animal by inserting a viral gene into the DNA of a mouse, permitting such animals to serve as models for the study of human diseases
5. 1984devising the polymerase chain reaction (PCR), an ingenious method of sequencing DNA from minute samples of DNA
6. 1997eloning the first mammal, the lamb Dolly, from an adult cell
7. 2000 to 2004deciphering the human genome; sequencing the genome of the fruit fly Drosophila melanogaster; DNA of rice sequenced (first decoding of a crop); initial sequencing and comparative analysis of the mouse and brown Norway rat genomes; somatic cell nuclear transfer (SCNT) technology produces a single embryonic stem cell line from a human blastocyst, representing the first published report of cloned human stem cells
8. 2005 to 2009 ereating human stem cell lines from human embryos by cloning and then extracting patient-specific, immune-matched human embryonic stem cells to create genetic matches in patients with disease or injury

## REVOLUTION IN THE BIOLOGIC SCIENCES

In 1953, James D. Watson (1928 ), an American postdoctoral student who earned a PhD in genetics from Indiana University at age 22, teamed with English physicist Francis H. C. Crick (1916 2004) who was pursuing a PhD in X -ray studies of protein in the Cavendish

Laboratory, Cambridge, England. Watson and Cricks breakthrough, deduced from other scientists research, published and unpublished, posited that the DNA molecule consisted of two polynucleotide linear strands coiled around each other to form a double helix. ${ }^{125}$

The young researchers constructed a ball-andwire model of DNA, proposing that the two helical strands connected like the steps of a spiral staircase by nucleotide base pairs held together by hydrogen bonds. Their eventual Nobel Prize rewarded their contribution about DNAs architecture and the 3dimensional fit of its molecular components (fueled in part by substantial theoretical contributions about DNAs helical structure from Kings College, London, colleague Rosalind Franklin (1920 1957; see Introduction).

In their 1953 landmark publication in Nature that described DNAs molecular structure, Watson and Crick state that their research efforts were stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Drs. M. H. F. Wilkins and R. E. Franklin and coworkers at Kings College, London. This statement, interpreted with the hindsight of many years of investigative follow-up by historians and researchers, paints quite a different picture of Rosalind E. Franklins prior discoveries about DNAs structure, which eventually led Watson and Crick to deduce DNAs final configuration correctly. Franklins sophisticated X-ray diffraction photo reflecting her expertise with X-ray crystallography (shown to Watson and Crick surreptitiously without Franklins knowledge) provided the missing piece about DNAs double helix that empowered Watson and Crick to decipher the puzzle quickly after viewing the photo (Fig. 3). Interestingly, unlike many biologists, Watson and Crick did not conduct experiments. Their technique involved thinking, arguing, and rethinking ideas and concepts about how to put together pieces of a complicated puzzle with many interconnected components.


Figure 3 The technique of X-ray crystallography bombards crystals with thin X-ray beams of single (monochromatic) wavelength to determine a substances 3-dimensional crystal structure. The right photo shows Franklins X-ray photograph of DNA; she focused the x-ray beam on extra-wet DNAB fibers for a longer-than-usual time, with a 62-hour exposure to obtain the vivid photo of DNAs cruciform pattern. Without her knowledge or permission, this recent X-ray was shown to Watson and Crick, and putting it together with the knowledge about base pairing, they correctly deduced that DNA must have originated from a helix-shaped molecule.

For historic perspective, we recommend two books with different views about how the DNA puzzle was solved. Watsons ${ }^{127}$ colorful personal interpretation details one of the most important discoveries in all of science by one of the scientists who made the discovery.

Double helix: two DNA strands twisted in a spiral around each other
Base pairs: two complementary nucleotide bases (G-C or A-T) in a double-stranded DNA molecule held together by hydrogen bonds Hydrogen bonds: weak, interactive bonding from simultaneous attraction of a positive hydrogen atom to other atoms with negative charges

Template: copy, replica, or pattern; sequence of nucleotides from which a complementary DNA or RNA strand forms
Template strand: original DNA strand that guides the synthesis of a new DNA strand by complementary base pairing

Human genome: the full complement of genetic material in a human cell; contains about 80,000 to 140,000 genes and from 3.12 (Celera Genomics estimate) to 3.15 (National Human Genome Research Institute estimate) billion nucleotide base pairs chromosome: threadlike strand of DNA and proteins in the nucleus of cells that includes the genes that transmit hereditary information
X chromosome: sex chromosome present in two copies in female animals
Y chromosome: sex chromosome present in one copy in male animals
Genotype: the individuals genetic makeup at the molecular level comprising the entire set of genes
Phenotype: observable characteristics or attributes resulting from the expression of genes
Escherichia coli (E. coli): rod-like anaerobic bacterium with 4.6 million base pairs, found in the colon of humans and other mammals; studied in many disciplines for its genetic characteristics


Dr. Rosalind Franklin

Sayre ${ }^{102}$ provides a compelling and insightful first full account of Rosalind Franklins previously unacknowledged major contribution to discovering DNAs structure.

From the Watson and Crick decisive discovery, we know that DNAs helical structure carries the biologic blueprint for specifying the order in which the bodys 20 amino acids assemble to create a protein. Each protein has its own unique amino acid sequence; this sequence ultimately dictates the protein molecules final shape and distinctive chemical and functional characteristics. We also know that each double-helix strand provides a template for synthesizing a new strand, something Watson and Crick had hinted at in their seminal Nature paper. A template strand represents an original DNA strand. Once faithfully copied, each newly created double-helix strand is a duplicate of its predecessor, with its genetic code sequence preserved. This mechanism of self-replication preserves the genetic flow of information to ensure that successive generations receive the same coded DNA messages. In fact, all living things on Earth share a common molecular plan. Each of a humans 100 trillion cells relies on four basic molecular building blocksnmeleic acid, protein, lipid, and polysaccharidealong with other nano-sized biomolecules, to perform their functions efficiently. In addition, all living cells shuttle the flow of information from DNA to RNA to protein. We cannot overstate the full impact of what Watson and Crick deduced about DNAs structural configuration. Their contribution and subsequent years of investigation have impacted every facet of biomedical science, from how primordial DNA formed and survived to the nature of deadly diseases and the all-out search for their eventual cure. Their unraveling of DNAs structure also profoundly affected all of science, particularly subsequent discoveries about the human, virus, plant, and animal genomes (see next section).

The fields of molecular biology have shown explosive growth during the past 50 years. Discoveries have been so startling that almost every year since 1958 a Nobel Prize has been awarded for research related to molecular biology. Since its 1901 inception, 4 of the only 10 women awarded a Nobel Prize in science won for molecular biology related research. ${ }^{83}$ Polish superstar scientist Marie Curie (1867 1934) earned two Nobel Prizesin physics (1903) and chemistry (1911).

## HUMAN GENOME

The human genome represents the full complement of genetic material in a human cell. A private company, Celera Genomics (www.celera.com/), and the publicly funded National Human Genome Research Institute (www.genome.gov/) announced on June 26, 2000, their completion of the first assembly draft of the human genome. That institute produced a very high-quality version of the human genome sequence, freely available in public databases (April 2003). Scientists know for sure that the total number of base pairs determines genome size. The genome, distributed among 23 pairs of chromosomes, each repeated over and over like a genetic stutter without interruption, imparts our individual uniqueness. At conception, one complete chromosome set from the father ( 22 plus an $\mathbf{X}$ or $\mathbf{Y}$ sex chromosome) joins with one complete set from the mother ( 22 plus an X sex chromosome) to give each human offspring 46 chromosomes. The helical DNA structures (genotype) contain the genetic blueprint or roadmap of instructions for almost every aspect of our being ( phenotype). The phenotype reflects the expression of our gene pool from the physical dimensions, texture, color, composition, and shape of every internal and external body part to our personalities with all their idiosyncrasies. The human genome greatly exceeds the genome size of other organisms. For example, the bacterium Escherichia coli shown in Figure 4A (E. coli; primary member of the large bacterial family Enterobacteriaceae) contains 4.6 million base pairs, while yeast contains 15 million base pairs. In contrast, the smallest human chromosome (the male or Y chromosome Fig. 4B, bottom) consists of 58 million base pairs (http://ghr.nlm.nih.gov/ chromosome $=\mathrm{Y}$ ), and occupies the estimated 20,000 to 25,000 total genes in the human


Figure 4 A. The bacterium Escherichia coli (E. coli). B. The smallest human chromosome. Human males have $X$ (larger; top) and $Y$ (smaller; bottom) chromosomes.
genome. The largest human chromosome contains 250 million base pairs. For some idea of the enormity of the genetic structures, consider the following analogy:


#### Abstract

A double-spaced $8.5 \times 11$ inch page of text using normal margins contains about 3000 letters, or roughly 250 words. Porting the human genome to pages would equal the number of letters in 1000 copies of the Sunday New York Times or 1200 copies of the 4th edition of our 900-page Exercise Physiology text. Stated another way, reading one letter of code every second would require about 100 years without a break to peruse the entire genome! A single DNA strand in one diploid human cell with 23 pairs of chromosomes, if unwound and stacked end to end, would stretch to the height of a person 60 inches tall, yet it occupies a width of only 50 -trillionths of an inch; and it is not only DNAs remarkably large size but also its relative molecular weight. For example, the chromosome of Escherichia coli has a molecular weight of $2500 \times 106$, contrasted with a molecular weight of only 180 for the monosaccharide glucose.


To unravel the submicroscopic secrets of genetic material, sophisticated detection techniques help scientists decode the human genome. Most of the DNA sequences never become part of the final transcript that ultimately directs protein synthesis. In 2003, the Human Genome Project (www.ornl.gov/sci/TechResources/Human_Genome/home.html) achieved its major objective of sequencing the total DNA of the human genome. By November 2000, more than one-half the genome had been identified, sequenced, and recorded in public databases (e.g., www.acedb.org/). The December 1999 issue of Nature featured a milestone scientific achievement the sequence or genetic map for 12 contiguous segments of human chromosome 22, the second smallest of the 23 chromosomes (chromosome 22 contains about 1.6 to $1.8 \%$ of the total genomic DNA). ${ }^{37}$ The DNA sequence includes the longest, continuous stretch of DNA ever deciphered and assembled. It contains over 23 million letters. The sequencing of chromosome 22 allowed scientists for the first time to view the entire DNA of a chromosome. At least 27 human disorders link to chromosome 22 genes, including ovarian, colon, and breast cancers; cataracts; congenital heart disease; schizophrenia; neurofibromatosis; mental retardation; and disorders of the nervous system and fetal development (www.ornl.gov/sci/techresources/Human_Genome/launchpad/chrom22.shtml).

Scientists view this monumental genomic accomplishment as somewhat like completing an intricately detailed inaugural chapter in the human genetic instruction book composed of many complex chapters. An international collaboration from eight laboratories in the United Kingdom, Japan, the United States, Canada, and Sweden helped to complete the analysis of the bodys 23 chromosomes through 2006 (www.ornl.gov/sci/techresources/Human_Genome/project/ timeline.shtml). Knowing the identity and order of the chemical components of the DNA of the 23 pairs of chromosomes found in almost every human cell has provided an important tool to determine the basis of health and disease.

In a material sense, a relatively few discrete genetic instructions ultimately determine all of the subtlety of our species, including the thousands of years of accomplishment in fields of study

Diploid: having two representatives of every chromosome (i.e., two copies of each gene)

Neurofibromatosis: hereditary disorder characterized clinically by the combination of patches of hyperpigmentation in both cutaneous and subcutaneous tumors over the entire body

from architecture to poetry and medicine to computer science and zoology. Anatomic and psychologic differences between any two unrelated individuals really reflect relatively few differences in their genomic blueprintperhaps one or two gene sequences out of thousands. For example, the person next door, golf champion Tiger Woods, and the brilliant Austrian physicist Lise Meitner (1878 $1968{ }^{107}$; deprived of a Nobel Prize for contributing to the discovery of nuclear fission because of her religion and professional animosities) are far more alike than different, yet the variety among individuals approaches infinity!

## NUCLEIC ACIDS

Figure 5 shows the central configuration differences between the two nucleic acids, DNA and RNA; the three yellow text boxes highlight the important differences. Dr. Lise Meitner

Both structures carry and then transmit the hereditary information among the same type of cells when they divide (i.e., liver cells produce liver cells) and from generation to generation through reproductive cells. Within all living cells, genes encode the hereditary set of instructions that determine an organisms unique characteristics, from a simple bacterium such as Streptococcus pneumoniae to the complex multicellular organism Homo sapiens. As organisms within a species increase in complexity, the total information stored within the genome also increases tremendously. In subsequent sections, we describe just how much encoded information must be transcribed and translated to ultimately create proteins, which characterize thousands of unique cells, tissues, and organs that define the organism. Think of DNA as the raw material or building blocks of genes, and RNA as the link or intermediary to protein synthesis. Two excellent Internet sites provide a starting point for the study of DNA and the revolution it spawned (www.dnai .org/index.htm and www.dnaftb.org/dnaftb/), and a third excellent Web site is devoted to animations about most of the key processes involved in DNA and associated activities (http:// highered.mcgraw-hill.com/sites/dl/free/0072437316/120060/ravenanimation.html).

## DNA and RNA

The nucleic acids DNA and RNA consist of polarized polymers of repeating subunits, or nucleotides. A nucleotide consists of a nitrogen-containing organic base having 6 carbon atoms,


Figure 5 Differences in molecular configuration between DNA and RNA.


Figure 6 The components of a nucleotide, nucleotide-numbering nomenclature, and how nucleotides join together by phosphodiester bonding.
a 5-carbon sugar, and a phosphate molecule (Fig. 6). A nucleotides main support structure (backbone) consists of the sugar and phosphate molecules. The sugar-phosphate backbone lies on the outside of the helix, with the amine bases on the inside. In this configuration, a base on one strand points at a base on the second strand. When nucleotides join to form polynucleotides, they link at specific carbon locations on the sugar molecule. These locations, numbered, in the red circles from $1^{\prime}$ to $5^{\prime}$, begin with $1^{\prime}$ to the right of the oxygen ( O ) atom in the ring. The prime symbol ( ') distinguishes the carbons in the sugar from carbons in the base. Note from Figure 5 that RNA has one additional O atom in its sugar. Thus, the ribose sugar in RNA differs from the deoxyribose sugar in DNA. Nucleotides link when the phosphate at carbon 5' of one sugar combines at the carbon 3' position of another sugar. The phosphate group attaches to the $5^{\prime}$ carbon; the base attaches to the $1^{\prime}$ carbon. DNA and RNA synthesis always proceeds in the $5^{\prime}$ to $3^{\prime}$ direction.

The top of Figure 7 shows the successive levels (stages) of DNA packaging in a chromosome, proceeding from condensed metaphase (upper left) to supercoiled (middle right), loosely condensed, and uncondensed chromatin fiber stages. The negatively charged DNA molecule encircles and binds to a cluster of eight positively charged histone proteins (http://genome.nhgri.nih.gov/histones/). The histone (purple ball-like structure) clamps the DNA to the core of the molecule. The term nucleosome describes DNA wrapped around the puck-shaped histone proteins. Examining this region by electron microscopy reveals that one beadlike nucleosome contains 146 nucleotide base pairs wound twice like a rope around one cluster of the eight histones. The cluster contains two each of four different protein subunits (H2A, H2B, H3, H4), with each specific subunit having a different molecular mass. A DNA strand with about 60 base pairs and a ninth histone molecule links each cluster to the next one. During replication, the DNA uncoils from the histone core. The DNA molecule shown at the bottom of the figure eventually packs into the single metaphase chromosome displayed at the top left of the figure. The inset table of Figure 7 provides relevant information about chromosome folding in the DNA double helix, nucleosomes, 30-nm fiber, loops, minibands, and chromatids.

Polynucleotide: two or more nucleotides joined together; the phosphate at carbon $5^{\prime}$ of one sugar combines at the $3^{\prime}$ position of another sugar
Deoxyribose: sugar with 5 carbon atoms
Metaphase: step in mitosis (or meiosis) in which microtubules organize into a spindle and chromosomes move to the cells equator to align in pairs but have not yet migrated to the poles
Histone: positively charged small nuclear protein molecule cluster that binds to DNA (DNA winds around it) before it uncoils at the replication site; histones neutralize negatively charged DNA
Nucleosome: DNA coiled around a cluster of histone proteins; linked nucleosomes form chromatin
Electron microscope: electron beams with wavelengths thousands of times shorter than visible light replace light, allowing significantly higher resolution and magnification; the electrons pass through an ultrathin, specially prepared stained section of an embedded and dehydrated specimen maintained in a vacuum
Chromatid: one of the two doublestranded DNA daughter molecules of a duplicated, mitotic chromosome joined by a centromere


Figure 7 Double-helix DNA molecule packaged in a chromosome from the condensed metaphase stage, to supercoiled stage, to loosely condensed stage, and uncondensed chromatin fiber stage. The inset table provides summary details about chromosome folding from the DNA double helix to the chromatid. nm (nanometer), one-millionth mm.

The packaging of DNA within cells reflects a remarkable architectural accomplishment. The inset table summarizes DNA folding and how compacting the molecule enhances the efficiency of replication. In the compacted configuration as chromosomes, no transcription takes place, to ensure that DNA remains intact to survive mitosis. The chromatids (listed in the last line of the table) with 1 million minibands represent duplicate strands of DNA held together by a centromere just before the DNA separates into two daughter chromosomes. Figure 8 shows the details for chromosome 2 and the general nomenclature for identifying specific genes on the short p and long q arms of a chromosome. The right of the figure reveals the architectural details of a condensed metaphase chromosome.

## Linking Nucleotides: Phosphodiester Bonding

The chemical reaction when two nucleotides link together eliminates a water molecule, a process termed dehydration synthesis; it involves the phosphate molecule from one nucleotide and the hydroxyl $(\mathrm{OH})$ molecule of another nucleotide. The resultant phosphodiester bond (Fig. 9) shown for RNA and DNA is a relatively strong covalent bond. The new polymer, now two units long, still has free phosphate and OH groups for linking to other nucleotides. This linkage forms an incredibly long chain with thousands of nucleotides, although the example shows only a few. In DNA measurement, the term kilobase ( $\mathbf{k b}$ ) represents a unit of DNA fragment length equal to 1000 nucleotides. Another nucleic acid, adenosine triphosphate (ATP), contains a 5-carbon sugar base (adenine) and three phosphate groups. Unlike DNA and RNA that transfer genetic information, ATP continually transfers chemical energy to power the bodys cells throughout life.


> View of a metaphase chromosome with its kinetichore (three-layered protein disc containing chromatin) and kinetichore microtubules located in the centromere region (point of chromosome constriction with specific DNA sequence).

The letter $p$ denotes the short (top) arm of the chromosome; the letter q the longer (bottom) arm. Each arm has a region numbered from the centromere to the tip of the chromosome (telemere). Each banded region within p and q is also numbered. Thus, each chromosome can be identified by its own "address"; in the example, 2 p25 refers to chromosome 2, p arm (short), region 2 , band 5.

Mitosis: separation of duplicated chromosomes to create identical daughter cells with mirror-image (genetically identical) chromosomes; prophase, metaphase, anaphase, and telophase are the four phases of mitosis
Centromere: region of a mitotic chromosome (indentation) before replication where two daughter chromatids join
Daughter chromosome: descendent chromosome following replication of the original (mother) chromosome
Dehydration synthesis: removal of the equivalent of a water molecule from two subunit molecules that form a new, larger molecule
Phosphodiester bond: strong covalent bond formed when two nucleotides link together, eliminating a water molecule; bonding involves the phosphate molecule from one nucleotide and the hydroxyl $(\mathrm{OH})$ molecule of another nucleotide
Covalent bond: sharing one or more pairs of electrons between two atoms
Kilobase (kb): a unit of length for DNA fragments equal to 1000 nucleotides
Adenine: one of the four bases in DNA; always pairs with thymine adenosine triphosphate (ATP), contains a 5-carbon sugar base (adenine) and three phosphate groups. Unlike DNA and RNA that transfer genetic information, ATP continually transfers chemical energy to power the bodys cells throughout life

Figure 8 Chromosome 2. Left. Identification of gene 2 p25 on chromosome 2. Right. Metaphase chromosome.


Figure 9 Linking of nucleotides by phosphodiester bonding in RNA and DNA. The general schema shown at the bottom left illustrates the relative position of the sugar, base, and phosphate groups within a nucleotide along the $5^{\prime}$ to $3^{\prime}$ direction, including phosphodiester bonding.

Complementary strand: when one DNA strand runs in the $5^{\prime}$ to $3^{\prime}$ direction, the complementary strand runs oppositely from $3^{\prime}$ to $5^{\prime}$
Antiparallel: arranged in parallel but with opposite orientation as in DNA

Guanine: one of the four bases in DNA; always pairs with cytosine Cytosine: one of the four bases in DNA; always pairs with guanine Thymine: one of the four bases in DNA; always pairs with adenine Chargaffs rule: pyrimidine content ( T C ) equals purine content (A G), where ([T] [A]; [G] $[\mathrm{C}])$; (A T) $/(\mathrm{G} \mathrm{C}$ ) varies between different organisms but is constant within an organism

## Structure of DNA

Figure 10 shows the DNA molecule composed of a sequence of sugar phosphate chains with hydrogen bonding between the nitrogenous bases. In the double-stranded DNA molecule, the strands are not identical. They lie parallel but line up in opposite directions. One strand runs in the $5^{\prime}$ to $3^{\prime}$ direction, and its complementary strand runs from $3^{\prime}$ to $5^{\prime}$. The top left of the figure illustrates the antiparallel arrangement of the DNA strands, including a close-up view of the hydrogen bonding between the base pairs that holds the parallel spiral ribbons together. The deduction by Watson and Crick of the antiparallel nature of the DNA strands resolved one of the remaining mysteries about DNAs structure and ultimately how replication proceeds.

## Base Pairing

One of the golden rules of DNAs molecular arrangement, displayed in Figure 11, relates to the pairing of the four bases, the letters of the DNA alphabet. Guanine (G) always links with cytosine ( $\mathbf{C}$ ), and adenine (A) always links with thymine ( $\mathbf{T}$ ) in the same proportions within all DNA molecules. Stated somewhat differently, whenever a G base occurs in one of the strands, a C base occurs opposite it in the opposing strand. Likewise, when an A base occurs in one strand, a T base occurs in the other strand. The proportionality of the four bases was confirmed in 1950 by Erwin Chargaff (1905 2002) of Columbia University, who determined the relative amounts of each base in DNA. Chargaffs rule determined regularities among the four chemical bases of DNA (www.cumc.columbia.edu/news/journal/journal-o/fall-2003/dna.html). The molar amount of thymine always equaled the molar amount of adenine, and similarly, molar amounts of guanine always equaled cytosine on one DNA strand $([T]=[\mathrm{A}] ;[\mathrm{G}]=[\mathrm{C}])$. Watson and Crick relied on this information to piece together DNAs structure. In their model, each rung of the DNA ladder


Figure 10 DNA molecule. Top. Antiparallel arrangement of a DNA double strand from the $5^{\prime}$ to $3^{\prime}$ and $3^{\prime}$ to $5^{\prime}$ directions. Note the hydrogen bonding between $G$ and $C$ and $A$ and $T$. Bottom. DNA molecule with its sequence of sugar phosphate chains and hydrogen bonding between nitrogenous bases. The specific sequence of base pairs ultimately determines every proteins specific characteristics. Adenine always binds with thymine.
consists of a purine connected to a pyrimidine. The term base pairing refers to the joining of complementary bases ( G with C , or A with T ). The G and A nitrogenous bases consist of two rings (called a purine), while the two other bases, C and T , have a single ring (called a pyrimidine). Thus, each base pair consists of one larger purine base mated to a smaller pyrimidine base (http://library.med.utah.edu/NetBiochem/pupyr/pp.htm). Adenine and thymine form two strong hydrogen bonds between the base pairs, but not with G or C . Similarly, G and C form

Complementary bases: pairing in DNA between bases A T or T A, and C G or G C
Purine: nitrogen-containing, double-ring basic compound in nucleic acids; purines in DNA and RNA include adenine and guanine Pyrimidine: nitrogen-containing, single-ring basic compound in nucleic acids; pyrimidines include cytosine and thymine in DNA and cytosine and uracil in RNA





PYRIMIDINE BASES: SINGLE-RING STRUCTURE
Figure 11 Base pairing. A. Configuration details of the DNA double-helix molecule with base pairing and hydrogen bonding for adenine (A) thymine ( $T$ ) and guanine ( G ) cytosine (C). The two spiral ribbons represent the sugar (deoxyribose) phosphate backbone of DNA. Note that two hydrogen bonds shown in dark red form between A and T and three form between G and C. This happens because the two polynucleotide chains that contain them lie antiparallel to each other. B. The five bases classified as purines (A and $G$ ) or pyrimidines ( $C$, uracil, $T$ ).
three strong hydrogen bonds to keep the C G base pair intact, but not with A or T . The additive effect of millions of relatively weak hydrogen bonds within the DNA molecule keeps the helix from separating. Applying Chargaffs rule within an organism, the pyrimidine content (TC) equals the purine content (AG); however, the relative amounts of pyrimidines and purines differ among organisms.

The top of Figure 11 illustrates the DNA double-helix molecule, with the base pairing and hydrogen bonding for A T and G C. Precise X-ray measurements have determined that the DNA double helix has a width of 2.0 nm (nanometers; $10{ }^{9} \mathrm{~m}$ [or 10 ] one-millionth millimeter, or $1000 \mathrm{~nm}=1 \mu \mathrm{~m}$ ), with exactly 10 base pairs in each full turn, with the height of each turn equal to 3.4 nm . The bottom of the figure shows the five bases classified as either a purine or pyrimidine. Note the pyrimidine base uracil. In RNA (next section), uracil replaces thymine, so that adenine pairs with uracil as A U. The inclusion of uracil helps to distinguish RNA from DNAbesides RNAs extra oxygen atom in the ribose sugar and usually singlestrand configuration. The simple mnemonic cut the pie helps to associate the pyrimidine or purine bases: CUT represents cytosine, uracil, and thymine, with the pyrimidines represented by pie.

The heat required to dissociate the H bonds between two strands of DNA determines the DNA molecules melting point. Proportionality exists between the number of bonds in the base pair and the energy required to break the bonds. Thus, the three hydrogen bonds that hold C and G together require more heat to break (higher melting point) than the two hydrogen bonds between A and T.

## Forms of RNA

The three forms of RNA include:

1. Messenger RNA (mRNA) molecules, which serve as a template for protein synthesis, based on the molecular sequence from a small section of the DNA molecule
2. Transfer RNA (tRNA) molecules, which, as the name implies, transfer amino acids to the growing peptide chain on the ribosome
3. Ribosomal RNA (rRNA) molecules, which account for about $50 \%$ of the mass of ribosomes and whose structures aid in assembling amino acids into polypeptides

Each of the three RNA forms has its own polymerase, or complex enzyme: polymerase I is associated with rRNA, polymerase II with mRNA, and polymerase III with tRNA. RNA polymerases, unlike their DNA counterparts, do not require a primer to initiate RNA chain synthesis. The term primase refers to the RNA polymerase that produces the primer for DNA synthesis. The three RNA polymerases have between 6 and 10 protein subunits that differ in molecular structure and regulatory function. About $97 \%$ of cellular RNA exists as rRNA; mRNA accounts for about $2 \%$, and tRNA less than $1 \%$. Compared with the DNA in a single chromosome that contains up to 250 million base pairs, RNA contains no more than a few thousand, which makes an RNA molecule considerably shorter. This makes sense because RNA carries only part of the information from one segment of the DNA molecule that it copied. In a subsequent section on protein synthesis, beginning on page 954, we discuss how mRNA duplicates DNAs genetic information and the roles of rRNA and tRNA in protein synthesis.

## Codons and Natures Genetic Code

First presented by Marshall Nirenberg (1968 Nobel Prize in Physiology or Medicine; interpretation of the genetic code and its function in protein synthesis) and Johann Matthaei (best known for discovering that the RNA sequence UUU directs the addition of phenylalanine to any growing protein chain) of the NIH in 1961 at the International Congress of Biochemistry in Moscow (and 3 years later by Philip Leder and Marshall Nirenberg), the coded message carried by the mRNA molecule exists as a series of three bases, or codons

Uracil: base that replaces thymine in RNA that pairs with the adenine base

Melting point: The temperature range or a solid where it changes state from solid to liquid, and the solid and liquid phases exist in equilibrium
Messenger RNA (mRNA): molecule that carries genetic information (complementary copy of one of the two DNA strands) between a gene and the ribosomes that translate the genetic information into proteins
Transfer RNA (tRNA): RNA molecules that transport a specific amino acid to ribosomes; translating information in the mRNA nucleotide into the amino acid sequence of a polypeptide
Transfer RNA (tRNA) molecules, which, as the name implies, transfer amino acids to the growing peptide chain on the ribosome
Ribosomal RNA (rRNA): structural part of a ribosome that contains RNA molecules
Ribosomal RNA (rRNA) molecules, which account for about $50 \%$ of the mass of ribosomes and whose structures aid in assembling amino acids into polypeptides
Polymerase (DNA or RNA): enzyme that catalyzes nucleic acid synthesis on preexisting nucleic acid templates; assembles RNA from ribonucleotides or DNA from deoxyribonucleotides Primer: a short nucleotide segment that pairs with a single DNA strand at a free $3-\mathrm{OH}$ end (template strand) so DNA polymerase can synthesize a DNA chain; cells use RNA primers, while the PCR method uses DNA primers
Primase: enzyme that synthesizes the RNA primer to initiate DNA synthesis

Codon: sequence of three DNA or RNA bases (nucleotides) that encode (specify) a single amino acid

Methionine: nutritionally essential amino acid; most natural source of active methyl groups in the body. The triplet sequence A-U-G on mRNA codes this amino acid

Translation: polypeptide formation (protein synthesis) on a ribosome using the amino acid sequence specified by an mRNA nucleotide sequence
Stop codon: 3 of the 64 codon combinations that terminate a polypeptide assembly


Figure 12 The codon tablethe alphabet of the universal genetic code. From the time that Watson and Crick correctly deduced DNAs helical structure in 1953, different coding schemes attempted to explain DNAs alphabetic configuration (including imaginative proposals by physicists George Gamow, Richard Feynman, and Edward Teller); in 1964, Paul Leder and Marshall Nirenberg established the final code-breaking sequences for RNA synthesis. ${ }^{79}$ The three-letter codon word in mRNA is complementary to the corresponding three-letter codon within DNA from which it was transcribed.
(http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/Codons.html). Each DNA and RNA three-letter codon block of information corresponds to one of the bodys 20 amino acids. A codon codes for one amino acid, but most amino acids are represented by more than one codon. If only one base coded for an amino acid, only four amino acids could be coded instead of 20. Even if two adjacent bases coded for an amino acid, there would still not be enough combinations to make 20 amino acids. Fortunately, scientists deduced that three bases coding for an amino acid ( $4^{3}=64$ combinations) met the requirement to include all the amino acids. For example, the triplet sequence A-U-G on mRNA displayed in Figure 12 (green box within left yellow panel) refers to a specific code for the sulfur-containing essential amino acid methionine. The A (adenine) is called the first letter; U (uracil), the second letter; and G (guanine), the third letter. With only 20 amino acids and 64 codons, several codons code for more than one amino acid. In fact, most amino acids have more than one codon or sequence of letters, with no intervening code disrupting the sequence.

## Sequencing of Codons

The amino acid serine exemplifies a four-codon sequence that differs only in the base occupying the third nucleotide or letter. The sequence is U-C-U, U-C-C, U-C-A, and U-C-G, with identical first two letters. The first two bases are the defining letters of the codon sequence. Reading from the $5^{\prime}$ end of each codon, the first and second letters remain generally constant for each amino acid, while the base in the third position wobbles. Thus, for example, the codon for phenylalanine contains a U or C as the third letter. Because both $\mathrm{U}-\mathrm{U}-\mathrm{U}$ and U-U-C code for phenylalanine, phenylalanine is inserted into a newly synthesized polypeptide if U-U-U or U-U-C is read during translation or protein synthesis.

Codon Table. Similar to the English alphabet with its 26 letters, the codon table in Figure 12 provides the genetic code alphabet, but with only four distinct lettersthe code words in the analogy. When we exclude the three stop codons (red boxes) that signal termination of linkages in polypeptide chains, the remaining 61 codons represent the useful information for protein
synthesis. The stop codons, U-A-A, U-A-G, and U-G-A, signal the end of a genetic message (i.e., termination of protein synthesis), like periods at the end of a sentence. When the translation machinery encounters one of these chain terminators, translation halts, releasing the polypeptide from the translation complex. Recall that the start codon for methionine (A-U-G) initiates polypeptide formation; it also can code for methionine within peptide chains. A Codon Wheel Table provides a relatively simple alternative compared to the codon table in Figure 12 to view the first, second, and third nucleotides in the codon (www.dna20.com/codontablewheel.php).

## HOW DNA REPLICATES

A DNA replication fork refers to the Y-shaped region of replicating DNA molecules. As the double helix unwinds, nucleotide duplication occurs on both strands at a rate of about 50 nucleotide additions per second. Each strand serves as a template to create two new daughter strands by complementary base pairing. This mechanism provides each daughter helix with one intact strand from the parent (original strand) and one newly synthesized strand. Each strand, a complementary mirror image of the other, can serve as a template to reconstruct the other strand. Figure 13 presents a schematic overview of DNA replication. Replication begins with the untwisted, unzipped appearance of two DNA strands (the helicase unwinds a


Figure 13 Replication bubble and DNA replication. Note the straight (not helical) double strands of DNA in stage 1 after untwisting by DNA gyrase and unwinding by helicase. The DNA represents an elongated bubble as the double strand opens and DNA begins to divide (stage 2, continuous synthesis). In stage 3 (discontinuous synthesis), replication proceeds in opposite directions along each end of the Y-shaped replication forks.

DNA replication fork: Y-shaped region of replicating DNA molecules where the enzymes replicating a DNA molecule bind to an untwisted, single DNA strand
Helicase: enzymes that catalyze (use the energy of nucleotide hydrolysis) to unwind and separate double-stranded DNA or RNA during its replication


Figure 14 Three stages of DNA replication. Stage 1, unwinding; stage 2, continuous synthesis; stage 3, discontinuous synthesis.
segment of the DNA) on the top, where replication starts at specific zones called origins of replication and ends where RNA primers (green) start new DNA chains on the leading strand. Unwinding a segment of DNA breaks the hydrogen bonds between the two complementary strands of DNA. Several origins of replication exist along a chromosome, replicating simultaneously in opposite directions. Multiple replications reduce the time to propagate DNA by an order of magnitude, because complete duplication of one strand of human DNA takes approximately 6 hours. The number of base pairs along the chromosomes replication region ranges from 10,000 up to 1 million, with an average of about 100,000 base pairs.

## Stages of DNA Replication

Figure 14 amplifies the three stages of DNA replication illustrated in Figure 13. In stage 1, helicase enzymes (orange) unwind the molecules double helix. This stabilizes the strands, while single-strand binding protein (SSB) maintains separation between the two DNA strands. In stage 2, DNA polymerase (purple sphere) immediately acts on DNAs leading strand to add nucleotides toward the strands $3^{\prime}$ end (red). The process of creating the strand, called continuous synthesis, proceeds uninterrupted. The other DNA strand, known as a lagging strand, is created in shorter segments with gaps in its structure away from the replication fork, compared with the leading strand. In stage 3, discontinuous synthesis, a 10-nucleotide RNA primer, under the influence of DNA polymerase I, adds 1000 nucleotides ahead of the lagging strands 5 ' end until its gap fills. Thus, new DNA nucleotides replace the existing RNA nucleotides. DNA ligase then affixes the newly created, smaller Okazaki fragments, 100 to 200 nucleotides long, to the lagging strand in the $5^{\prime}$ to $3^{\prime}$ direction to make a complete DNA strand.

## Pivotal Role for DNA Polymerase

DNA polymerase plays the central role in lifes processes because this enzyme consistently duplicates the genetic information from generation to generation. The rich instructional bank of DNA information has been modified and improved over more than 3 billion years to build proteins and other molecules atom by atom according to selective molecular directions. For every cell that divides, DNA polymerase duplicates its entire DNA, so that cells transfer one copy to each daughter cell. DNA polymerase can be considered the most accurate of the thousands of enzymes because it creates an exact DNA copy, transmitting less than one error in


Figure 15 Four stages of the cell cycle and its molecular control mechanisms. Note the three checkpoints and the question(s) posed prior to DNA synthesis during the $S$ phase.
a billion bases. Stated another way, one might find only one grammatical mistake in a thousand novels! The excellent match of C to G and A to T provides much of the specificity needed for this high accuracy, but DNA polymerase adds an extra step. After it copies each base, it proofreads it and deletes any wrong base sequence from its grasp. Polymerases can vary in structure from relatively simple to complex. In humans, polymerases are complex structures that unwind the helix, build an RNA primer, and construct a new strand. Some even have a ring-shaped structure that clamps the polymerase to the DNA strand. Polymerase function varies from day-to-day DNA repair and maintenance to the complex task of DNA replication when the cell divides. Here, we discuss the important role of DNA polymerase in forensic medicine in building a large quantity of identical DNA strands from a miniscule amount of DNA from a crime scene or paternity case.

## Control of DNA Synthesis

Several molecular control mechanisms trigger DNA synthesis in cells. The cell cycle illustrated in Figure 15 depicts the four phases of a cells life. Like a clock or thermostat, each phase has defined on and off periods regulated by enzymes that start and terminate a particular stage. DNA replication (synthesis) occurs in the $S$ phase, which lasts approximately 6 hours. The three checkpoints serve as the thermostats sensors, each with specific regulator enzymes called cyclins governing a specific function. Toward the end of the G1 (growth) stage, cyclin enzymes achieve a critical activity level that triggers a response when the cell achieves adequate size within a favorable environment. If cell size and environment prove satisfactory, the cell proceeds to $S$ phase for DNA synthesis. Following DNA synthesis, the G1 cyclins degrade as the cell prepares to enter mitosis (M phase). The next checkpoint occurs between the G2 and M phases, a crucial time in the cell cycle. When the DNA has been replicated without error, the cell enters mitosis and then progresses to complete telophase. Mitosis produces two cells genetically identical to the original parent cell.

## Cell Life Cycle Controllers

Figure 15 provides details of the workings of cell life cycle controllers. Cyclin-dependent kinases (cdk1 and cdk2) activate specific cyclins. Once this occurs, the complex of the two protein kinases regulates how the cell proceeds through its cycle. After each stage, cyclin

Cell cycle: four stages of a cells life cycle
Cyclins: specific cell-regulator enzymes that activate and deactivate protein kinases in the cell cycle and help to control progression from one stage in the cycle to the next. They are destroyed after their function by a ubiquitinsignaled process
G1: period within the cell cycle preceding DNA synthesis
Mitosis: nuclear division that produces two daughter nuclei identical to the original nucleus
G2: period within the cell cycle from the end of DNA synthesis and start of the $M$ phase
Telophase: final stage in mitosis (or meiosis); the spindle disappears and daughter sets of separated chromosomes decondense, the cytoplasm splits, a nuclear envelope resurrounds the chromosomes, and nucleoli appear
Kinase: enzyme that shuttles a phosphate group (PO4) from ATP or another nucleoside triphosphate to a different molecule
Protein kinase: enzyme that transfers phosphate groups to other proteins, changing their activity

Erythropoietin: hormone produced by the kidneys that initiates red blood cell precursors and their maturation to erythrocytes

Insulin-like growth factor (IGF): small protein hormone with the potent effect of increasing aspects of cellular growth and development; IGF-1 (also known as somatomedin C) controls the general effects of growth hormone on growth

Cancer: accelerated, unplanned growth and division of mutant cells that form larger than normal cell clusters that become tumors

Transcription: RNA polymerase assembles an mRNA molecule complementary to the genes nucleotide (making an RNA copy of a gene)

Functional protein: protein with its own set of genetically determined information to carry out specific function(s)

DNA gyrase: enzyme that relaxes supercoiled DNA
Supercoiled DNA: configuration of twisted DNA packed into a cell prior to replication
DNA helicase: enzyme that catalyzes the unwinding of doublehelical DNA by using energy released from ATP hydrolysis
DNA polymerase III (Pol III): enzyme involved in making DNA when chromosomes replicate
Replication bubble: site where DNA divides
degradation temporarily halts cdk activity. With mitosis complete, the process begins again, accumulating cyclins for the next initial G1 growth stage.

The cdk2 protein turns on in the transition between the G1 and S stages; cdk1 drives the cell cycle from stage G2 to M stage. In other words, the cyclin-dependent protein kinases phosphorylate their target cyclin proteins through the different stages of the cell cycle. Signaling proteins called growth factors operate in concert during the cycle. For example, mitosispromoting factor (MPF) governs the sequence of events between the G1 and M phases of the cell cycle. Other growth factors also exert their effect. For example, the hormone erythropoietin produced by the kidneys (see Chapters 20, 23, and 24) initiates proliferation of red blood cell precursors and their maturation to erythrocytes. Nerve growth factor (NGF) modulates neuronal cell growth during development of the nervous system, interleukin-2 participates in immune cell proliferation, and insulin-like growth factor (IGF) facilitates many metabolic events related to cellular growth and development, including a role in the brains center for smell, ${ }^{104}$ the role of muscle strength and aerobic training in the elderly, ${ }^{117}$ and a role in increased breast cancer risk and or death. ${ }^{58}$

A unique feature of growth factors relates to how they control the transition stages during cellular growth and differentiation. Failure to work in concert with cyclins and kinases during cellular proliferation terminates control of cellular proliferation, causing cells to continue to divide unchecked. This can serve both positive and negative functions. The latter produce lethal effects because DNA synthesis would progress to the M stage by successfully reproducing a mutant cancer gene. If highly specialized genes called tumor suppressors (e.g., the $p 53$ gene) cannot halt the cell cycle long enough for DNA repair enzymes to function, then cell growth proceeds rapidly and unchecked to produce tumors. Also, deleterious mutations can pass to progeny cells; the successive buildup of mutations in all likelihood ultimately develops into cancer.

## PROTEIN SYNTHESIS: TRANSCRIPTION AND TRANSLATION

Protein synthesis involves two prominent events:

1. Transcription in the cell nucleus that creates a single-stranded RNA copy of the genetic information stored in the double-stranded DNA molecule
2. RNA translation in the cell cytoplasm to form proteins

In essence, the DNA molecules nucleotide base sequence defines the proteins ultimate 3 -dimensional shape. Our tour of protein synthesis begins by considering a roadmap of the prominent events in assembling proteins from precursor biomolecules (i.e., lipids, carbohydrates, proteins, and nucleic acids). The story originates in the cells ribosomes and ends with creation of a fully functional proteina unique molecule whose structure dictates its operation and specific mode of action.

## Generalized Overview

Figure 16 provides a generalized overview of six stages in protein synthesis. Prior to stage 1, the DNA under enzyme control untwists to expose its code. Before DNAs hydrogen bonds break, DNA topoisomerase enzymes (e.g., DNA gyrase) relax the supercoiled DNA by literally cutting the DNA to create a double-stranded break, but maintain hold of both ends of the DNA. The two halves of the molecule then rotate relative to each other (they untwist) before rejoining. Once the strand untwists, DNA helicase unwinds the helical DNA molecule by separating the hydrogen bonds between the base pairs. The singlestrand binding protein (SSB) binds to one of the unpaired DNA strands to inhibit its reemerging with its neighbor (complementary) strand. This prevents the strands from recoiling and re-forming the double helix. DNA polymerase III (Pol III) serves as a verifier to ensure that the bases pair correctly. If they do, the enzyme joins the nucleotides together. If not, the mismatched base pair is rejected. A previous section (How DNA Replicates, p. 951) provides further details about the DNA replication bubble and three stages of DNA replication.


Figure 16 Generalized overview of six stages (numbered yellow boxes) in protein synthesis. Notable features include the schematic depiction of events during transcription (stages labeled 1 and 2 within the cells nucleus) and translation (stages labeled 3 to 6 in the cells cytoplasm). The bottom inset box summarizes the two principle aspects of protein synthesis (transcription and translation) following replication of the DNA molecule.

Stage 1 signifies the start of transcription. This involves copying a discrete section of the genetic sequence directly from the DNA template to the growing RNA strand. The enzyme RNA polymerase I (referred to as I because it was discovered before the other polymerases) in Figure 16 binds to the specific promoter (initiator) region at the beginning of a gene. Linking to a specific nitrogenous base sequence, it alerts transcription to initiate formation of the complementary RNA strand. When RNA polymerase arrives at the end of the gene, it receives a stop signal from one of three nucleotide sequences (U-A-A, U-A-G, U-G-A; see Fig. 12) and disengages from the DNA. The newly assembled RNA strand, called the primary RNA transcript of

RNA polymerase I: enzyme that synthesizes RNA from a DNA template
Promoter: site on DNA where RNA polymerase binds and initiates transcription (promotes gene expression); required for expression and regulation of gene transcription
Primary RNA transcript: mRNA molecule transcribed as an exact complement to a gene

Nuclear pore complex: octagonal, disk-shaped structure that allows proteins to cross the nuclear envelope into the cytoplasm after protein receptors dock with the protein

Replication: duplication of DNA prior to cell division
the gene (stage 2), is processed and eventually exits the nucleus to the cytoplasm through the octagon disk-shaped nuclear pore complex. This complex selectively transports proteins across the nuclear envelope after specific protein receptors dock with the protein, allowing it to enter its channel and pass to the cytoplasm. Note that once mRNA leaves the nucleus in stage 2, it links to the ribosomes poly A site and waits to bind to the appropriately coded amino acid floating freely in the cytoplasm. A specific orientation of mRNA on the ribosome exposes only one codon at a time to match and bind with its anticodon contained on a tRNA.

Within the cytoplasm, translation proceeds through stage 3 (tRNA binds amino acids), stage 4 (tRNA binds to a ribosome, signifying the start of amino acid assembly), and stage 5 (the peptide chain increases in length), until stage 6, when a fully functional protein forms. The inset box at the bottom of Figure 16 summarizes the two key aspects of protein synthesis following DNA molecule replication:

1. Transcription of information in the genetic code from DNA molecules to RNA molecules in the nucleus (RNA synthesis) for decoding
2. Translation of genetic information in the cytoplasm to synthesize proteins

## Transcription of the Genetic Code: RNA Synthesis and Gene Expression

A gene, located along a specific chromosome at a specific site, contains the sequence (code, or plan) required to synthesize a protein. The gene within the DNA molecule ranges from several thousand to millions of bases. Unlocking the regulation of a particular gene provides the driving force for many molecular biologists passion for the field.

The left side of Figure 17 highlights the five stages of gene expression in human cells. The same two basic sequences of molecular events occur whether in the simplest bacteria (prokaryotes) that dominated Earth during its first 2 billion or so years of evolution or in eukaryotes that evolved about 1.5 billion years ago. The eukaryotes include thousands of uniand multicellular organisms (including humans) with membrane-bound organelles. The cells of these organisms include a true nucleus with chromosomes. In contrast, prokaryotes have no defined nucleus and generally have no membrane-bound organelles, the DNA remains single stranded, and the main eventstranscription and translationeecur coupled, not separately in the nucleus and cytoplasm, respectively. In eukaryotes, in contrast, translating the code for protein synthesis does not occur until the RNA strand exits the nucleus. The bottom red box of the figure illustrates the proposed flow of genetic information that Francis Crick in 1956 termed the central dogma.

The Watson and Crick hypothesis posited that chromosomal DNA functions as the template for RNA molecules. These molecules then move to the cytoplasm to dictate a proteins amino acid arrangement. The down arrow (Fig. 17, right) from DNA emphasizes the proposition that DNA provides the template for self-replication. The next phase emphasizes that all cellular RNA molecules were made on (transcribed from) DNA templates. Concomitantly, RNA templates determined (translated) the proteins. The unidirectionality of the two arrows between stages 3 and 4 and 4 and 5 indicates that protein templates would never determine RNA sequences, nor would RNA templates create DNA. With few exceptions, the central dogma has stood the test of time and remains essentially valid. Except in some instances in which the reproductive cycle of retroviruses adds a step using a reverse transcriptase enzyme, proteins almost never serve as templates for RNA. If they did, the arrows would go bidirectionally between DNA and RNA. Interestingly, at the time Crick proposed the central dogma, little direct experimental support existed for this mechanistic concept that RNA serves as the template for DNA.

## Examples of Gene Expression

Beginning with conception, gene expression lays the eventual groundwork for each persons diverse cells, tissues, organs, and systems. Gene expression explains why no two people match exactly in any outer or even inner physical traits. No two hearts, livers, kidneys, brains, vertebrae, adrenal glands, intraabdominal fat distributions, teeth, nostrils, ears, or


Figure 17 Gene expression and translation. Left. Five stages of gene expression in eukaryotes. Transcription (stage 1) produces an mRNA copy of the gene. In translation (stage 4), the information in mRNA molecules directs which amino acid to produce and where to position the amino acids when the ribosomes synthesize polypeptides. Translation refers to the creation (assembly) of a protein on the ribosome; mRNA copies the specific coded information from the DNA strand. Posttranslational modifications can alter polypeptides in their transition to a functional protein (stage 5). Right. Cricks 1956 working hypothesis (central dogma) posits that two distinct phases play the defining role in expressing the genetic information encoded in DNA molecules. In phase 1 (transcription), RNA polymerase enzyme assembles an mRNA molecule with its nucleotide sequence complementary to the genes nucleotide sequence. In phase 2 (translation), a ribosome assembles a polypeptide (protein) in which mRNAs nucleotide sequence specifies the final amino acid configuration.
fingerprints match precisely. Even identical twins with the same starting genetic machinery have unique and subtle outward physical characteristics and often not-so-subtle distinctive personalities. At times, some aspect of gene expression remains repressed or off, no longer needing to remain active or on. Most of the time, gene expression fits or modulates to the bodys current metabolic state, persisting throughout the individuals life span. The biologic catalyststhe enzymes containing a minimum of 100 amino acid residueseffectively control the genetic machinery and subsequent transformation and control of different energy forms. Six potential regions within the nucleus and cytoplasm shown in Figure 18 regulate gene expression. When the mRNA travels to the cytoplasm from the nucleus, protein regulation via translation in the cytoplasm at sites 3 to 6 can begin, as can further modifications once a protein forms as indicated at site 6 .


Figure 18 Six potential sites regulate gene expression.

## Protein Enzymes

Acting as biomolecular switches, enzymes selectively regulate thousands of cellular activities, coupling some and uncoupling others, all orchestrated in fractions of a second throughout an organisms life. To categorize different kinds of enzymes, the Enzyme Commission of the International Union of Biochemistry and Molecular Biology (IUBMB; www.iubmb.org/) devised a nomenclature and numbering system for the following six major classes of enzymes, each with subgroups and sub-subgroups:

1. Oxidoreductases: catalyze oxidation reduction reactions
2. Transferases: catalyze transfer of functional groups between molecules
3. Hydrolases: catalyze hydrolytic cleavage
4. Lyases: catalyze removal of a group from or addition of a group to a double bond, or other changes involving electron rearrangement
5. Isomerases: catalyze intramolecular rearrangement
6. Ligases: catalyze reactions that join two molecules


Figure 19 Structure of transcription complex involved in transcriptional control. At the start of the coding sequence along DNAs double helix ( purple ropelike structure), the basal (transcription) factors labeled (from left to right) A, TATA binding protein, B, F, E, and H correctly position RNA polymerase and then release it to transcribe mRNA.

## Transcription Control

Factors that affect gene expression during transcription include diverse switches, or regulator enzyme activator proteins and repressor proteins. These operate at the site of the active gene and also at sites thousands of nucleotides away from the starting site. This geography of operation provides great regulatory freedom in how genes initially switch on and off prior to and during transcription. For example, some enzymes accelerate the capture of RNA polymerase to enhance transcription, while others repress transcription by delaying different sequences of events. In essence, activator and repressor proteins control transcription rate in the following two ways:

1. Activator proteins bind to DNA at sites called enhancer sites. Figure 19 shows the transcription complex (proteins involved in transcription) correctly positioning RNA polymerase at the proper gene location. The folding of the DNA strand brings the enhancer site into close proximity to the transcription complex. This increases communication between the activator proteins and the transcription complex. Another group of proteins, termed coactivator proteins, transmits signals from activator proteins to other factors (called basal factors) close to the DNA strand, helping to position RNA polymerase correctly at the precise location in DNAs coding region.
2. Repressor proteins bind to silencer protein binding sites along the DNA strand. The silencer sequence, adjacent to or overlapping the enhancer region, can prevent an activator protein from binding to a neighboring enhancer site. This delays or cancels transcription from initiating at a discrete mRNA coding sequence.

Activator protein: binds to DNA at enhancer sites to position RNA polymerase correctly on the gene Repressor protein: blocks action of RNA polymerase on DNA that turns genes off

Enhancer site: where gene expression increases from contact with the transcription complex
Coactivator protein: transmits signals from activator proteins to basal factors
Coding region: location on the DNA strand where transcription occurs


Figure 20 Top. Enzyme substrate interaction. Bottom. Reaction rate versus substrate concentration with and without enzyme action.

## Enzyme Turnover Number

Some enzymes fulfill their functions more quickly than others. An important way to measure an enzymes performance relates to how quickly it binds to and releases from its substrate(s) during biomolecular reactions; that is, its turnover rate or number. To encourage a reaction, an enzyme must correctly position or orient itself with its substrate. The electrical properties of a substrate change depending in part on its correct spatial arrangement with the substrate. In essence, the enzymes positive and negative charges align with the substrates positive and negative charges to favorably continue a chemical reaction.

The top of Figure 20 shows an enzyme arranging to link up with its intended substrate to create an enzyme substrate complex. Once the enzyme fulfills its function, the complex breaks down, releasing its product. The enzyme then almost instantaneously catalyzes another reaction. The rate of end-product formation depends on two factors:

1. The concentration of substrate
2. The nature of the enzyme substrate complex.

As the concentration of substrate increases, the reaction rate moves toward its maximum. At this point, all of the enzymes active sites fully engage the substrates active sites. Continued new product formation now depends only on the rapidity of substrate processing, referred to as turnover number. This can vary tremendously, from 1 to 10,000 molecules per second, but a turnover number of 1000 substrate molecules per second characterizes many enzymes. A high turnover ensures that enzymes remain turned on at their optimal concentration during gene expression. The enzymes binding sites, while they remain in the on position with their substrate for extremely brief periods, may do so more dynamically than previously believed. Instead of remaining coupled for the entire period, other similar binding sites may switch places with the originally bound site (analogous to hit-join-and-run), suggesting that enzyme molecules maintain more mobility than previously thought. Future research will
determine whether changes in binding site cycling will allow other proteins in the signaling chain to participate in still other gene-regulating pathways. If so, then the elaborate nature of enzyme turnover rates and unique protein receptor interactions take on even greater complexity than previously believed.

## Gene Expression and Human Exercise Performance

The current and future decades in exercise physiology research will continue to build upon the rapidly developing knowledge base about gene expression and the human gene map for exercise performance and health-related phenotypes (see Medicine \& Science in Sports and Exercise 2001;33:885; with annual updates through 2009, and the obesity gene map database; http://obesitygene.pbrc.edu/, with access to 1999 to 2005 publications from the Human Genomics Laboratory). ${ }^{100}$

In the not too distant future, sport scientists will routinely incorporate simplified molecular biologic techniques to assess an individuals potential for strength, speed, endurance, and other traits that can be turned on to selectively enhance exercise performance. While it might seem far-fetched now, choosing astronauts for extended-duration missions to other planets may rely on molecular biology to select candidates with more resistant genes to protect against bone loss or spatial disorientation with prolonged microgravity exposure. Coaches and trainers will undoubtedly apply technologies from molecular medicine to genetically screen young children for gene clusters that indicate potential for desirable athletic traits (and traits related to training responsiveness), such as predominance of a specific muscle fiber type, abundance of targeted aerobic enzymes, muscle capillaries, or left ventricular cavity size.

Today, sports scientists use laboratory and field testing to screen athletes for performance and physiologic capacities, including the application of molecular genetics with the ACTN3 gene that encodes the protein actinin in skeletal muscle to assess potential for sports and athletic performance. ${ }^{90,94}$

Gene expression is tightly controlled. When muscle tissue rebuilds, gene expression for actin and myosin protein filament enlargement remains on, while gene expression for generating new muscle cells remains off because cellular hypertrophy, not hyperplasia, usually prevails. These on off genes are referred to as housekeeping genes. In bodily processes such as coding for the proteins involved in aerobic metabolism, gene expression does not shut down but remains continually on until death. The same applies to all cell and tissue metabolic activities controlled by enzymes that dominate cellular and subcellular events. Organisms from bacteria to humans use the same two basic principles of gene expression. First, an RNA duplicate is made of a particular gene with its unique coding sequence on a DNA template that represents some combination in succession of G, C, T, A. Second, the RNA copy containing the sequence of the genetic code on the ribosome (located outside the nucleus) orchestrates the sequential construction of amino acids into a protein possessing unique biomolecular characteristics.

## Exons and Introns

The RNA primary transcript molecule contains all of the information needed from the gene to create a protein. The RNA primary transcript structure discovered by Crick, ${ }^{126}$ called a coding region or exon, shown in the green primary transcript within the nucleus in Figure 21, also contains additional, unwanted stretches of nucleotide spacers, or noncoding regions termed introns (introns shown within the primary transcript of Fig. 21). The 1993 Nobel Prize in Physiology or Medicine was awarded for the discovery of split genes, or introns (http://nobelprize.org/nobel_prizes/medicine/laureates/1993/press.html). Approximately 97\% of DNA consists of introns. An example of just three exons and two introns shows the individual numbering for the base pair sequences within each exon and intron. For example, the numbers 130 designate the base pairs for the first exon along the RNA strand, while 105146 signify the base pairs for the last exon. The two introns with their base pairs have the numbers 3031 and 104 105. During transcription, note the removal of intron links 3031 and 104 105, leaving the remaining three exons that splice together (their base pairs now

Housekeeping genes: genes automatically switched on all the time to maintain essential cell functions
Genetic code: sequence of nucleotides, coded in triplets (codons) along the mRNA that determine the amino acid sequence in protein synthesis; the genes DNA sequence can predict the mRNA sequence; the genetic code in turn predicts the amino acid sequence
Ribosome: small cellular component (organelle) composed of specialized ribosomal RNA; site of polypeptide (protein)

Exon: protein-coding DNA sequence of a gene
Intron: DNA base noncoding sequence that interrupts a genes protein-coding sequence; the sequence transcribes into RNA but gets excised from the message before it translates into protein


Figure 21 Example of exons and introns, individual numbering for the base pair sequences, and intron excision and exon splicing to form the final (mature) mRNA transcript. For this structure, note the three-letter codons shown in white lettering along the green mRNA, and the corresponding amino acids listed in the blue circles below. The codon table in Figure 12 (p.950) lists the full names of these amino acids.
numbered 1 146) to create the final mRNA transcript. This must occur before the mRNA strand leaves the nucleus and enters the cytoplasmic space (cytosol).

The cytoplasm cannot receive partially processed transcripts. Intron removal likely occurs because these structures provide no known usable code for any part of the polypeptide initially specified by the gene. These clusters of repeated, apparently nonfunctional and random DNA sequences scattered throughout the genome exist as either short interspersed elements of 500 or fewer base pairs (called SINEs) or long interspersed elements of more than 1000 base pairs (LINEs) in length. The mature mRNA transcript displayed at the bottom of Figure 21 contains the correct sequence of codes to create proteins. The example shows the specified order for seven amino acids inserted into the elongating polypeptide chain, determined originally during translation based on codon sequence.

## RNA Splicing

RNA splicing removes unwanted intron sequences from the primary transcript before it is translated, allowing translation to avoid those sequences. Introns usually occupy an area 10 to 30 times greater than exons. Small nuclear RNA (snRNA; composed of proteins and a special type of RNA) play a contributing role in RNA splicing. Another protein (small nuclear ribonucleoprotein, or snRNP) contains snRNA. This structure can bind to the $5^{\prime}$ end of an intron, while a different snRNP binds to the introns 3 ' end. Introns interact to form a loop that joins the free ends of the intron. A collection of snRNPs is known as a spliceosome. Its function is to excise the intron (allowing the entron to join it but without the snRNPs). The final, mature mRNA strand is shorter than the primary transcript, owing to the excision of about $90 \%$ of the introns in the primary transcript prior to translation. Consider exon splicing a unique phase of protein construction at the start of protein assembly. Splicing manipulates intron sequencing in many ways to form polypeptides. The hemoglobin $(\mathrm{Hb})$ molecule, for example, requires 432 nucleotides to encode its 144 amino acids, yet before intron excision, 1356 nucleotides exist in the primary mRNA transcript of the $H b$ gene. Regulation of gene expression occurs by changes in how splicing takes place during different stages of a cells development and the type of cell involved.

## mRNA Packaging: Polyadenylic Acid and Guanosine TriphosphateTails and Caps

Before the RNA transcript migrates through the nuclear pore as the final transcripted mRNA, a polyadenylic acid (poly [A]) tail, 100200 adenine nucleotides long, joins one end at the $3^{\prime}$ region via the action of the enzyme poly $(\mathrm{A})$ polymerase, and a terminal portion or cap (methylated guanosine triphosphate or GTP) joins near the $5^{\prime}$ end. Much as a college student wears a cap and gown during the graduation ceremony before entering the real world, so mRNA must be capped and tailed to prepare the transcripted molecule for translation before it exits the nucleus to participate in subsequent protein synthesis. The newly formed cap performs the important function of initiating translation when it binds the mRNA to the smaller of the ribosomes two subunits.

The top of Figure 22 shows how the GTP cap and poly(A) tail join to RNA. Note that the capping enzyme (symbolized by the shorter curved purple arrow) cleaves two phosphates (circles enclosed in red) from GTP and one phosphate from the mRNA strand. In forming the cap, the GTP now attaches near the end of the first base of the mRNA. The bottom of Figure 22 illustrates the addition of the poly(A) tail when a specific endonuclease enzyme (orange) recognizes the sequence A-A-U-A-A-A on the mRNA and snips the strand near that point. This permits a tail of 100200 adenine residues to affix to the $3^{\prime}$ end of the mRNA strand. The addition of poly(A) promotes mRNA stability. It permits the mRNA molecule to maintain translation for up to several weeks, sometimes producing 100,000 protein molecules. Recall that transcription that uses DNA occurs inside the cells nucleus, whereas ribosomal assembly takes place in the cytoplasm. The capping and tailing function enables the mRNA to exit the nucleus to begin the next phase of protein synthesis.

## Exiting the Nucleus

The mRNA now contains a copy of the specific nucleotide sequence from the DNA gene. The mRNA then shuttles the coded message, after the transcription stage, through the nuclear membrane into the cytoplasm where protein synthesis (translation) begins. Translation includes three main stages:

1. Initiation
2. Elongation
3. Termination

Using high-resolution X-ray crystallography, researchers have determined that a tunnellike groove runs through the middle of the larger 50S subunit, providing the location that links amino acids together. ${ }^{93}$ Thirty-one separate proteins affix to the outside of the

RNA splicing: excision of unwanted sequence of introns from the primary transcript so the exons fuse together

Polypeptide: unbranched string of amino acids linked by peptide bonds formed during gene translation

Polyadenylic acid [poly (A)] tail: chain 100200 adenine nucleotides long; joins one end at the 3' region of the final transcripted mRNA before the RNA transcript migrates through the nuclear pore
Guanosine triphosphate (GTP): initiates translation when it binds mRNA at the $5^{\prime}$ end of the molecule to the smaller of the ribosomes two subunits; referred to as the cap on the final transcripted mRNA


Figure 22 Caps and tails. Top. Addition of a guanosine triphosphate (GTP) cap to mRNA. The red dashes indicate where the cut occurs by the action of the capping enzyme. Bottom. Addition of a poly (A) tail to mRNA. The mRNA molecule exits the nucleus once capping and tailing occurs, carrying the coded message for the upcoming translation phase in protein synthesis.
subunit where they also reach inside the ribosome. Because a protein needs to be within a 3 distance to induce any effect and because the proteins on the surface and those that reach around the surface remain within 18 , the source of any protein interaction must be RNA. In this case, adenosine 2486 is the nucleotide in question, with an associated nitrogen atom. Therefore, the RNA gives the catalytic power to protein synthesisin essence, ribosomes serve as ribozymes. This finding helps to explain why some bacteria remain resistant to antibiotics. A mutation on one of the ribosomal proteins within the ribosomal groove locks up with part of the antibiotic molecule, preventing the peptide from exiting the region and thus stopping further antibiotic binding and subsequent damage to the bacterium.

## Translation of the Genetic Code: Ribosomal Assembly of Polypeptides

Translation initiates protein construction. Once the mRNA enters the cytoplasm through the nuclear pore, it seeks out a ribosome with which to bind. The nucleus is the original source of the millions of ribosomes in the cells cytoplasm. A ribosome consists of a large and a small subunit, the latter fitting into a depression on the ribosomes larger surface. A ribosome has three sites that associate with mRNA:

1. A-site (A for attachment)
2. P-site (P for polypeptide)
3. E-site (E for exit)

## Ribosomes and Polypeptide Synthesis: Initiation of Protein Construction

The cells ribosomes provide the catalysts for initiating protein synthesis and serve as submicroscopic factories to produce polypeptides. Figure 23 illustrates a four-step sequence of a ribosome binding to one end of an mRNA molecule and the subsequent three nucleotide increments down the mRNA molecule. Decoding of genetic information occurs when the ribosomes bound to mRNA translate a genetic code sequence. The tRNA then interacts with a specific amino acid, adding one at a time to the end of the progressively elongating polypeptide chain. Sequential linking of amino acids by peptide bonding ultimately forms the specific protein with its unique genetically determined information to achieve its specific function(s).

## Role of tRNA

The tRNA molecule shown in Figure 24 has a 3-dimensional structure resembling a cloverleaf, with an amino acid at one end and three nitrogenous bases that match the mRNAs codon (called an anticodon) at the other end. The tRNA with matching codon serves as a relay or go-between in protein synthesis. In effect, the tRNA acts as a personal shuttle to deliver a specific free-floating amino acid to the ribosomes A-site. For example, the triplet U-A-C represents the codon for the amino acid methionine. When the tRNA with the matching U-A-C anticodon (it carries no other amino acid) interacts with the free-floating U-A-C amino acid, it binds to it by action of the activating enzyme aminoacyl-tRNA synthetase. Each amino acids specific activating enzyme serves two purposes:

1. It deciphers and then binds (couples) to a specific amino acid.
2. It identifies the anticodon on the tRNA molecule.

Some activating enzymes decipher the sequence of one anticodon and thus only one tRNA, while others recognize multiple tRNA molecules. Thus, the activating enzyme reads the genetic code on both the particular amino acid, such as the essential amino acid tryptophan and its tRNA tryptophan anticodon sequence A-C-C. Figure 24 shows three views of tRNA:

1. A computer-generated model
2. A 3-dimensional representation that highlights internal base pairing with hydrogen bonding
3. A 2-dimensional cloverleaf model with the tRNA anticodon shown in blue

Figure 23 Ribosomes, the initiators for protein synthesis. Polypeptide synthesis proceeds from the top in step 1 with the anticodon of tRNA complementary to the mRNA codon. The tRNA occupies the ribosomes A-site, with an anticodon complementary to the mRNAs codon at the opposite A-site. The ribosome translocates down the mRNA one codon at a time. Step 2: The lengthening polypeptide chain fMet (f, formyl-methionyl; Met, amino acid methionine) is transferred to Leu (leucine), the incoming amino acid. The ribosome ejects the original tRNA (step 3) with its amino acid, exposing the next codon on the mRNA chain. When the tRNA molecule recognizes the next exposed codon, it binds to that codon, thus lengthening the growing peptide chain (step 4). fMet represents an addition to the lengthening polypeptide chain already occupied by Leu.

Polypeptide chain: repeated polypeptide units
Peptide bonding: chemical linking that binds amino acids in a protein; formed when the carboxyl group of one amino acid reacts with a second amino acids amino group
Anticodon: three complementary bases at the end of a tRNA molecule that recognize and bind to an mRNA codon
Aminoacyl-tRNA synthetase: activating enzyme that covalently links amino acids to the $3^{\prime}$ ends of their cognate tRNA



Figure 24 Three views of tRNA: computer-generated model, 3-dimensional model, and cloverleaf model. Note that the anticodon displayed in the cloverleaf model (complementary three-nucleotide sequence) matches up with the mRNA codon using complementary (antiparallel) binding between the anticodon (blue) and codon (green).

This example represents the complementary three-nucleotide sequence $\mathrm{C}-\mathrm{A}-\mathrm{U}$ matching mRNAs codon G-U-A.

## Polypeptide Elongation and Termination

The polypeptide chain increases in length when an amino acid from tRNA translocates to it. The A-U-G codon shown in Figure 23 within the mRNA message initiates the start signal for peptide elongation. The same A-U-G sequence that encodes tryptophan also encodes methionine. The first A-U-G message sensed in the mRNA molecule initiates translation. The ribosome translocates down the mRNA a distance of three nucleotide blocks (one codon) at a time. After each third nucleotide, the ribosome ejects the original tRNA with its amino acid, exposing the next codon on the mRNA chain. When the tRNA molecule recognizes the next exposed codon, it binds to it, thus lengthening the growing peptide chain. The elongation procedure for building the polypeptide continues repeatedly until a stop codon terminates the process.

Figure 25 schematically illustrates the three stages in polypeptide termination. The three stop codons, or base sequences, include U-A-A, U-A-G, and U-G-A. These codons turn off the signal in the mRNA message, preventing addition of another amino acid sequence to the chain. Stage 1 shows the stop codon U-A-A on the mRNA strand within the A-site of the ribosome, where one of three kinds of releasing factorseRF1, eRF2, or eRF3locks into position to split apart the linking covalent bond. In stage 2, the polypeptide chain releases from tRNA at the ribosomes P-site, to effectively end protein synthesis. Once the polypeptide


Figure 25 Three stages in polypeptide termination.
and tRNA uncouple from the termination complex, the small and large ribosomal units recycle along with mRNA in stage 3 for further mRNA translation.

## Protein Delivery System: The Golgi Complex

Once the ribosome produces its polypeptide, newly formed strands can exit a cell through its outer membrane into the external interstitial fluid environment. The highly membranous Golgi complex structures within the cell provide the transfer mechanism for moving materials from the cell to its external environment. Italian physiologist and microscopist Camillo Golgi (1843 1926), who shared the 1906 Nobel Prize in Physiology or Medicine for his work on nervous system anatomy (http://nobelprize.org/nobel_prizes/medicine/articles/golgi/), first called attention in 1898 to these minute intracellular structures using the light microscope. Many biologists of his time doubted the existence of such structures; 60 years later, the electron microscope confirmed their existence in exquisite detail.

The Golgi complex receives a polypeptide from the cells endoplasmic reticulum. Figure 26 shows polypeptide transport into the Golgi complex, where this molecule may

Golgi complex: stack of membranebound vesicles between the endoplasmic reticulum and plasma membrane; involved in posttranslational modification of proteins, and sorting and delivering them to different intracellular compartments
Endoplasmic reticulum: tubules, vesicles, and flattened sac structures of the cells endomembrane system; ribosomes cover its outer rough, granular surface


Figure 26 Polypeptide transport into the Golgi complex. The Golgi complex accepts polypeptides on one of its surfaces after the ribosomes release them, repackaging them as glycoproteins, and expels them contained in secretory vesicles for final expulsion through the plasma membrane or delivery to another cell area. The Golgi structures modify proteins within their lumen for use within cells or outside of cells once they pass through the plasma membrane.
become a glycoprotein. When a polysaccharide binds to a lipid, it forms a glycolipid. Glycoproteins or glycolipids then collect within the flattened, membranous sacs called the cisternae region of the Golgi complex, where specialized enzymes modify the protein component. The transport vesicles that hold proteins that pass from the endoplasmic reticulum pinch off and break away from the roughened endoplasmic surfaces. The tiny vesicles attached to the cells outer membrane expel their contents to the extracellular spaces via secretory vesicles. In essence (but not always), the Golgi complex takes up the polypeptide on one of its surfaces and then modifies and repackages it into molecules that leave the Golgi complex via a transport vesicle at its other membrane.

## Termination of Protein Synthesis

The end-point of protein synthesis creates one of thousands of completed or functional proteins, each with a specific function and mode of action depending in part on its structure. TABLE 1 shows eight categories of proteins and their biologic functions.

It usually takes between 20 seconds and 2 minutes to synthesize most proteins, depending on the proteins complexity. The Hb molecule and its amino acid sequence serves as an excellent example of the four levels of protein structure (Fig. 27). This generalized example begins with

TABLE 1 Eight Categories of Proteins and Their Biologic Functions

| Protein Category | Function | Example |
| :--- | :--- | :--- |
| 1. Contractile | Form muscles | Actin, myosin |
| 2. Enzyme | Catalyze biological processes | Protease |
| 3. Hormone | Regulate body functions | Cortisol |
| 4. Protective | Fight infection | Antibodies |
| 5. Storage | Store nutrients | Calcium within bone |
| 6. Structural | Form structures | Endoplasmic reticulum |
| 7. Transport | Deliver substances among <br> cells, tissues, organs | Hemoglobin |
| 8. Toxic | Defense mechanism | Snake venom (disintegrins) |



## Primary structure

Polypeptide strands
form when peptide
linkages join amino linkages join amino acid monomers
 $0-$
0
0
0
0
0 Secondary structure
Polypeptide strands
form $\beta$-pleated sheets
(with hydrogen
bonding) or $\alpha$ helices

Tertiary structure
Polypeptides fold into specific 3-D shapes like a roll of dough twisting itself into a pretzel

## Quaternary structure

Two or more polypeptide chains form a functional protein like the hemoglobin molecule composed of two $\alpha$ chain and two $\beta$ chain subunits. The quaternary structure refers to the protein's subunit structure

Polypeptide strands

Figure 27 Four protein structures (primary, secondary, tertiary, quaternary) in the synthesis of the complex hemoglobin molecule first deciphered by Max Perutz in 1960 and published in Nature (1960;185:416). The purified molecules precise arrangement was calculated from the way its crystals diffracted a beam of X-rays. Hemoglobins tertiary structure contains eight-helical regions; the quaternary structure contains four polypeptide chains (two and two). Knowledge of the configuration of new protein structures has increased exponentially since Perutz first worked out the details of hemoglobins structure; as of July 9, 2001, the Protein Data Bank (www.rcsb.org/pdb/) contained 15,531 unique structures into which proteins can fold. Of these, X-ray diffraction identified 12,817 unique structures and Alpha polypeptideNMR identified 2384 chains.

Primary structure: specific linear sequence of amino acids determined by the nucleotide sequence of the gene that encodes the protein
Secondary structure: coiled protein similar to the pairing of strands in DNA or folded back onto itself to give a flat look; formed from regular repeating interactions among closely linked residues in the primary sequence using hydrogen bonding
Helix: one possible secondary structure of polypeptides; righthanded peptide chain maintained by hydrogen $(\mathrm{H})$ bonds between carbon $(\mathrm{C})$ and oxygen $(\mathrm{O})$ atoms of every fifth amino acid along the chain. The degree of rotation remains regular for bonds on either side of the carbon (with nitrogen, $\mathrm{C}, \mathrm{H}$, and amino side chain attached to it) along the polypeptide chain
Tertiary structure: final 3dimensional folding of a polymer chain; interactions between residues remain farther apart
Quaternary structure: highly complex, 3-dimensional structure or functional protein formed by joining two or more polypeptides

Proteolysis: protein degradation

Proteasome: proteolytic enzyme that degrades unwanted proteins in the cytoplasm of eukaryotic cells
Ubiquitin: small protein that attaches by covalent bonding to a protein marked for destruction by proteosomes
the linear sequence of amino acids from the amino acid at the amino-terminal end through to the carboxyl-terminal residue. The polypeptide strand formed when peptide linkages join amino acid monomers represents proteins primary structure. In a secondary structure, the protein can twist into a 3-dimensional form known as an $\alpha$ helix. It can also fold back onto itself to give a flat look ( $\beta$-pleated sheets), with regular repeating interactions using hydrogen bonding among closely linked residues in the primary sequence. Interactions among residues farther apart in the primary structure determine a tertiary structure, such as disulfide bond formation between two cysteine residues. In this conformation, the protein literally folds up on itself, much like a roll of pretzel dough twisting into a pretzel. The topology of the $\alpha$ helices and $\beta$-pleated sheets play important roles in determining the final shape assumed by a protein. ${ }^{29}$ The complex Hb molecule consists of two $\alpha$ subunits and two $\beta$ subunits (tetramer). The term quaternary structure refers to proteins subunit structure; Hb contains multiple subunits.

## Hemoglobin and the Evolutionary Tree

Figure 27 shows that the Hb molecule contains two $\alpha$ and two $\beta$ chains; the heme group is associated with each chain. The central iron atom (shown in red) binds with one oxygen molecule and acts as a magnet to attract and hold it. Interestingly, our closest blood relative, the chimpanzee, has an identical $\alpha$ chain. The Hb amino acid sequence in cows and pigs diverges from that of humans by about $12 \%$, while for chickens the divergence increases to $25 \%$. Molecular biologists have constructed an evolutionary tree for many proteins (e.g., the iron-containing mitochondrial cytochromes) as a way of tracking evolution.

Some proteins change relatively slowly, taking hundreds of millions of years to evolve. Histones change at a rate of 0.25 mutations per 100 amino acids per 100 million years. In contrast, other proteins such as neurotoxins and immunoglobulins mutate more rapidly (rates of 110 to 140). Variation in the resistance to change makes sense because crucial cellular functions like energy generation in the citric acid cycle or correct folding of DNA requires that gene sequences remain almost invariant. Proteins sensitive to relatively large variations in their operational properties sustain faster evolutionary changes.

## Proteolysis: The Ultimate Fate of Proteins

Protein synthesis from amino acids and degradation into amino acid constituents progresses unabated throughout life. The rates of protein synthesis and degradation, a process called proteolysis, regulate the organisms total protein content at any given time independent of the proteins structural configurations (bone or muscle) or functions (metabolic and intracellular enzymes). For example, the structural proteins ${ }^{a}$ in bone may not decay significantly for months or years, while enzyme proteins in intermediary metabolism or those that regulate cell growth may survive for only minutes or fractions of a second. The enzymes that control proteolysis (proteases) hydrolyze the amino acids peptide bonds, splitting them into the constituent molecules. Figure 28 illustrates how a relatively large trash can shaped proteasome formed from protease enzymes degrades the unwanted proteins in the cells cytoplasm. These cylindrical structures capture proteins destined for destruction by recognizing a small marker or tag protein (ubiquitin) that attaches by covalent bonding to an active site on the protein. Once tagged, the ubiquinated protein enters the proteasome, which degrades it to small peptide units

[^63]

Figure 28 Proteasomes in the cell cytoplasm maintain a balance between protein synthesis and protein degradation. The free ubiquitin tag (displayed in red) attaches to an active site on the designated protein, identifying it for degradation to its peptide components within the proteasomes cylindrical structure. Once ejected, the ubiquitin recycles to another unwanted protein.
before expelling it along with the ubiquitin tag. Proteasomes degrade many types of proteins, from denatured or misfolded ones to misformed or oxidized amino acids.

## Summary of Main Sequence of Events in Protein Synthesis

Table 2 charts the sequence of key events in the flow of genetic information in living cells from DNA $\rightarrow$ RNA $\rightarrow$ protein.

## MUTATIONS

The slightest aberration in the sequence of the 3 billion letters of the genome can produce catastrophic and irreversible effects on health and well-being. Fortunately, an exquisite array of internal repair mechanisms (specialized protein complexes) correct mismatches along the double helix, thus avoiding a phalanx of dreadful, life-altering genetic disorders. On a daily basis, factors in the external environment continually threaten the bodys DNA from cosmic and ultraviolet radiation bombardment, to radioactive decay and gamma waves, including dangerously reactive free radical species (see p. 977). A mutation results from a minor alteration or misspelling in DNA sequence that cripples the corresponding RNA or protein.
Sickle cell anemia provides a salient example when an abnormality occurs in the hemoglobin molecule, as illustrated in the second row of the inset table below:
Normal hemoglobin $\boldsymbol{\beta}$-chain amino acids
Valine Histidine Leucine Threonine Proline Glutamic acid Glutamic acid
Sickle cell anemia hemoglobin $\boldsymbol{\beta}$-chain amino acids
Valine Histidine Leucine Threonine Proline

Mutation: gene with permanently altered or defective genetic information that causes heritable changes
Sickle cell anemia: usually fatal hereditary disease affecting hemoglobin; develops when the amino acid valine substitutes for glutamic acid because of a change in its codon nucleotide sequence from G-A-A to G-U-A; the disease afflicts 2 of every 1000 African Americans; the erythrocyte becomes irregular, thin, elongated, and crescent-shaped, severely affecting oxygentransport capacity

## TABLE 2 Essential Concepts and Sequence of Events in Protein Synthesis

- A nucleotide sequence from DNA provides the genetic information required to begin transcription into RNA.
- The enzyme RNA polymerase binds to the specific promoter region of a gene; nucleotide sequences in the DNA indicate where to begin and end transcription.
- RNA polymerase manufactures messenger RNA (mRNA) molecules to mirror the base sequence of DNA; transcription copies a sequence of the genetic code direction from DNA to an mRNA strand; this includes both coding and noncoding segments of genetic information.
- The RNA transcript contains the information it needs to create a protein; RNA splicing removes random, intervening sequences of unwanted junk nucleotides (introns) from mRNA.
- The mRNA strand (linked entrons) carrying a duplicate copy of the genetic code shuttles the coded message (sequence of codons), exiting the nucleus and entering the cytoplasm to begin protein synthesis.
- Translation initiates protein construction; the A-U-G codon acts as the start signal.
- In the cytoplasm, the mRNA molecule searches to bind with a ribosome (ribonucleoprotein, a protein-manufacturing machine).
- The anticodon of transfer RNA (tRNA) positions itself to match up with a three-nucleotide sequence of codons, each codon corresponding to one amino acid; the codon contains a copy or transcription of the DNA code.
- With the four RNA nucleotides, 64 different codons in the genetic code exist, with each amino acid having at least one (and usually more than one) codon.
- Binding takes place at the ribosomes attachment site between the tRNA molecule (carrying the same genetic sequence on its anticodon) and the complementary base sequence of the mRNA codon (e.g., G-A-C with C-U-G).
- The ribosome, coupled to one end of the mRNA molecule, shifts (translocates) over one codon (three nucleotide blocks) to the polypeptide site, allowing exposure of a new codon; a new incoming tRNA (with its amino acid) links to the ribosomes attachment site; the amino acid at the ribosomes polypeptide region releases and binds to a new amino acid on tRNA at the ribosomes attachment site; thus, the tRNA with one amino acid now gains another amino acid, then another one, and so on; successive addition of new amino acids elongates the peptide chain.
- Protein synthesis terminates when a chain-terminating nonsense stop codon (UAA, UAG, UGA) turns off the signal for adding more amino acids to the peptide chain.
- A complete (fully assembled) protein exists in one of four geometric configurations (primary, secondary, tertiary, quaternary), shown in Figure 27.

Junk DNA: DNA sequences that perform no currently known useful purpose but still remain part of chromosomes

Genetic engineering: laboratoryaltered DNA that changes its characteristics, usually in four stages that involve: (1) cleaving the source DNA, (2) creating recombinants, (3) cloning copies of recombinants, and (4) locating cloned copies for the desired gene; screening makes the desired clones resistant to antibiotics and gives them different properties for easy identification

In the sickle cell condition, the amino acid valine shown in red substitutes for glutamic acid and alters hemoglobins $\beta$ chain because of a codon change from G-A-A to G-U-A. Many human diseases generally form from protein abnormalities caused by a change in the sequence of only one of the $3 \times 10^{9}$ or more DNA nucleotide pairs in the human genome. Not all of the coding sequences in amino acids make sense. The term junk DNA (also called noncoding $D N A$ ) describes such DNA sequences. These inherited sequences perform no currently known genetically useful purpose, ${ }^{11,120}$ yet they remain part of the chromosomes. Junk DNA replicates inside a cell the same way any other DNA molecule replicates, but without gene expression.

## Varieties of Mutations

The guiding principle of the central dogma discussed earlier implicitly states that any change in the inherited genetic material produces a ripple effect on replication, transcription, and translation. This ultimately means that a mutation in the original daughter chromosomes passes on sets of characteristics to the next generation so the offspring inherits the mutation. One can accomplish little short of a temporary, stop-gap measure using genetic engineering to replace the defective sequences or arrest their development a distance far removed from the gene. For example, small deletions hundreds of thousands of bases away from a particular gene (PAX6) can alter the genes expression and cause a mutation in which a typical characteristic (e.g., iris in the eye) fails to develop, producing a developmental syndrome called aniridia (www.aniridia.org/). Poorly understood processes can silence genes up to 90 million bases down the chromosome. Once transcription uses the DNA template to make an RNA
copy of the inherited mutated sequences, the altered RNA translates the defective code during protein synthesis. All of the bodys vital processes depend on proteins for their intended functions; mutated genes pose a health hazard.

The doggerel below provides eight examples of different types of mutations and what can happen to disrupt the orderly sequence in the genetic code:

| Mutation Type | Example of Disruption in the Coding Sequence |
| :--- | :--- |
| Wild type | The cat sat on the mat |
| Substitution | The rat sat on the mat |
| Insertion (single) | The cat spat on the mat |
| Insertion (multiple) | The cattle sat on the mat |
| Deletion (single) | The c-t sat on the mat |
| Deletion (multiple) | The cat -the mat |
| Inversion (small) | The tac sat on the mat |
| Inversion (large) | Tam echt no tas tac echt |

A graphic example points out the probability for errors to creep into a DNA sequence. If the total DNA compacted in the bodys 10 trillion cells was laid end to end like a long link of sausages, it would stretch from Earth to the sun 667 timesnet a trivial length because of the 93 -million mile one-way distance to the sun! Thus, a single genetic code mismatch can wreak havoc on the normal sequence of DNA nucleotides and hence genes. A defect in code sequence often remains quiescent for nearly a lifetime before it emerges. For example, it may take 60 years before a seemingly minor misalignment in a receptor gene devastates heart function, causing congestive heart failure within a few months. When researchers identify this human gene variant years before its expression, as discussed below, they will prescribe highly specific drugs to combat the defect. Within the next decade, new classes of drugs will target specific mutated cells instead of the current shot-gun approach that attempts to cripple just about all cells with a massive pharmacologic overdose. A case in point concerns a stretch of genes along chromosome 21 where mutations give rise to Alzheimers disease, amyotrophic lateral sclerosis (ALS; known as Lou Gehrigs disease), epilepsy, deafness, autoimmune disease, birth defects, and manic depression. For Down syndrome (named after English physician John Langdon Down [1828 1896] who observed individuals in a British asylum in 1866 and published Observations on an Ethnic Classification of Idiots), researchers have been on a quest to develop animal models of this genetic form of mental insufficiency and other genetic abnormalities in hopes of developing genetically engineered strategies to eradicate them. Gene testing may also prove useful for patients who often respond differently to warfarin (Coumadin), a widely prescribed anti blood-clotting drug because of newly identified genetic variations. ${ }^{65}$

Misjudgments in drug doses can critically affect the clotting mechanism to potentially cause fatal bleeding. One gene, known as vitamin K epoxide reductase gene (VKORC1) makes the enzyme that destroys warfarin in the body. DNA variations responsible for changing the genes activity and the amount of protein it makes account for $25 \%$ of the overall variation in warfarin dosage; patients with a particular variation of the gene usually took similar doses of warfarin.

## Single Nucleotide Polymorphisms

Pharmaceutical and computer chip manufacturers have partnered to develop techniques to identify specific molecular markers called single nucleotide polymorphisms, or SNPs (pronounced snips), thousands of which reside within each persons genetic code. Most of these tiny nucleotide genetic code snippets are normally configured with no deviant code. Some, however, have a single mismatch in the nucleotide sequence that predisposes an individual to a particular disease or injury (e.g., ligament tear in football or gymnastics) or renders their immune system resistant to drug treatment. Identifying a specific gene variant allows appropriate lifestyle changes (e.g., nutrition, weight loss, exercise training) or introduction of a particular class of drugs to prevent emergence of the disease or disability, or delay its onset. Thirteen major multinational companies have formed a nonprofit alliance (www.hapmap.org)

Single nucleotide polymorphism (SNP): polymorphism due to variation at a single nucleotide

Photolithography: optimal technology for etching (transferring) electrical circuits on suitable media (silicon wafer with silicon dioxide)
Mutagen: ionizing radiation, ultraviolet radiation, or a chemical agent that disrupts the genetic machinery (sequence of DNA code) and causes mutations
Teratogen: agent that causes extreme mutations
Carcinogen: any agent that causes cancer; for example, smoke from cigarettes contains known carcinogenic agents (e.g., carbon monoxide, formaldehyde, and the metals aluminum, copper, lead, mercury, zinc)
Benign tumor: tumor that remains in one location; it no longer responds to normal growth control and lacks the capacity to invade distant sites
Malignant tumor: tumor that invades other tissues and forms secondary or tertiary cancers
Sarcoma: cancers forming from connective, muscle, or bone tissue
Carcinoma: cancers formed from epithelial tissue
Metastasize: spread of cancerous cells from the original tumor mass to form secondary cancers (metastases) elsewhere in the body
Oncogene: mutant gene that promotes the loss of cellular growth control, transforming a cell to a malignant state; many oncogenes directly or indirectly control a cells growth rate
Protooncogene: gene that produces a protein that regulates cell growth; altering a protooncogene can transform it to a cancercausing oncogene
to identify 300,000 variants on human chromosomes and develop drugs that target the disease by its genetic profile. A new Entrez database, dbSNP (www.ncbi.nlm.nih.gov/sites/ entrez? $\mathrm{db}=\mathrm{snp}$ ), similar in operation to the Entrez nucleotide database collection (www.ncbi.nlm .nih.gov/sites/entrez? db=nucleotide) that includes GenBank (www.ncbi.nlm.nih.gov/Genbank/) and BLAST (http://blast.ncbi.nlm.nih.gov/Blast.cgi), also has been created. These NCBI genome resource guides include detailed information about mammals, birds, amphibians, echinoderms, fish, insects, worms, plants, fungi, and protozoa.

SNP assessment (Fig. 29) uses microarrays of chips (biochips) and a library of artificial DNA to compare the individuals DNA sample with the chips existing gene sequences. A microarray (DNA chip) is a spatial array of oligonucleotide probes arranged on a tiny supporting surface. The probe (representing sequences of nucleotides in known genes) is synthesized on the support surface. This allows the researcher to know the position and sequence of each probe. With this information, the DNA chip can identify organisms and select genes by hybridization of the source DNA to the oligonucleotide probes on the chip. One of the hallmarks of this process is to achieve $100 \%$ accuracy, because even a small error (incorrect identification) could prove disastrous from a worldwide health standpoint. ${ }^{25}$ For example, $99.9 \%$ accuracy in matching the 300,000 biochip SNPs for only 1000 people would create 300,000 errors! Once SNP biochips become more widely available, the next step requires development of technologies that follow the trail from where the gene gives its instructions to create a specific protein to where the proteins reside in the body. The technique of photolithography involves a combination of etching, chemical deposition, and chemical treatments in repeated steps on an initially flat substrate or wafer. Etching microcircuits on a silicon chip could also encode a single biochip containing the entire human genome. Figure 29 illustrates the four main stages to identify SNPs and their specific genetic sequences or anomalies. The challenge to molecular biologists is to map as many SNP genotypes as possible (hence the need for faster sequencers) for purposes of analyzing an individuals genome, because the latter is linked to the predisposition/susceptibility to disease. ${ }^{73,84,118}$

## Cancer

The bodys defense mechanisms include error-correcting proteins that literally erase an apparent aberration in DNA sequencing. Unfortunately, the external effects of ionizing and ultraviolet radiation and chemical and pharmacologic mutagens exert catastrophic effects on genetic machinery, specifically the code sequence in DNA. In extreme cases of mutations, structural defects in embryos produce gross deformities such as missing limbs and multiple organs. In these cases, the extreme form of chemical mutagen known as a teratogen (teras in Greek means monster) produces the effect.

The term carcinogen refers to any agent that causes cancer. In cancer, cell growth proceeds unchecked, forming larger than normal cell clusters that become tumors. A benign tumor remains in one location; cells from a malignant tumor migrate to invade other tissues and form secondary cancers. Cancers that form from connective tissue, muscle, or bone are called sarcomas; the most prevalent cancers (breast, lung), called carcinomas, originate from epithelial tissue. Malignant tumors tend to metastasize or spawn cells that invade healthy tissue when they travel via the lymphatic or vascular circulation to form new secondary cancers termed metastases. Mutation of a gene into an oncogene (cancer-causing gene) often produces numerous cancers, many of which cannot be eradicated by surgery and/or drugs that target specific cells or tissues. Cancer occurs from a failure to turn on specific genes that code nucleotide sequences to repress uncontrolled cell division. A tumor cell can develop from a mutation in any of the stages that regulate cell growth and differentiation. In colon cancer, for example, loss of the APC gene (adenomatous polyposis coli) on chromosome 5 q alters the guts normal epithelial tissue lining. This leads to abnormal alterations in DNA, activation of the $k$-ras protooncogene on chromosome 12q, and loss of two other genes (DCC on chromosome 18 q and p53 on chromosome 17 p ). These alterations induce malignant colon carcinoma and metastasis. A new cell-imaging technology (imaging mass spectrometry) can pinpoint the exact location in tissues that produce high levels of the protein thymosin b-4 believed to trigger tumor growth. ${ }^{109,133}$ Digital computer images that identify the location of specific tissue proteins allow researchers to determine when new proteins invade tumor cells


Figure 29 Four main stages in SNP biochip technology that looks at many genes at once to determine which are expressed in a particular cell type. Thousands of individual genes can be spotted on a single square-inch slide. Note the relative size of the SNP biochip made possible by barcode scanning the microarrays on the biochip. Rapidly identifying the microarrays allows them to link to genes, probe samples, reagents, and experimental protocols. Consult (www.lab-on-a-chip.com) for research links about microarray technology, and Agilent Technologies for new products and specifications (www.agilent.com).

Vasculogenesis: in vivo formation of blood vessels by differentiation of vascular precursor cells; in implanted bioartificial organs, molecular biology techniques can stimulate the growth of new blood vessels or treat peripheral vascular diseases, wounds, and ulcers from compromised microvasculature
Angiogenesis: new blood vessel formation, usually during embryo development but can also occur abnormally around malignant tumors

Gene therapy: introducing genes into cells (genetic surgery) to alter phenotype (i.e., cure diseases like cystic fibrosis using engineered adenovirus carrying a good gene to replace the crippled cystic fibrosis gene); gene therapy cures symptoms but cannot correct the genetic defect in next-generation germ cells
Apoptosis: death of a cell following preprogrammed instructions. The dead cell is eventually removed by phagocytosis; a small family of proteases called caspases transmit the apoptotic death signal
or when normally produced proteins disappear. Protein imaging opens a new vista in cancer screening for searching out specific molecules for comparison between normal and disease states, and developing strategies to arrest existing cancers.

Researchers know that as some cancerous cells become more lethal, they form into primitive channels to create blood vessels (vasculogenesis). The new blood vessels eventually connect with preexisting vessels at the edge of the tumor. This process, completely independent of angiogenesis, may explain why therapies that attack angiogenesis may not treat some cancers effectively. The figure below shows angiogenesis and subsequent vascularization of


Progressive vascularization of a tumor.
tumors. First, the tumor proliferates as it forms a small mass of cells. Note the lack of blood vessels in $A$. Without blood vessels the tumor remains small. Second, protein factors in $B$ stimulate the endothelial cells of nearby blood vessels to grow toward the tumor cells. Third, blood vessels in $C$ proliferate, creating almost unlimited tumor growth. Note the approximate quadrupling of tumor cells.

Researchers have developed gene therapy strategies to attack tumor growth (e.g., angiogenesis inhibitors) in clinical trials (www.cancer.gov/CLINICALTRIALS). For example, a pharmaceutical company in cooperation with the National Cancer Institute in 2003 received FDA approval to market Velcade (bortezomib; www.fda.gov/CDER/drug/infopage/velcade/ default.htm) to treat multiple myeloma in patients who previously received at least two prior therapies and demonstrated disease progression on the last therapy. This new class of drug targets the proteosome to remove abnormal, aged, or damaged proteins. By blocking proteosome activity, Velcade causes a buildup of proteins within the cell. One of these proteins, BAX, promotes cell suicide or programmed cell death called apoptosis ${ }^{19}$ (apopt, falling off; osis, process), by blocking the activity of an antiapoptosis protein. As BAX levels increase in response to Velcade, BAX inhibition of $b c l-2$ also increases, and the cell ultimately undergoes apoptosis. ${ }^{30}$

The new anticancer approach uses a peptide that targets tumor blood vessels, invades cells, and literally tricks cancer cells into obliterating themselves. The peptide contains two domains: one that seeks out tumor blood vessels and one that triggers apoptosis. This normally occurring process in invertebrate and vertebrate biology represents one of natures numerous defensive mechanisms to purge the organism of cells damaged by mutation, viral invasion, external radiation, malignancy, and other deleterious cellular events (not always abnormalities).

Researchers are studying four main areas of apoptosis: ${ }^{1,95,97}$

1. Molecular mechanisms involved in apoptosis induction
2. Control of intracellular protease pathways responsible for induction
3. Biochemical events during apoptosis, particularly events that mediate cell death
4. Role of mechanisms in normal development and disease

Anticancer drugs foster eradication of specific cancers once SNPs or a related technology identifies them. A subsequent section discusses the fight against mutation-caused diseases with a new generation of genetically engineered vaccines.

## Mitochondrial DNA Mutations and Diseases

Scientists normally view the chromosomes as the sole repository for DNA. DNA, however, also exists in mitochondria. The Mitomap database (www.mitomap.org/) reports published and unpublished data on human mitochondrial DNA variation. The complete human mitochondrial genome, including the human mitochondrial sequence published in 2008, consists of 16,569 base pairs, with the genetic blueprint for 37 molecules that produce about $90 \%$ of the bodys energy needs. In Chapters 5 and 6, we described energy release during cellular respiration when electron transfer ultimately produces water by uniting oxygen and hydrogen in the synthesis of significant quantities of energy-rich ATP. Researchers have determined the mitochondrial DNA (mtDNA) codes for 13 proteins that regulate respiratory chain oxidation and for 24 RNA molecules ( 2 tRNAs, 22 rRNAs) that manufacture subunits of respiratory chain proteins. Thus, a defect (mutation) in mtDNA can induce devastating and unpredictable effects on basic cellular metabolic processes that can devastate neural, muscular, renal, and endocrine tissues. Figure 30 lists 12 diseases from mtDNA mutations. The ring of DNA displayed in the schematic view shows different base pairs of mtDNA, numbered counterclockwise from the top center position labeled $O_{H}$ in white. Mitochondrial DNA mutations also may be implicated in aging, affecting the impact of free radicals on tissues of the cardiovascular system. In addition to studying serious human diseases caused by deleterious mutations, other uses of mtDNA fall into two additional categoriesforensic medicine and molecular anthropology. In forensic medicine, mtDNA analysis proves particularly useful because the high number of nucleotide polymorphisms (sequence variants) allow discrimination among individuals and/or biologic samples. Even when degraded by environmental insult or time, minute samples of body fluids or fragments of hair, skin, muscle, bone, and blood may yield enough material for typing the mtDNA locus. ${ }^{6,60,75,110}$ The likelihood of recovering mtDNA in small or degraded biologic samples exceeds that for nuclear DNA. Mitochondrial DNA molecules exist in hundreds to thousands of copies per cell compared with only two nuclear copies per cell. Also, because mtDNA is inherited only from the mother, any maternally related individual can provide a reference sample in situations where an individuals DNA cannot be directly compared with a biologic sample. In molecular anthropology, mtDNA analysis examines the extent of genetic variation in humans and the relatedness of world populations, including other mammals. ${ }^{49,86,101}$

Because of its unique mode of maternal inheritance, mtDNA can reveal ancient population histories to delineate migration patterns, expansion dates, and geographic homelands (www.talkorigins.org/faqs/homs/mtDNA.html). Mitochondrial DNA has been extracted and sequenced from Neanderthal skeletons, providing evidence that modern humans do not share a close relationship with Neanderthals in the human evolutionary tree. The Neanderthal mtDNA studies strengthen the arguments that Neanderthals should be considered a separate species that did not contribute significantly to the modern gene pool. ${ }^{96,99}$

The DNA Analysis Unit II of the FBI laboratory (www.fbi.gov/hq/lab/html/ mdnau1.htm) began conducting mtDNA analysis in 2001, and its various laboratories currently conduct more than a million examinations annually from skin, fabric, hair, bones, and teeth.

DNA neither cares nor knows. DNA just is. And we dance to its music.
Richard Dawkins, author and winner of Best Documentary Series, The Genius of Charles Darwin, at the British Broadcast Awards 2009

Free radical: highly reactive ionized atom or molecule with a single unpaired electron in the outer orbit; can cause a mutation by reacting violently with DNA
Forensic medicine: branch of medicine concerned with the uses of medical knowledge applied to the law

Locus: location of a specific gene on a chromosome

Molecular anthropology: application of molecular biology and genetics to contemporary populations and origins of ancient specimens

Figure 30 Mitochondrial DNA diseases. The ring of DNA displayed in the central schematic view shows the genes associated with a particular disorder. Many of the mitochondrial DNA diseases are inherited, but they also can occur spontaneously in the developing embryo and become widespread during fetal development. The mutations also can form in different tissues (at different times during the life span), often taking years to become fully expressed and often potentially lethal or severely debilitating. (Adapted from Wallace DC, et al. Report of the committee on human mitochondrial DNA. In: Cuticchia AJ, ed. Human gene mapping: a compendium. Baltimore: Johns Hopkins University Press, 1995:910 954. Also available at www. mitomap.org.

| Disease | Features |
| :---: | :---: |
| Alzheimer's disease | Progressive loss of cognitive capacity |
| CPEO (chronic progressive external ophthalmoplegia) | Paralysis of eye muscles and mitochondrial myopathy |
| Diabetes mellitus | High blood glucose levels; numerous complications |
| Dystonia | Abnormal movements involving muscular rigidity; degeneration of brain's basal ganglia |
| KSS (Kearns-Sayre syndrome) | CPEO combined with retinal degeneration, heart disease, hearing loss, diabetes, kidney failure |
| Leigh's syndrome | Progressive motor and verbal skill loss and degeneration of basal ganglia (potentially lethal childhood disease) |
| LHON (Leber's hereditary optic neuropathy) | Permanent or temporary blindness stemming from optic nerve damage |
|  |  |
| MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes) | Dysfunction of brain tissue (often causing seizures, transient regional paralysis, and dementia) with mitochondrial myopathy and toxic blood acidity |
| MERRF (myoclonic epilepsy and ragged red fibers) | Seizures combined with mitochondrial myopathy, hearing loss, and dementia |
| Mitochondrial myopathy | Deterioration of muscle; poor exercise tolerance; muscle often displays ragged red fibers filled with abnormal mitochondria |
| NARP (neurogenic muscle weakness, ataxia and retinitis pigmentosa) | Muscle strength and coordination loss; regional brain degeneration and retinal deterioration |
| Pearson's syndrome | Childhood bone marrow dysfunction (leading to loss of blood cells) and pancreatic failure; survivors often progress to KSS |

## NEW HORIZONS IN MOLECULAR BIOLOGY

Watson and Cricks pioneering achievements in deciphering the molecular structure of DNA ushered in a new era. Advanced genetic engineering techniques affect not only medically related research ${ }^{26,66,106}$ but also strategies involving human exercise performance. ${ }^{13,56,114}$

The successful sequencing of the human genome, announced on June 26, 2000, was one of the most remarkable scientific feats in the history of medical science. Understanding the genetic blueprint of human life will speed the discovery of innovative new drugs to battle existing medically related diseases.

## Medically Related Research

Almost every aspect of medicine now benefits from molecular biology/molecular genetics research. Within the past 25 years, researchers have developed new strategies to fight many diseases, including cancer, AIDS, asthma, diabetes, influenza, heart and vascular disease, rheumatic fever, and malaria. The new disease fighters use genetic engineering to improve the immunologic antigen defense machinery against viral, bacterial, fungal, or parasitic pathogens. All pathogens contain antigens in their structure, so a new generation of genetically engineered vaccines will severely blunt their destructive effects. Figure 31 provides a capsule view of four disease-fighting approaches with vaccine techniques that manipulate the genetic code.

1. Live vector vaccines (www.niaid.nih.gov/daids/vaccine/live.htm). Genes from a dangerous virus such as HIV are inserted into a virus that is harmless to humans. When injected, the altered virus prompts a strong immune response to combat the pathogen.

## Live vector vaccines



Reassortment vaccines


Naked vaccines


Recombinant subunit vaccines


Figure 31 Genetic engineering a new generation of four vaccine types to fight human diseases.

Pathogen: any virus, microorganism, or other substance that causes disease; Streptococcus bacteria cause scarlet fever, rheumatic fever, and pneumonia in humans; in plants, destructive diseases caused by bacteria (mostly pseudomonads) include blights, soft rots, and wilts. Viruses cannot replicate independently; they exist only within the cells of other organisms. Viruses usually contain a protein coating (capsid) and a lipid-rich protein envelope around the capsid (a piece of bad news wrapped up in a protein) and reproduce using the metabolic apparatus of their host
Vector: plasmid, retrovirus, or bacterial or yeast artificial chromosome used to transfer a segment of foreign DNA among cells or species to produce more end product; the vector represents the genome that transports alien DNA into a host cell
Virus: small structure that grows by infecting other cells; adenovirus, retrovirus, and adenoassociated viruses are the most commonly used viral gene vectors
Immune response: immediate defensive reaction of the immune system upon encountering an invasion by a foreign substance such as a pathogen
2. Reassortment virus vaccines (http://virology-online.com/viruses/Influenza.htm). Combining genes from different pathogenic strains creates a decoy virus that looks dangerous to the pathogen but remains harmless while triggering an appropriate immune response.
3. Naked DNA vaccines (www.niaid.nih.gov/daids/vaccine/dna.htm). A pathogens DNA is injected directly into the body. The cells incorporate the DNA, using the preprogrammed specific genetic instructions to create antigens to fight offending pathogens or existing tumors.
4. Recombinant subunit vaccines (www.niaid.nih.gov/daids/vaccine/recombinant.htm). Culturing a pathogens genetic code (genes) produces massive quantities of a specific antigen. The disease-fighting vaccine is made from the cultured antigens rather than from the whole pathogen.

Some genetically engineered vaccines trick the immune system into creating antibodies to seek out and destroy undesirable molecules before they cross the blood brain barrier. For example, small cocaine molecules escape the bodys protein antibody defenses without mechanisms to stop them. Engineered vaccines can create a larger cocaine derivative, which the immune system can then recognize and disarm. This aspect of genetic design, although relatively expensive to make drug therapies, offers new hope in battling addictive diseases.

Figure 32 lists the bodys 22 numbered chromosomes, including X and Y chromosomes, and specific genes on each chromosome linked to cancers and metabolic endocrine, neurologic psychiatric, and cardiovascular disorders. The right side of Figure 32 profiles

## Supercharged Carrots and Lettuce

Researchers have uncovered a way to tweak a gene that increases the transport of calciuma-nutrient relatively low in foods from the plant kingdomacross carrot and lettuce leaf cell membranes into vacuoles. The scientists loaded their super-vegetables with a modified calcium proton antiportor (known as short cation exchanger 1, or sCAX1), which pumps calcium into plant cells. For carrots, volunteers absorbed $41 \%$ more calcium compared to a group that consumed the typical carrot. The supercharged lettuce contained $25 \%$ to $32 \%$ more calcium than controls. The relevance of this tinkering and nutrient-boosting enhancement of a dietary staple is its potential to impact prevalent nutritional disorders (e.g., building strong bones in osteoporosis prevention). Such studies highlight the possibility of increasing plant nutrient content through expression of highcapacity molecular biology transporters.


## References

1. Morris, J, et al. Nutritional impact of elevated calcium transport activity in carrots. PNAS 2008;105:1431.
2. Park S, et al. Sensory analysis of calcium-biofortified lettuce. Plant Biotechnol J 2009;7:106.

## Chromosome 1

- Malignant melanoma
- Prostate cancer
- Deafness

Chromosome 2

- Congenetial
hypothyroidism
- Colorectal cancer

Chromosome 3

- Susceptibility to HIV
infection
- Small-cell lung cancer
- Dementia


## Chromosome 4

- Huntington's disease
- Polycystic kidney disease


## Chromosome 5

- Spinal muscular atrophy
- Endometrial carcinoma

Chromosome 6

- Hemochromatosis
- Dyslexia
- Schizophrenia
- Myoclonus epilepsy


## Chromosome 7

- Growth hormone
deficient dwarfism
- Pregnancy-induced
hypertension
- Cystic fibrosis
- Severe obesity


## Chromosome 8

- Hemolytic anemia
- Burkitt's lymphoma


## Chromosome 9

- Dilated cardiomyopathy
- Fructose intolerance

Chromosome 10

- Congenital cataracts
- Late onset cocayne syndrome

Chromosome 11

- Sickle-cell anemia
- Albinism

Chromosome 12

- Inflammatory bowel disease
- Rickets


## Chromosome 13

- Breast cancer, early onset
- Retinoblastoma
- Pancreatic cancer

Chromosome 14

- Lukemia/T-cell lymphoma
- Goiter

Chromosome 15

- Marfan's syndrome
- Juvenile epilepsy


## Chromosome 16

- Polycystic kidney disease
- Familial gastric cancer
- Tuberous sclerosis-2

Chromosome 17
(shown at right)
Chromosome 18

- Diabetes mellitus
- Familial carpal tunnel syndrome


## Chromosome 19

- Myotonic dystrophy
- Malignant hyperthermia


## Chromosome 20

- Isolated growth hormone deficiency
- Fatal familial insomnia

Chromosome 21

- Autoimmune polyglandular disease
- Amyotrophic lateral sclerosis


## Chromosome 22

- Ewing's sarcoma
- Giant-cell fibroblastoma


## X chromosome

- Colorblindness
- Mental retardation
- Gout
- Hemophilia
- Male pseudohermaphroditism


## Y chromosome

- Gonadal dysgenesis

Mitichondrial DNA

- Leber's hereditary optic neuropathy
- Diabetes and deafness
- Myopathy and cardiomyopathy
- Dystonia

Chromosome 17


Figure 32 Links on the bodys chromosomes to specific cancer, metabolic endocrine, neurologic psychiatric, and cardiovascular disorders. Right. Close-up of disorders found on chromosome 17. On this chromosome, red designates the specific gene name and its location. Graphic illustrating how different carcinogens (chemical and other) affect the nucleotide sequence of the p53 gene responsible for about $50 \%$ of human cancers. The p53 genes name comes from the product it encodes, a polypeptide with a molecular mass of 53,000 daltons ( 1 dalton equals $1 / 12$ th the mass of carbon 12 ; for comparison, a water molecule weights 18 daltons, and hemoglobin weighs 64,500 daltons).


Figure 32 (Continued)
chromosome 17 on which seven deadly cancers have already been identified. The bottom of Figure 32 shows the mechanism of action of different chemical carcinogens on this particular nucleotide sequence of the tumor suppressor gene p53. About $50 \%$ of human cancers occur from inactivating this gene. Each carcinogen produces a distinctive nucleotide substitution. Note the C or G substitution that displaces six T nucleotides.

Many areas of medicine other than cancer benefit from new findings in molecular biology. ${ }^{121}$ Individuals with advanced sleep-phase syndrome (ASPS) cannot resist the urge either to sleep or to wake up early. Research indicates that ASPS does not reflect a learned behavior
or some other factor but follows a specific inherited pattern. Eventually, researchers may tie disorders to a single gene, opening new vistas to the genetics of the biologic clock in humans, ${ }^{51,63}$ with potential applications to many aspects of human exercise performance. Some of the same medical research techniques have found their way into the arsenal of technologies to probe secrets about topics of interest to exercise physiologists. These include blood pressure control; endurance and strength-training adaptations; maturational shifts related to caloric input and output; hormonal balance with exercise; and pulmonary, cardiovascular, and body weight regulation (including anorexia nervosa). ${ }^{44,88}$

## DNA Technologies

By isolating a small fragment of DNA from a chromosome in an animal species (including humans), scientists can remake an exact copy of the DNA segment in a test tube to preserve the precise sequence of its nucleotide base pairs. Researchers use several terms to describe this process of eventual gene reconfiguration or manipulation on chromosomesgenetic engineering, gene splicing, or recombinant DNA.

A crucial step along the path to genetic engineering occurred in 1967 when Dr. Arthur Kornberg (1959 Nobel Prize in Physiology or Medicine; discovered the mechanisms in the biologic synthesis of DNA and RNA) synthesized biologically active DNA. This was followed in 1970 in classic experiments by Drs. David Baltimore, Renato Dulbecco, and Howard Temin, who won the 1975 Nobel Prize in Physiology or Medicine for discoveries concerning the interaction between tumor viruses and a cells genetic material. They discovered that a specific enzyme tumor virus (reverse transcriptase) made a DNA copy from RNA. The researchers used purified mRNA from muscle or liver tissue to show that this enzyme interacts with the mRNA. Reverse transcriptase duplicates the mRNA to the specific sequence of complementary DNA (cDNA). DNA polymerase can then convert the single-stranded DNA to a double strand for eventual cloning into a bacteriophage or other vector. These experiments proved transfer of the content stored in the genetic material to DNA; subsequent experiments also proved that purified DNA from one cell introduced into other cells produce new particles of RNA tumor virus.

In 1973, two American researchers, Stanfords Stanley Cohen, cofounder of Genentech (www.gene.com/), one of the first biotechnology corporations, and Herbert Boyer (1986 Nobel Prize in Physiology or Medicine with Rita Levi-Montalcini, for discovering cell growth factors) at the University of California, San Francisco, built upon the research described above. They introduced the recombinant DNA technique shown schematically in Figure 33. They successfully cut DNA from an amphibian gene (primitive frog Xenopus) into segments, using a restriction endonuclease enzyme (EcoRI) to cut the plasmid. They then rejoined the 9000 -nucleotide segment to form a circular plasmid called pSC101, so-named by Cohen because it was the 101st plasmid he isolated.

Their experimental procedure (explained further in the section on RNA cloning) produced the first plasmid to clone a vertebrate gene. In essence, the frog bacterial molecule represented recombinant DNA using gene splicing to rejoin the two ends of the pSC 101 plasmid. This technique can be likened to cutting and pasting text or images from one section of a document to another in a computer software program. The endonuclease first cleaves the amphibian DNA, setting it free. The two ends of the rRNA gene now join the pSC101 plasmid cleaved by EcoR1. Fundamentally, gene splicing creates a new genetic blueprint in a test tube that leapfrogs natures own genetic engineering methods based on natural selectiona process that normally comingles genes within Earths plant and animal species over tens of millions of years of evolution.

With the opening of trade routes and exploration in the ancient world, different sizes, shapes, and characteristics of plant and animal species from one location gained options to share their genetic code with similar species in other more distant locations thousands of miles away. Unknowingly, humans helped to selectively breed (genetically engineer) plants and animals, in effect revising and updating the original gene pool that now forms the great variety of flowers, vegetables, and animals around us. What took nature millions of years to accomplish, scientists can now duplicate in a day and produce thousands of copies of DNAs exact nucleotide sequence from a particular gene in a given genome. By manipulating DNAs configuration, a newly created gene can be inserted into cells of plants and animals, to create new cells or species with unique characteristics expressed by the new genetic instructions.

Gene splicing: attaching a fragment of DNA from one species (e.g., mammal) to another species (e.g., bacterium) to clone mammalian DNA
Recombinant DNA: forming a hybrid DNA molecule by fusing DNA fragments from different species; attaching a segment of DNA from one species to a second species, followed by inserting the hybrid molecule into a host organism such as a bacterium
Reverse transcriptase: enzyme that allows a single-stranded RNA template to synthesize a double-stranded DNA copy for insertion elsewhere in the genome
cDNA: single-stranded DNA complementary to an RNA and synthesized from it using reverse transcriptase; this kind of DNA only codes exons
Bacteriophage: any virus that infects bacteria
Restriction endonuclease: enzyme that cleaves a specific short DNA nucleotide sequence whenever it occurs at a target site

Cloning: creating a cell(s) or molecule(s) from a single ancestral cell or molecule

Genomic library: collection of DNA fragments from an organisms genome; a library includes noncoding DNA and cDNA

Gel electrophoresis: separation of electrically charged substances (e.g., proteins) through a gel mesh according to size; smaller substances migrate faster than larger substances when they pass through the electric field from the top (negative) to bottom (positive) electrode through a slab of agarose gel, a polysaccharide extracted from seaweed
Plasmid: small circular molecule in bacteria without chromosomal DNA; serves as a vector for transferring genes among cells


Figure 33 Drs. Stanley Cohen and Herbert Boyer produced the first recombinant DNA organism in 1973. Their pioneering experiment combined the cleaved plasmid vector (pSC101 shown at the right) with a fragment of amphibian DNA (shown at the top left) using restriction endonuclease enzyme (EcoR1) to produce the recombinant plasmid shown at the bottom. The cells that contained the plasmid that carried the tetracycline gene grew and formed a cell colony (containing the frog ribosomal RNA gene).

## DNA Cloning Isolates Human Genes

DNA cloning progresses in several stages. The first involves mechanically breaking the genetic material within a DNA sample or, alternatively, using restriction endonucleases that precisely cut the nucleotide sequence along DNAs double helix into smaller segments to facilitate manipulation. The collection of DNA pieces formed by endonuclease cleavage represents single, random segments of the organisms entire DNA, which includes all of the genetic material. The term genomic library describes the collection of cloned fragments. Many genomic libraries exist in the public domain (e.g., http://dlc.dlib.indiana.edu/archive/00002650/), so researchers can use them without having to reduplicate the particular DNA sequences of interest. Figure 34 shows formation of a genomic library from human DNA. This basic strategy led to tremendous advances in the role such techniques play related to almost all aspects of the medical sciences. ${ }^{9,55,129}$

A restriction endonuclease cleaves a short strand of human double-helix chromosomal DNA, usually four to six base pairs in length, into millions of fragments. Restriction endonucleases have become a fundamental tool in molecular biology research because treatment of DNA with the same restriction endonuclease allows any two DNA fragments to join togetherproviding for an essentially endless supply of DNA for further experimentation. One of the most widely used chemical techniques, gel electrophoresis (Greek phoresis, to be carried), perfected by 1948 Chemistry Nobel Laureate Arne Wilhelm Tiselius (1902 1971; for research on electrophoresis and adsorption analysis, and discoveries concerning the complex nature of the serum proteins), separates DNA fragments within an electric field. The DNA strands inserted into a circular plasmid carrier molecule recombine the DNA (hence the term recombinant DNA). This occurs when the enzyme DNA ligase, with addition of ATP, covalently links the DNA fragment to the previously opened plasmid composed of several thousand nucleotide pairs. Once inserted, the ligase rejoins the ends of the plasmid to produce the new recombinant plasmid molecule known as a vector. Recombinant plasmids are then inserted into bacteria (e.g., E. coli) to ensure that only one bacterium receives one plasmid. At this stage, the total culture of bacteria represents the genomic library illustrated in Figure 34.


Figure 34 Creating a genomic library from human DNA. The library consists of bacteria with specific DNA fragments contained in carrier substances such as plasmids. Note in the example how four different-colored DNA segments (red, blue, purple, green) from the original human DNA shown at the top end up within the bacterial host. The rest of the DNA fragments also can make clones.

The next stage of DNA cloning grows the bacterium in a nutrient-rich broth that sustains cell multiplication that doubles its number every hour. This therefore doubles the number of recombinant DNA copies. By simple multiplication, doubling the number of DNA copies each hour over 24 hours produces almost 17 million new copies from a single bacterium! The bacteria are then broken apart (lysed), and the millions of DNA copies culled from the larger bacterial chromosome and other cellular contents to provide pure replicas of the original DNA segment. Recovering this segment occurs after the specific restriction enzyme isolates the segment from plasma DNA for separation by gel electrophoresis (see Fig. 37).

## Practical Application in Bioremediation

Implementation of bacterial cloning has practical applications in the field of bioremediation, which uses bacteria to degrade dangerous compounds. For example, the pink-colored bacteria that smell like rotten cabbage, Deinococcus radiodurans (D. radi), shown in Figure 35, have been genetically cloned from strains of $E$. coli previously made resistant to toxic wastes.

Restriction enzyme: cuts DNA at precise locations, and with DNA ligase, reassembles the pieces into a desired order. Cutting between G and A leaves overhanging sticky end chains because base pairs formed between the two overhanging portions glue the two strands together where the sticky ends match, assembling them into customized genomes (e.g., designer bacteria that make insulin or growth hormone, or genes for disease resistance added to agricultural plants)


Figure 35 Bioremediation. Left. Electron photomicrograph of D. radi (sequenced in the DOE Microbial Genome Program as a cluster of four cells or tetrad). D. radi and related species have been identified worldwide, ${ }^{77}$ including in Antarctic granite and in tanks of powerful cobalt-60 irradiators in Denmark. Right. D. radi growing on a nutrient agar plate; the orange color is from carotenoid pigment. (Images from the Uniformed Services University of the Health Sciences, Bethesda, MD; www.usuhs.mil/).
D. radi was isolated in 1956 from a can of ground beef that had been sterilized by gamma radiation but still spoiled. Researchers determined that $D$. radi survived approximately 17 kGy ( 1.7 million rads), a value equal to 3000 times the lethal dose of radiation for humans. The economic value of $D$. radi is straightforward; easily producing trillions of copies of the new bacterium will save hundreds of billions of dollars in biohazard cleanup. For example, $D$. radi consumes heavy metals and radioactive waste, thus, it can scavenge toxic wastes buried at 1000 sites throughout the United States and other sites worldwide, a legacy from nuclear weapons production between 1945 and 1986. Researchers have also fused a gene that encodes toluene dioxygenase (the enzyme that decomposes toluene) to a $D$. radi promoter (site that activates the gene) and then inserted it into one of the bacteriums chromosomes. The resulting recombinant bacterium upgraded $D$. radi for degrading toluene and other organic compounds at levels exceeding those at radioactive waste sites. $D$. radi not only survives high radiation doses, but also long periods of dehydration and ultraviolet irradiation. D. radi apparently repairs its radiation-damaged DNA base pairs by use of redundant genetic signals. The 2 billion-year-old microbe has from 4 to 10 DNA molecules. The protein, RecA, matches the damaged DNA base pairs and splices them together. During the repair process, cell-building activities shut down and the broken DNA pieces stay in place. The complete genome of $D$. radi has been decoded and can be accessed from the TIGR Web site, www.jcvi.org/. The DNA of $D$. radi consists of 3.3 million chemical base units. The genome contains two circular chromosomes, one of about 2.6 million and the other 400,000 base pairs, and two smaller circular molecules (megaplasmid of 177,000 base pairs and plasmid of 45,000 base pairs). Despite its high tolerance for radioactivity, D. radi decomposes at 45 C .

## Locating Specific Genes with Plasmids

Creating cloned DNA involves locating a specific gene within the plasmid or viral culture. Consider the analogy of entering a five-story department store without signs or a computer database to search for a single unmarked item. One could begin searching on the first floor, proceeding to every shelf and cupboard of every floor until finding the item, but the inefficiency of this strategy seems obvious. To facilitate locating a specific gene, a specific DNA probe of known nucleotide sequence, labeled with colored fluorescent markers or radioisotopes, searches the pool of millions of copies of DNA fragments. The probes used in hybridization reactions capture a single DNA or RNA strand to form another nucleic acid with a complementary nucleotide sequence. The probe searches the genomic library until it locates a matching code on a specific chromosomal gene or a specific RNA sequence in cells or tissues.

Searching for a single gene remains complicated because the gene can contain both coding exons and noncoding introns. If the clone with its isolated sequences contains only exons (i.e., only the uninterrupted coding sequences), then the new genomic library is called a cDNA library (the $c$ refers to a copy or complementary DNA). Different cDNA libraries reflect different tissues because the libraries contain the specifically transcribed mRNA from the original source tissue. A cDNA library contains the genes coding regions, often including
the leading and trailing sequences of the mRNA. The absence of chromosomal DNA serves as a cDNA clones most distinguishing feature. The enzyme reverse transcriptase uses the source cell or tissue mRNA to construct DNA. Cloning cDNA molecules is similar to cloning genomic DNA fragments. Each different type of tissue (e.g., heart, liver, kidney) has a different cDNA library associated with it. Cloned DNA makes it possible to manufacture exact copies of pure genetic material relatively quickly from among millions of nucleotide sequences.
The uninterrupted coding sequence for a particular gene gives the cDNA clone a clear advantage for duplicating the gene in bulk or deducing a proteins amino acid sequence. Like genomic libraries, cDNA libraries exist in the public domain for sharing among researchers; commercial vendors also make them available for purchase. Many Internet sites provide valuable links to databases for mammals and other vertebrates, fungi, plants, eukaryotes, prokaryotes, viruses, specific gene groups, and large-scale genome sequencing centers (e.g., www.ddbj.nig.ac.jp/). Figure 36 illustrates the basic difference in creating genomic DNA and cDNA libraries. In both cases, fragments of digested DNA (shown as purple fragments) are inserted into cloning vectors such as phage.

## Electrophoresis and Gel Transfer Methods

The electrophoresis technique moves charged particles such as proteins through an electrically charged supporting medium. The negatively charged phosphate groups of DNA molecules migrate to the positive pole (anode) of the apparatus. Figure 37 shows two ways of


Genomic DNA Library

cDNA Library

Figure 36 Basic differences in creating genomic DNA and cDNA libraries.


Figure 37 Gel electrophoresis: separating DNA fragments by molecular size. A. Two restriction endonucleases cleave DNA into two segments for placement at the top of a thin agarose gel slab supported in a vertical position. An electric current separates the DNA fragments as they pass through the hydrated gel according to their mobility; small fragments move more quickly through the electric current and fixate at the bottom of the gel at the positive electrode. Larger fragments settle nearer to the top. The top right photo reveals the DNA bands fluoresced under ultraviolet light. Note: The restriction enzyme takes the initials of the bacterial type and strain from its source; EcoR1 refers to E. coli strain RY13, and the 1 means this restriction enzyme was found first in the strain. The cleavage site is 5 GAATTC 3 and 3 CTTAAG 5; the HindIII source is Haemophilus influenzae Rd. The cleavage site is 5 AAGCTT 3 and 3 TTCGAA 5. B. Autoradiography technique displays radioisotope ${ }^{32} \mathrm{P}$-labeled DNA bands on exposed photographic paper placed over the agarose gel. C. Dr. Kristin Stuempfle, Department of Health and Exercise Sciences, Gettysburg College, reviewing the film of a sequencing gel on a light box.
separating DNA fragments. The top example (A) shows cutting the same DNA molecule from the $\lambda$ (bacteriophage) genome with two different restriction endonucleases, EcoR1 and HindIII (hundreds of other enzymes with distinct specificity have been isolated). Small fragments migrate faster than large fragments when they pass through the electric field from top (negative) to bottom (positive) through a slab of agarose gel. Heating the gel causes its protein fibers to congeal and form a grid through which DNA fragments pass. Separating DNA fragments by size in an electric field makes it relatively easy to distinguish among DNA segments. Note the bands at the lower right panel of the gel. These represent smaller DNA fragments than the upper longer fragments. The DNA shows up clearly in the bottom right photo because soaking the medium with a DNA- or RNA-specific dye (ethidium bromide) stains DNA orange (pinkish in photo), which becomes clearly visible under ultraviolet light. Extraction of DNA provides samples of pure DNA fragments. Purified DNA can be used in cloning experiments or for matching in size to other DNA fragments. ${ }^{64,115}$

Figure 37B shows an alternative technique using the labeled radioisotope ${ }^{32} \mathrm{P}$ to expose DNA bands when photographic paper placed over the gel reveals particles emitted from the isotope. Figure 38 illustrates three gel transfer methods to separate fragments of genetic material and proteins: Southern blotting, Northern blotting, and Western blotting.


Gel electrophoresis

Ultraviolet light: electromagnetic rays at higher frequencies than the violet end of the visible spectrum
Radioisotope: isotope that becomes more stable by emitting radiation
Southern blotting: technique that detects single-stranded DNA from transferring DNA fragments to nylon paper with a DNAbinding probe
Northern blotting: hybridization technique that binds a DNA probe to a target RNA molecule; the technique detects a specific RNA sequence in a cell

Western blotting: technique for separating genetic fragments using a probe (usually an antibody) that binds to a target protein

Figure 38 Identifying DNA sequences by three gel transfer methods. A. Southern blot (named for Dr. E. M. Southern) produced when single-stranded DNA on a sheet of nitrocellulose is placed in a tray of buffer atop a sponge. The pattern on the gel is copied, or blotted, to the radioactively labeled nucleic acids. This process produces radioactive bands, which means that nucleic acid bands hybridize with those labeled by radioactivity. B. Northern blots are produced when RNA on a nitrocellulose blot hybridizes with a single-stranded DNA probe without using alkali (alkali hydrolyzes RNA). C. Western blot gel electrophoresis separates proteins using antibody probes to target specific proteins.

In vitro: in an artificial environment such as a test tube or culture medium

Anneal: rejoin separated single complementary strands of DNA to form a double helix

Thermus aquaticus: thermally stable bacterium that survives at very high temperatures found in hot springs and geysers. The bacterium provides the important Taq DNA-replicating polymerase; voted 1989 Molecule of the Year by the prestigious journal Science

## DNA Amplification with the Polymerase Chain Reaction

The polymerase chain reaction (PCR) method developed in 1987 by Dr. Kerry Mullis (1993 Nobel Prize in Chemistry; invention of the PCR method) represents a milestone in molecular biology. ${ }^{89}$ The PCR method, carried out in vitro without prior transfer in living cells, artificially amplifies an extremely small amount of DNA and rapidly creates billions of copies of a specific region of a single DNA molecule. Figure 39 illustrates the basic concept of the PCR, in which purified DNA polymerase copies a DNA template in three cycles of replication. In the first step of the initial cycle, a minute amount of double-stranded DNA is heated to about 94 C for several minutes to denature (separate) the strands. Each strand has a known sequence of nucleotides on either side of the target nucleotides. Next, two short, specifically designed synthetic primers of known DNA sequence (shown in green and red) hybridize or anneal to one of the two separated strands at the exact beginning and ending position of the target DNA nucleotide sequence. In other words, only the target sequence, bracketed by the primers, duplicates because no primers attach elsewhere along the DNA fragment.

The annealing process cannot withstand the initial high temperature required to separate the double helix, so it occurs at a lower 54 C . At this temperature, the single-stranded DNA fragments match complementary nucleotide sequences at the ends of the target DNA sequence. DNA synthesis would not proceed without appropriate primers. Adding a heat-resistant DNA polymerase to the reaction in step 3 synthesizes a new DNA strand, now creating two strands. The most widely used polymerase (Taq) is isolated from the heat-resistant bacterium Thermus aquaticus. The temperature, now increased to 70 C for another minute or two, lets the polymerase elongate new DNA strands that begin at the primers. Because the PCR technique requires that reactants cycle through a varied temperature profile during incubation, the PCR apparatus (thermocycler) automatically progresses through a preset thermal sequence. This first cycle, repeated 20 to 40 times, doubles the amount of DNA synthesized in each succeeding cycle.

The PCR method only clones DNA fragments with known beginning and ending sequences. With prior knowledge of the code, it takes only 20 repeat cycles to duplicate enough target DNA to produce $1,048,536$ copies $\left(2^{20}\right)$ of the original sequence. The second and third cycles displayed in Figure 39 show how the PCR method eventually copies millions (or billions) of the original DNA sequence. The second cycle repeats the first cycle. It progresses through each temperature change, first to separate strands at about 94 C , then to anneal the primers at a cooler 54 C , and finally through polymerase action to make two additional DNA strands at 72 C. Note that the third cycle produces eight double-stranded DNA molecules; after seven cycles, the newly created DNA consists of double strands with flush ends (same length) uniquely identical to the original target sequence. The next 17 cycles produce the additional $1,048,528$ copies, and just 10 more cycles produce 1000 million more target molecules!

## Applications of PCR

The PCR technique has impacted numerous fields besides molecular biology ${ }^{69}$; they include biotechnology, entomology and the environmental sciences, molecular epidemiology, forensic science, genetic engineering, most medical specialties, microbiology, proteomics, the food industry, and even apparel manufacturing. For the 2000 Sydney Olympic Games, a special ink containing a small DNA snippet from a saliva swab from two Australian athletes was affixed to labels, tags, pins, and stickers of official Olympic merchandise to thwart counterfeiters. An electronic scanner could check the invisible ink to verify an items authenticity. The same DNA-marking strategy, impossible to reverse-engineer, can verify rare and one-of-a-kind objects from premium grade oil to fine wine. PCR also can identify diverse viruses and bacteria or any DNA extracted from a current or ancient plant or animal organism. It identifies the unique sequence of a miniscule amount of DNA nucleotide material, even in substances millions of years old.

The amplification potential for PCR remains truly awesome. It requires only $1 / 10$ th of one-millionth of a liter $(0.1 \mu \mathrm{~L})$ of a substance such as saliva or another body fluid or tissue to prove that the genetic samples sequence originated from a specific person or species. The


Figure 39 Artificial DNA amplification using the PCR method. Cycle 1. Three stages during the first PCR cycle. Cycle 2. Second PCR cycle produces four double strands of DNA. Cycle 3. Third cycle produces eight double-stranded DNA molecules. Each succeeding cycle produces twice as much DNA as was produced in the previous cycle. Thirty cycles produce more than 1 billion DNA fragments. Several hours of production create hundreds of billions of copies.
The thermocycler PCR apparatus controls reaction temperature to ensure that repeated replication cycles and separation occur systematically on a preset schedule.

## Paternity: fatherhood

Autoradiography: process that produces an image (autoradiograph) on a photographic film placed flat on an electrophoresis gel; shows the position of radioactive molecules transferred to the gel

Transfection: introduction of an external donor source of DNA
into a recipient host
Gamete: egg or sperm
Transgene: genetic engineering technique that places a foreign gene in the cells of a different species
Pronucleus: fertilized egg containing the haploid egg or sperm nucleus
Founder mice: original engineered mice (with one copy of a transgene) bred together to create transgenic animals

Heterozygous: having two different copies (alleles) of the same gene
Homozygous: having two identical copies (alleles) of the same gene

PCR method can easily produce 1 g of substance (about 500 base pairs long), equal to onemillionth of a gram $\left(10^{6}\right)$, enough to completely sequence or clone DNA. In fact, beginning with less than a picogram ( 0.000000000001 or $10^{12} \mathrm{~g}$ ) of DNA with a chain length of 10,000 nucleotides (about 100,000 molecules), in several hours PCR can produce several micrograms of DNA ( $10^{11}$ molecules). Interestingly, scientists have identified the genetic blueprint of insects trapped within 80-million-year-old amber (fossilized pine resin) from a miniscule amount of DNA, using present-day insects to match the DNA sequences. In a controversial report published in Nature (October 2000), scientists reported reviving a bacterium (spore) from a drop of fluid trapped for 250 million years in a crystal of rock salt excavated 1850 feet below the earths surface. In extinct fossils, on the other hand, not enough DNA sequences exist for cloning because the DNA decomposes significantly every 5000 years. Although some gene fragments may survive, cloning a Jurassic Park prehistoric monster falls outside the realm of possibility with todays available molecular archeology technologies.

In forensic medicine, a single hair salvaged from a crime scene can be matched for its DNA sequence to hair samples from a suspect or victim. When a PCR-generated DNA sequence matches the original DNA template strand sequence, chances of misidentifying the true suspect become almost infinitesimal against a coincidental DNA match. In fact, if an individuals known DNA profile matches the DNA profile from the crime scene, the probability is 82 billion to 1 that the crime scene DNA comes from that person!

Paternity cases routinely involve DNA analysis using PCR techniques such as DNA fingerprinting autoradiography to identify parental offspring correctly (Fig. 40). In the figures example, the DNA from suspected fathers 1 and 2 did not match the known marker DNA from the child; thus father 3, with an exact banding match, was deemed the biologic father. The control DNA from a known source verifies the validity of the test procedures. The many variations of the PCR method allow researchers to produce hybrid genes with desirable (or undesirable) traits. Fusing DNA segments from different biologic specimens transferred to the gel opens a tremendous avenue to study genetic variation in cells and tissues. It also elucidates how errors in specific gene sequences relate to diseases and how genetic engineering can combat them.

## Injection Experiments

Injection transfection performed in cultured cells refers to a microtechnique for introducing an outside (exogenous) DNA donor source into a recipient host. Injection of purified DNA with a known sequence of nucleotides for a particular gene presents a potentially desirable strategy for expressing an outcome trait in the host. Injection strategies have been useful in exercise physiology-related animal research. By injecting a gene with a particular trait into the egg of a mother, the new trait can be turned on in the offspring. This allows researchers to observe the effects of knocking out a section of one gene and replacing it with another segment to glean insight into the functional role of that gene product.

Consider the example in Figure 41 that illustrates the basic principle of microinjection applied to a rodent (mouse) model. Immediately after the gametes join (one egg and one sperm), a microinjection technique using a thin glass needle inserts a target gene (transgene) into the larger male pronucleus just before the cells fuse into a single egg. The $\operatorname{egg}(\mathrm{s})$ is then surgically harvested and implanted into the womb of a female rodent who serves as the foster mother. When the mother produces progeny, the newborns, referred
to as founder mice, should carry a copy of the transgene on a single chromosome (i.e., be heterozygous for the transgene). When two founder mice breed, $25 \%$ of the progeny receive two copies of the transgene (i.e., are homozygous for the transgene), $50 \%$ have one transgene, and $25 \%$ have no transgenes. These percentages follow basic laws of inheritance discovered by geneticist Gregor Mendel (see p. 938). Researchers have used hundreds of strains of transgenic organisms created with the above procedures to study the metabolic and developmental characteristics of many diseases.

Working with transgenic organisms has proved beneficial for experimenting with different genetic manipulations (including mutated genes) to shed light on possible


Figure 40 DNA fingerprinting autoradiography compares DNA fragments after their separation by gel electrophoresis to identify the childs father. Matched patterns of DNA banding from different tissues or body fluids confirm the original DNA source. Specific restriction enzymes sever the DNA fragments at precise sites in the chain. Thus, snippets of DNA, known as RFLPs (restriction fragment length polymorphisms), have different lengths and hence different molecular weights. A match between the known marker DNA and the sample (e.g., father 3) provides prima facie direct evidence that father 3 is the biologic father. As of July 2, 2009, 240 previously convicted criminals have been exonerated on the basis of DNA analysis of forensic evidence, often years following incarceration (www.innocenceproject.org/). The Innocence Project, affiliated with the Benjamin N. Cardozo School of Law at Yeshiva University, New York, is a national litigation and public policy organization dedicated to exonerating wrongfully convicted people through DNA testing and reforming the criminal justice system to prevent future injustice. We recommend the following book for its riveting (but disturbing), frank discussion about the criminal justice system and the important role DNA fingerprinting should play to ensure that the accused have the opportunity to present objective evidence (data) about criminal wrongdoing: Scheck, B et al. Actual innocence: when justice goes wrong and how to make it right. New York: Doubleday, 2003.
mechanisms for disease conditions. Consider the following four ways researchers carry out such experiments:

1. Replacing a normal gene with a mutant gene (trading places) and observing effects on the offspring (a knockin animal model)
2. Inactivating or interrupting a normal genes function and observing effects on the offspring (a knockout animal model)
3. Adding a mutant gene and observing the combined effects of the mutant gene and normal gene on the offspring
4. Increasing the expression of a given protein by increasing the number of copies of a gene

Because of its relevance to exercise physiology, we take a closer look on page 997 at strategies for disabling genes related to obesity using the elegant knockout or gene targeting techniques that led to the 2007 Nobel Prize in Physiology or Medicine awarded to researchers Mario R. Capecchi, Sir Martin J. Evans, and Oliver Smithies for their ground-breaking advances related to powerful techniques for introducing specific gene modifications in mice by embryonic stem cells and DNA recombination in mammals (http://nobelprize.org/ nobel_prizes/medicine/laureates/2007/press.html).

Knockin animal model: replacing a normal gene with a mutant gene (akin to trading places at a specific gene location or locus), and observing the effects on the offspring
Knockout animal model: specific gene(s) inactivated (disabled) by inserting a gene cassette that disrupts the coding sequence (or operation) linked to a specific target gene


Figure 41 Generalized procedure for creating transgenic offspring by injecting a target gene (transgene) into a fertilized egg. Some of the progeny, called founder mice, carry the transgene in their chromosomes, but the process may fail in others.

## Cloning a Mammal

Genetics researchers use three methods to clone a mammal:

1. Somatic cell nuclear transfer (SCNT)
2. Roslin technique
3. Honolulu technique

SCNT Method. Figure 42 illustrates the eight-step SCNT technology (also called therapeutic cloning) to create stem cells from somatic cells (cells other than a sperm or egg cell). This modern technique had its genesis when experimental embryologist Hans Spemann (1869 1938; 1935 Nobel Prize in Physiology or Medicine for discovering the organizer effect in embryonic development at the gastrula stage) with codiscoverer Hilde Mangold (1898 1924) pioneered microsurgical techniques while working with embryos. Spemann and Mangolds histologic evidence from experiments with five manipulated embryos proved the reality of the concept of induction (interaction between two groups of cells in which one group directly influences the developmental fate of the other). In the SCNT technique, two cells are requireda donor cell and an oocyte (an unfertilized egg cell early in development).
Somatic cells are secured from the patient and prepared for the next step, which transfers the nucleus of the cell (with its DNA) into an enucleated oocyte (not having a nucleus eliminates most of the genetic information). This process (step 3) prompts the cell to begin forming an embryo (a fertilized egg that can begin cell division). In step 4, the embryo undergoes cell division until it develops into the blastocyte stage, a mass of about 100 cells. At this stage of development, the mass remains a group of undifferentiated cells. The next phase of the process (step 5) separates the inner cell mass (ICM) from the cell by a microchemical technique called immunosurgery (using different chemicals to dislodge the ICM from the cell wall). The cultured ICMs produce pluripotent stem cells (step 6), the most versatile kinds of cells, with the potential to become different types of tissues (i.e., skin, brain, heart, muscle, kidney, bone, pancreas, intestine). In essence, stem cells are relatively unspecialized cells that have not yet


Figure 42 Eight-step SCNT (somatic cell nuclear transfer) technology to create stem cells from somatic cells. Tissue rejection is eliminated with SCNT because the new grafts (tissues) are autologous (donor and host are the same individual). SCNT is not reproductive cloning because it uses only unfertilized egg cells to generate stem cells. ${ }^{82}$ The International Society for Stem Cell Research provides additional details about SCNT (www.isscr.org/public/therapeutic.htm).
differentiated into any specific type of tissue. Once the cells become differentiated (e.g., acquire the features of a specialized cell and develop into specific tissues), as shown in step 7, the new line of specialized cell types can be reintroduced into the patient. This begins the process of creating new tissues to replace or repopulate damaged or diseased tissues.

Roslin Method. In 1997, scientists at Edinburghs Roslin Institute in Scotland (www.roslin.ac.uk/) tapped the complete genetic library contained within the zygote (i.e., cell totipotent potentiality) to clone the Dorset sheep Dolly. This milestone represented the first such viable intact donor derived from adult mammalian cells. ${ }^{128}$ The researchers removed an unfertilized oocyte from an adult ewe and replaced its nucleus with the nucleus from a mammary gland cell of an adult sheep. They then implanted this egg in another ewe, producing the healthy offspring sheep. The idea behind the nuclear transfer experiment was to produce genetically engineered transgenic mammals inexpensively that could reliably produce large quantities of pharmaceuticals in their milk. A likely benefit would be large quantities of human proteins for drug synthesis to treat diseases such as cystic fibrosis, hemophilia, and emphysema, with potential benefits toward aging and cancer research. Milk produced from transgenic sheep, goats, and cattle can yield up to 40 g of protein per liter at relatively low cost. This circumvents the need to use purified, expensive blood to harvest protein, with risk of contamination from AIDS or hepatitis C. Proteins produced in human cell cultures have high cost and relatively low yields. Transgenetically produced proteins have application in the nutraceutical industry, xenotransplantation, animal models of disease, and cell therapy.

The first Dolly experiments represented a milestone in cloning technology, but not before unleashing a firestorm of criticism concerning ethical and scientific issues related to the possibilities of eventual experiments with human cloning. Figure 43 shows that Dolly possesses the same genes as the cells from the ewes udder. The reproductive cell cycle

Totipotent: the cell possesses the required genetic information or blueprint to form an intact organism
Nuclear transfer: DNA removed from an unfertilized egg and introduced into the nucleus of a specially prepared cell by an electrical pulse or chemical to fuse the two substances together to initiate their development
Nutriceutical: genetically engineered product that alters or modifies characteristics of a product or its byproduct
Xenotransplantation: transfer of organs or tissues from a donor of one species to a recipient of another. Successful transplants require that the immune system of the recipient accept the donor organ successfully


Figure 43 Steps in cloning a mammal. Dorset sheep Dolly (bottom photo) has genes identical to those of the ewe that donated the original genes (Dorset sheep, upper left). Dolly, the first mammal to be cloned from adult DNA, was put down by lethal injection Feb. 14, 2003 (www.ornl.gov/sci/techresources/Human_Genome/elsi/cloning.shtml). Dolly suffered from lung cancer and crippling arthritis. The unnamed sheep from which Dolly was cloned died several years prior to Dollys creation.
developed normally following intermediate stages (keeping donor cells quiescent so that their DNA did not replicate or divide) until the early embryo developed. The researchers then transplanted the embryo into a receptive ewe (Scottish blackface sheep). Following several hundred unsuccessful implants, Dolly was born from the implanted ewe and survived. Dolly subsequently gave birth through normal mating to produce six additional, healthy lambs.

Honolulu Technique. This cloning technique developed by researchers in Hawaii ${ }^{123}$ differs substantially from SNCT and the Roslin methods (http://library.thinkquest.org/24355/data/ details/media/honoluluanim.html). The Honolulu technique does not generate clones either by injection or fusion of embryonic or fetal cells or by fusion of adult cells (how sheep Dolly was created). In contrast, adult mouse cells created new mice genetically identical to the parent mouse. Using a special pipette, the donor nucleus was microinjected into an egg whose nucleus was previously removed. The resulting cells were cultured and placed into a surrogate mouse, allowing the clone to develop. By repeating the procedure, the team created second and third generations of cloned mice that genetically matched their sister/parent, sister/grandparent, and sister/great grandparent. The research succeeded in cloning mice from adult cells by using (1) a new method, and (2) a new cell type able to repeat the procedure to produce clones of clones of clonesessentially creating identical mice born a generation or more apart. The Honolulu technique, in contrast to SNCT and Roslyn methods, allows researchers to manipulate adult donor nuclei. The same Honolulu technique also produced three live male offspring from tail-tip cells. Two died shortly after birth, but the surviving clone developed normally and mated successfully, producing two healthy litters. The Honolulu technique shows that animals of either sex can be cloned with somatic cells used in the process. The technique offers hope in preserving endangered species and transgenic animals.

## Gene Knockout Technique

Mice provide a useful model to study genetic manipulations because of control afforded the experimental subjects and the environment, and the animals shorter life span. Researchers can study a strain of normal-sized mice with black fur, obese mice with black fur, obese mice with white fur, and so on. Genetic tampering could verify whether the gene actually modulated the specific effect independent of its influence on fur color. Deactivating a gene(s) within the DNA known to produce an obese strain of mice should produce litters of normal-weight mice.

Figure 44 illustrates the 5-step experimental strategy for creating a transgenic mouse with a knocked-out gene.

Step 1. A DNA fragment receives a genetically modified gene (gene cassette shown in purple), thus altering the target genes usual nucleotide sequence.
Step 2. Growth of the cell culture produces one or more cell colonies containing the altered gene. Finding such a colony means the mutant gene altered the DNA fragment.
Step 3. Inject the genetically altered cells into the developing embryo of a previously mated female mouse.
Step 4. Place the developing embryo into a normal pseudopregnant mouse that gives birth to a litter in which most progeny possess cells with the altered gene.
Step 5. Mating two offspring with the mutant gene can produce an offspring with the mutant gene on each of two chromosomes. The grafted transgene also can be incorporated into the mice from another strain of mouse into a totally different organism.

If the original gene alteration inactivated the function of one of the genes, then the transgenic mouse inherits the mutant gene that replaced or knocked out the primary target gene. This strain of mice can be reliably bred to produce progeny with the foreign gene now permanently part of their germ line DNA. In studying the etiology of cancer, for example, two transplanted oncogenes (ras and myc) remain dominant in the host and always produce a mouse with cancer. The same strategy can apply to study mechanisms of obesity described below.

Quiescent: having all but the most fundamental functions of a cell or group of cells stopped; in essence, with switched-off genes that define the special functions of the cell (i.e., restricting food supply or creating an unfavorable internal cellular environment)

Gene cassette: artificially constructed DNA segment containing a genetic marker with restriction sites at both ends of the nucleotide segment

Pseudopregnant: ovulation induced by sterile copulation

Germ line: cell lineage consists of mature reproductive germ cells (sperm, egg)

Proopiomelanocortin (POMC): precursor of neurotransmitters (-endorphin) and hormones (melanocortin peptides), whose roles include pigmentation, adrenocortical function, food intake and fat storage, and immune and neural functions
Neurohormone: hormone formed by neurosecretory cells and liberated by nerve impulses (e.g., norepinephrine)


Figure 44 Creating a transgenic mouse with a knockedout gene. Transgenic mice represent a unique tool for understanding how interactions between individual genes and environmental stressors affect human health and disease.

## Knockout Mice to Study Mechanisms of Obesity

Researchers have developed transgenic mice that lack the gene that encodes for the complex molecule proopiomelanocortin (POMC) produced mainly in the brain and skin. POMC, a precursor of melanocortin peptides, possesses a wide range of physiologic properties that include roles in food intake and body fat accumulation. The researchers originally intended to study POMC-deficient mice to evaluate neurohormone signaling and CNS functioning. Their strain of transgenic mutant mice overate and became obese, with altered
pigmentation that produced yellowish fur on their abdomen instead of typical brownish-black fur. They also showed significantly less adrenal tissue than littermates of normal size and color. Figure 45A shows that after 1 month of age, the body weight of the mutant mice steadily increased to twice the weight of normal littermates.

These findings coincided with a previous report describing a rare genetic disease in two children caused by a mutant POMC gene. ${ }^{68}$ These red-haired children had no melanocortins, and they developed severe obesity soon after birth and suffered adrenal insufficiency. Panel $D$ in Figure 45 shows the rapid weight gain of this young girl and boy whose weight far exceeded typical age standards. The connection between the mice and children was striking; functional characteristics caused by the POMC gene mutation in humans paralleled those in the transgenic mice with yellow pigmentation and obesity.

Injecting the obese, POMC-deficient mice with the melanocortin peptide, melanocytestimulating hormone agonist ( MSH) produced a significant body weight loss within 1 day; within 1 week, body weight decreased by about $38 \%$ and declined further to $48 \%$ after the second week (FIG. 45B). A reversal also occurred in the pigmentation of the mice, and their fur lost its yellowish tinge. Within 10 days of terminating MSH therapy, the mice began to regain lost weight, reaching preinjection weight in another 14 days. Their yellow fur color in the ventral and dorsal sites also reappeared. In contrast, MSH injections and subsequent cessation of treatment produced no effect on body mass or fur pigmentation in normal control littermates. The researchers explained that weight loss during treatment exceeded expectations from the energy-balance equation. This occurred although the mutant mice ate significantly more food daily than the control mice ( 35.7 vs. 24.2 g; Fig. 45C). Because fat cells contain melanocortin receptors, and these receptors induce lipolysis, melanocortin-based drugs may eventually prove helpful as therapeutic agents to combat obesity. Interestingly, injections of MSH analogues also reduced excess body fat in another strain of obese transgenic mice deficient in the hormone leptin. ${ }^{50}$ In studies of 87 unrelated Italian obese children and adolescents, three new mutations were identified within the POMC signal peptide (substitution of Ser with Thr at codon 7; Ser with Leu at codon 9; Arg with Gly at codon 236). ${ }^{34}$ The researchers believe that the mutations in codons 7 and 9 of the signal peptide alter the translocation of pre-POMC into the endoplasmic reticulum and, therefore, explain the linkage between POMC and the genetic predisposition to obesity, a view shared by others studying this association. Further studies of genetic variations in the POMC coding region should provide new insights concerning the etiology of obesity. ${ }^{12,38}$ Ongoing experiments with transgenic animal and human models will help researchers understand the etiology of obesity and its treatment. ${ }^{52}$

Extremes in obesity have been linked to DNA polymorphisms in the translated portion of the leptin (LEP) gene. ${ }^{78}$ Leptin-regulated endocannabinoids (marijuana-like substances naturally produced in the brain) stimulate appetite and play a role in food regulation as a component in the leptin signaling cascades. ${ }^{35}$ In the not too distant future, excess body fat may provide a ready source of stem cells from which to create replacement tissues (e.g., bone, muscle, cartilage) for diseased or damaged ones. ${ }^{134}$ Incorporating a persons own stem cells would avoid rejection of transplanted tissue and circumvent moral objections concerning the use of human embryonic stem cells.

Newer approaches also apply genetic techniques using antisense RNA to suppress expression of a target gene as a way to assess gene function. By incompletely blocking the function of knockout genes, researchers should be able to uncover unexpected roles for sequenced genes. ${ }^{45,113,130}$

The field of proteomics (using sophisticated imaging software and molecular scanners integrated with protein chemistry techniques) also offers a new approach to study how proteins expressed in a genome act in complex, biologic processes. ${ }^{36,47}$

For example, scientists have developed an ion channel nanopore technique that discriminates among almost identical DNA molecules that differ by only one base pair or one nucleotide. ${ }^{119}$ This level of differentiation permits highly accurate molecular identification to unscramble intricacies of gene expression and ultimately to develop strategies that target mutagens. Recent research with 380 Europeans with early-onset and morbid adult obesity and 1416 age-matched, normal-weight controls identified three new genetic loci for obesity ( $N P C 1$, endosomal/lysosomal Niemann-Pick C1 gene; near MAF, encoding the transcription factor c-MAF; near PTER; phosphotriesterase-related gene). ${ }^{85}$

Lipolysis: splitting up (hydrolysis) or chemical decomposition of triglyceride
Leptin: protein hormone involved with appetite and fat storage

Antisense RNA: RNA complementary in sequence to mRNA, thus capable of base pairing with it by using the nontemplate strand of DNA to transcribe RNA from it. Analogous to two original strands in DNA base pairing with each other. In practice, synthesis of an oligonucleotide hybridizes a mutant mRNA sequence, stopping its translation into protein

Figure 45 POMC-deficient transgenic mice provide new clues to obesity. A. Body weight gain in mutant and control mice. B. Change in body weight with and without treatment. C. Differences in food intake with and without treatment. D. Extreme weight gain in a young boy and girl with the POMC mutation. The white lines represent growth curves for children representing the 3rd through 97th percentile (p). (Data from A, B, and $C$ modified from Yaswen L, et al. Obesity in the mouse model of proopiomelanocortin deficiency responds to peripheral melanocortin. Nat Med 1999;5:1066. Data in D from Krude H, et al. Severe earlyonset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19:155.)



B Days with MSH treatment






## HUMAN PERFORMANCE RESEARCH

Molecular biologists studying physical activity and exercise training seek to decipher signaling pathways by which genes transcribe the effects of a mechanical stressor and resultant phenotypic expression. For example, resistance training applies muscular overload of the biceps as a mechanical stressor, while increasing upper-arm strength and size represent expression of a phenotype characteristic. Crucial, unanswered questions concern where and how skeletal overload translates into newly acquired strength and muscle hypertrophy. The answers likely reside within signal transduction pathways leading from cell surface receptors to the nucleus, resulting in transcription of genes and subsequent protein synthesis. Little doubt remains that scientists will progressively uncover the secrets of the genome as they learn more about the intricacies of how different signaling processes interact, integrate, and differentiate to produce function and consequences, and possibly even share common intermediates. ${ }^{5}$

Consider a seemingly simple series of movements such as releasing the bowstring when shooting an arrow and the highly complex maneuvers of a triple back somersault from a $10-\mathrm{m}$ diving platform. The movement patterns of both activities require precise coordination and integration of neural stimulation and muscular action. In turn, each component of the movement demands specific timing and force requirements to achieve a desired outcome. At the molecular level, thousands of enzymes govern such precision requirements, each turning on and off at precisely the right time and in the correct sequence to make the movement successful (or unsuccessful). A better understanding of signaling processes governing enzyme activity between stressors and genes may someday explain the how and why of individual differences in human movement capacities. For example, why does one identical twin perform better than the other twin in a particular activity? Identical twins come from the same genetic pool, so one would expect few differences in performance between them, but this is not the case. Even if twins had identical experiences in mastering the mechanics of an activity, from practice time to coaching, their performance levels would differ. Fractions of a second or tenths of a centimeter often mean the difference between victory and second placewhether the performers are twins or Olympic-caliber athletes. A combination of biochemical individuality and known allelic variations should enable researchers to determine optimal nutritional profiles (i.e., targeted doses of vitamins, minerals, and other nutrients) to create personalized comprehensive lifestyle prescriptions tailored to the needs of each person. ${ }^{39}$ A tremendous challenge also exists among the disciplines to determine the molecular basis of disease expression, as for example, for type 2 diabetes or cardiovascular diseases. ${ }^{2,46,70,87,116}$

When reduced to the most fundamental level, all physical activities, or aspects of all life, ultimately depend on the multiplicity of molecular events that turn genes on and off. The new generation of molecular exercise scientists must expand research to uncover how different signaling mechanisms regulate transcriptional, translational, and posttranslational events. Elucidation of these mechanisms will enable scientists to manipulate experimental variables to answer questions related to our field. For example, how does long-term exercise intensity and duration alter levels of a specific mRNA or an upstream signaling molecule such as Ca2, an intermediary involved in multiple signal transduction cascades? ${ }^{40}$ A simple muscle contraction corresponds to a 100-fold increase in intramuscular Ca2 concentration (from 107 to $105 \mathrm{M})$. Some researchers believe that the huge Ca 2 influx, which coincides with myofilament cross-bridge cycling (see Chapter 18), serves as an important signaling messenger that links a muscles function to transcriptional dynamics. ${ }^{6}$ Other exercise-related physiologic regulators of transcription include hypoxia and cellular oxidative stress (or redox). The hypoxic state affects production of erythropoietin (EPO gene) and glucose transporter-1 (GLUT-1). Understanding the functional characteristics of how genes operate under hypoxic conditions will provide key information about oxygen delivery to cells and ultimately its use via citric acid cycle reactions, electron transport, and ATP synthesis associated with oxidative energy transformations. ${ }^{53}$

Oxygen free radicals and reducing agents (i.e., antioxidants) also modulate transcription. ${ }^{108}$ In Chapter 6, we discuss how the mitochondrions reduction of oxygen to form water serves as the final common step in ATP synthesis. Imprecise coupling of this pathway forms free radicals of oxygen. Diverse antioxidants within skeletal muscle then scavenge and

Reactive oxygen species (ROS): oxygen free radical formed from imprecise coupling during oxygens reduction to water in the final stage of electron transport oxidative phosphorylation
Thioredoxin: protein involved in oxidation reduction reactions to balance the cells redox state

Monoclonal antibody: pure antibody of a single type that only recognizes a single antigen; produced in cell culture
quench most of these reactive oxygen species (ROS). ${ }^{22,102,105}$ However, during highintensity endurance exercise when aerobic metabolism increases 15- to 20-fold, ROS form in greater numbers to possibly produce damaging effects similar to those produced by lipid peroxidation. ${ }^{49,67,111,74}$

The protein thioredoxin (reduces oxidized proteins) helps to balance a cells redox state during energy metabolism and also appears to affect transcriptional activity. ${ }^{54}$ Determining how ROS influence transcription will pave the way for improved understanding of long-term health effects (or potential risks) of aerobic-type activities. Researchers have discovered that endurance training nearly doubles mitochondrial protein and mitochondrial mass. ${ }^{91}$ This means that having a robust experimental model (endurance exercise/training) from which to study gene expression will surely lead to important discoveries about the essence of endurance exercise effects and adaptations per se. In fact, experiments have already described alterations in mRNA gene expression with long-term electrical stimulation, ${ }^{131}$ including exercise effects related to muscle mitochondrial and overall ${ }^{17,61}$ and molecular-related alterations in skeletal muscle and muscle fiber type. ${ }^{42}$ Microgravitys effects on gene expression in skeletal muscle provide a fruitful area for further study. ${ }^{8,59,80,111,132}$

Studies of identical twins attempt to explain why one individual tends to participate regularly in sports and physical activities while the other twin shows little inclination to remain physically active. As part of the Heritage Family Study, ${ }^{27,62}$ a search for genes related to body composition changes following 20 weeks of exercise training from 364 sib-pairs from 99 Caucasian families provided evidence of linkage of fat-free mass and insulin-like growth factor 1 genes, including gene sites for BMI and fat mass, and plasma leptin levels with the lowdensity lipoprotein receptor gene. Further study of the genomic basis of training-induced changes in body composition with systematic endurance-type training will help to enlighten mechanisms in body weight regulation.

Another viable area for application of molecular biology research to the sport sciences involves various gene therapy techniques (viral and nonviral delivery strategies):

1. To treat acute and chronic musculoskeletal injuries such as muscle tears, cartilage defects, and tendon ruptures
2. To reconstruct ligaments, osseous nonunions, and meniscus tears
3. To transplant tissue or genetic material

One hopes that inserting relevant genes directly into target tissues or systemically via vectors into the bloodstream will increase the probability of successful therapy and accelerated recuperation. ${ }^{81}$ Researchers in the molecular biology sciences are just now beginning to track down the flaws in human DNA that cause debilitating musculoskeletal disease, as for example, those involved with lumbar disks. ${ }^{4,79}$ One must temper such expectations by perhaps justifiable concerns that genetic engineerings potential benefits could also result in tinkering with issues related to doping and drug testing.

New techniques of molecular and cell biologysuch as nuclear magnetic resonancedetected carbon-14, nitrogen-15, and hydrogen exchangenow make it possible to study aspects of protein structure and functions. ${ }^{43}$ For example, the computer-generated structural model of a protein in Figure 46 shows color-coded regions of high- and low-stability constants when binding to another molecule such as monoclonal antibody D1.3. The red region that interacts directly with D1.3 shows the highest stability; the yellow and blue regions remain unaffected by D1.3 binding. Thus, high and low regions of stability within a protein molecule may relate differently to its functional associations with other molecules. The important implication for a fusion product from a protein synthesis is that sites within the conformational structure of a molecule may serve dual functions for cancer cells and antibodies, depending on the molecules configuration and structural residues.

As far as we know, no research in exercise molecular biology has studied whether exercise training might induce changes in a proteins structure. Will these changes alter the region(s) within the molecule for cooperative binding or interactions among binding pathways with other molecules?

Crucial questions concern what signals control cooperation among different molecules and whether changes occur selectively in some proteins (in certain regions within the molecule)


Figure 46 Computer-generated model of hen egg white lysozyme (HEWL) color coded to show regions of high (red) and lower (blue and yellow) stability constants when binding to monoclonal antibody D1.3 (along the red area). Lysozyme, discovered by Sir Alexander Fleming (1881 1955) 5 years before he discovered penicillin, protects against bacterial infection. This small enzyme, the first ever to have its structure solved, attacks the bacterial protective cell wall. Some bacteria build a protective outer layer of carbohydrate chains interlocked by short peptide strands, which brace their delicate plasma membranes against their high intracellular osmotic pressure. Lysozyme breaks these carbohydrate chains, destroying the cell membranes structural integrity, and the bacteria burst under their own internal pressure. The lysozyme from hen egg whites protects proteins and fats that nourish the developing chick. (Figure constructed using program GRASP [http://wiki.c2b2.columbia. edu/honiglab_public/index.php/Software:GRASP]. Dr. Ernesto Freire. Professor of Biology and Biophysics. Director of the Biocalorimetry Center. The Johns Hopkins University, Baltimore.)
and not others. For example, the following question requires an answer: What contributions do genetics and environmental factors make in affecting the complex etiology of many common and debilitating diseases? ${ }^{20}$ The model describing gene exercise interaction in Figure 47 affects health status indirectly by altering gene expression that itself affects intermediate phenotypes and disease outcome. ${ }^{112}$ In addition, increased physical activity (exercise) and training influence health. ${ }^{122}$ Often, indirect evidence can link a particular disease state with an outcome variable.

In the first comprehensive examination of strenuous physical activity and the risk of developing Parkinsons disease, ${ }^{28}$ Harvard researchers reported that men who exercised regularly and vigorously early in their adult life had a lower risk for developing Parkinsons disease than men who did not. The most physically active men at the start of the study cut their risk of developing Parkinsons by $50 \%$ compared with male study participants who were the least physically active. Men who reported having regularly engaged in strenuous physical activity in early adult life cut their risk by $60 \%$ compared with those who did not. Among women, strenuous activity in the early adult years was linked to a lower risk of Parkinsons, but the relationship was not statistically significant, and no clear relationship existed between physical activity later in life and Parkinsons risk.


Figure 47 Model of gene exercise interaction, intermediate phenotype, and multiple environmental factor interactions in determining health status along the disease wellness continuum. (Adapted from Bray MS. Genomics, genes, and environmental interaction: the role of exercise. J Appl Physiol 2000;88:788.) Note: The journal Medicine \& Science in Sports \& Exercise now publishes an annual update of the human gene map for performance and health-related fitness phenotypes. The inaugural issue (Rankinen T, et al. Med Sci Sports Exerc $2001 ; 33: 855$ ) contained specific reference to genes and their location published through December 2000; the most recent update highlights research through 2007 (Bray MS, et al. The human gene map for performance and health-related fitness phenotypes: the 20062007 update. Med Sci Sports Exerc 2009;41:35.)

A crucial challenge to this kind of information requires resolution: Scientists must connect the evidence about the interaction of the genes in Parkinsons with physical inactivity throughout life. ${ }^{24,98}$ This is true for all of the other major diseases and the possible role for a genetic basis of physical activity.

We hope that during the next decade, researchers from diverse disciplines will continue to cross boundaries to solve challenging questions in exercise physiology. We are encouraged that the University of Aberdeen in Scotland, to our knowledge, is first to offer an MSc in Molecular Exercise Physiology (www.abdn.ac.uk/sms/postgraduate/molecular-exercisephysiology.shtml), where the MSc program, including Diploma and Certificate programs, are described as an important new subfield in sports science that focuses on genetics and signal transduction in relation to exercise. In this program, molecular exercise physiologists aim to identify the genetic determinants of human performance on a molecular level and characterize the mechanisms responsible for the adaptation of cells and organs to exercise. Students must complete a full-time original research project that covers topics from method optimization to mechanisms that regulate the adaptation to exercise. We envision that other MS and PhD programs in kinesiology will routinely require students to complete course work in molecular biology as part of the required core or elective curriculum, and offer interdisciplinary study in molecular biology, genetics, biochemistry, and integrative physiology. Working together, exercise physiologists trained in molecular biology (or molecular biologists with training in exercise physiology) can profit from the insights of biologists, geneticists, pharmacologists, and chemists who study human physical activity at the molecular level. Their shared explorations will benefit all humanity.


Each (organic being) at some period of life, during some season of the year, during each generation or at intervals, has to struggle for life, and to suggest great destruction. When we reflect on this struggle, we may console ourselves with the full belief that the war of nature is not incessant, that no fear is felt, that death is generally prompt, and that the vigorous, the healthy, and the happy survive and multiply.

Charles Darwin, The Origin of Species

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[^0]:    CHAPTER 17 Functional Capacity of the Cardiovascular
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[^1]:    ${ }^{a}$ Buskirk ${ }^{11}$ provides a bibliography of books and review articles on exercise, fitness, and exercise physiology from 1920 to 1979. Berryman ${ }^{6}$ lists many textbooks and essays from the time of Hippocrates through the Civil War period in the United States.

[^2]:    ${ }^{b}$ According to Green, the dates for Galen $s$ birth are estimates based on a notation Galen made when at age 38 he served as personal physician to the Roman emperors Marcus Aurelius and Lucius Verus. ${ }^{24}$ Siegel s bibliography contains an excellent source for references to Galen. ${ }^{64}$

[^3]:    ${ }^{c}$ An important city on the Mediterranean coast of Asia Minor, Pergamos influenced trade and commerce. From AD 152 to 156, Galen studied in Pergamos, renowned at the time for its library of 50,000 books (approximately one-fourth as many as in Alexandria, the greatest city for learning and education) and its famous medical center in the Temple of Asclepios.

[^4]:    ${ }^{d}$ Jean Baptise van Helmont (1577 1644), a Flemish doctor, is credited with being first to prescribe an alkaline cure for indigestion. ${ }^{23}$ Observing the innards of birds, he reasoned that acid in the digestive tract could not alone decompose meats and that other substances ( ferments, now known as digestive enzymes) must break down food.

[^5]:    ${ }^{f}$ Edward Hitchcock, Jr., often is accorded the distinction of being the first professor of physical education in the United States, whereas, in fact, John D. Hooker was first appointed to this position at Amherst College in 1860. Because of poor health, Hooker resigned in 1861, and Hitchcock was appointed in his place. The original idea of a Department of Physical Education with a professorship had been proposed in 1854 by William Augustus Stearns, DD, the fourth president of Amherst College, who considered physical education instruction essential for the health of the students and useful to prepare them physically, spiritually, and intellectually. Other institutions were slow to adopt this innovative concept; the next department of physical education in America was not created until 1879. In 1860, the Barrett Gymnasium at Amherst College was completed and served as the training facility where all students were required to perform systematic exercises for 30 minutes, 4 days a week. The gymnasium included a laboratory with scientific instruments (e.g., spirometer, strength and anthropometric equipment) and also a piano to provide rhythm during the exercises. Hitchcock reported to the Trustees that in his first year, he recorded the students vital statistics-including age, weight, height, size of chest and forearm, capacity of lungs, and some measure of muscular strength. (Hitchcock, 1860; see Table 1.)

[^6]:    223. What is lean meat? How does muscle arpear to the naked eye? What are the three microscopic clements? Describe each. 229. What is the diameter of the Fibrils?
[^7]:    ${ }^{9}$ Probably unknown to Hitchcock was the 1628 manuscript of the Flemish fencing instructor at the French Royal Court, Gerard Thibault, who studied optimal body proportions and success in fencing. ${ }^{59}$ This early text, LAcad mie de lEsp e, appeared at a time when important discoveries were being made by European scientists, particularly anatomists and physiologists, whose contributions played such an important role in laboratory experimentation and scientific inquiry. Had Hitchcock known about this early attempt to link anthropometric assessment with success in sport, the acceptance of anthropometry in the college curriculum might have been easier. Nevertheless, just 67 years after Hitchcock began taking anthropometric measurements at Amherst, and 37 years following the creation of Harvard s physical education scientific laboratory in 1891, anthropometric measurements were made of athletes at the 1928 Amsterdam Olympic Games. One of the athletes measured in Amsterdam, Ernst Jokl from South Africa, became a physician and then professor of physical education at the University of Kentucky. Jokl was a charter member and founder of the American College of Sports Medicine. Thus, Hitchcock s visionary ideas about the importance of anthropometry finally caught on, and such assessment techniques are now used routinely in exercise physiology to assess physique status and the dynamics between physiology and performance. The more modern application of anthropometry is now known as kinanthropometry. This term, first defined at the International Congress of Physical Activity Sciences in conjunction with the 1976 Montreal Olympic Games, ${ }^{60}$ was refined in $1980^{59}$ as follows: Kinanthropometry is the application of measurement to the study of human size, shape, proportion, composition, maturation, and gross function. Its purpose is to help us to understand human movement in the context of growth, exercise, performance, and nutrition. We see its essentially human-enobling purpose being achieved through applications in medicine, education, and government.

[^8]:    ${ }^{h}$ According to Hitchcock and Selye s Anthropometric Manual, the device consisted of a lever acting by means of a piston and cylinder on a column of mercury in a closed glass tube. Water keeps the oil in the cylinder from contact with the mercury and various attachments enable the different groups of muscles to be brought to bear on the lever. By means of this apparatus, the strength of most of the large muscles may be tested fairly objectively (p. 25). In the photographs, note the attachment of the tube to each device. Interestingly, Hitchcock determined an individual s total strength as a composite of body weight multiplied by dip and pull tests, strength of the back, legs, and average of the forearms, and the lung strength. Hitchcock stated, The total strength is purely an arbitrary, and relative, rather than an actual test of strength as its name would indicate. And while confessedly imperfect, it seems decidedly desirable that there should be some method of comparison which does not depend entirely on lifting a dead weight against gravity, or steel springs. (Hitchcock and Seelye, 1889; see Table 1.)

[^9]:    ${ }^{i}$ We disagree with Berryman s ${ }^{6}$ assessment of the relative historical importance of the translation of the original Lagrange text. We give our reasons for this disagreement in a subsequent section titled First Textbook in Exercise Physiology: The Debate Continues.
    ${ }^{j}$ The reasons for Fitz s early departure from Harvard have been discussed in detail in Park s scholarly presentation of this topic. ${ }^{46}$ His leaving was certainly unfortunate for the next generation of students of exercise physiology. In his 1909 textbook Principles of Physiology and Hygiene (New York, Henry Holt and Co.), the title page listed the following about Fitz s affiliation: Sometime Assistant Professor Physiology and Hygiene and Medical Visitor, Harvard University.
    ${ }^{k}$ The originator of the American Journal of Physiology was physiologist William T. Porter of the St. Louis College of Medicine and Harvard Medical School, who remained editor until $1914 .{ }^{10}$ Porter s research focused on cardiac physiology. The three articles in volume 1 concerned (1) spontaneous physical activity in rodents and the influence of diet (C. C. Stewart, Department of Physiology, Clark University), (2) neural control of muscular movement in dogs (R. H. Cunningham, College of Physicians and Surgeons, Columbia University), and (3) perception of muscular fatigue and physical activity (J. C. Welch, Hull Physiological Laboratory, University of Chicago). As pointed out by Buskirk, ${ }^{11}$ the next four volumes of the American Journal of Physiology (1898 1901) contained six additional articles about exercise physiology from experimental research laboratories at Harvard Medical School, Massachusetts Institute of Technology, the University of Michigan, and the Johns Hopkins University.

[^10]:    ${ }^{l}$ The following books (including translations, editions, and pages) were published by Lagrange beginning in 1888: Physiologie des Exercices du Corps. Paris: Alcan, 1888, 372 pp. (6th ed., 1892); LHygiene de lExercice Chez les Enfants et les Jeunes Gens. Paris: Alcan, 1890, 312 pp. (4th ed., 1893; 6th ed, 1896; 7th ed, 1901, 8th ed, 1905); Physiology of Bodily Exercise. New York: D. Appleton, 1890, 395 pp.; De lExercice Chez les Adultes. Paris: Alcan, 1891, 367 pp. (2nd ed., 1892, 367 pp.; 4th ed., 1900, 367 pp.; Italian translation, Fisiologia degli Esercizj del Corpo. Milano: Dumolard, 1889; Hungarian translation, 1913); La Medication par lExercice. Paris: Alcan, 1894, 500 pp.

[^11]:    ${ }^{m}$ Possible pre-1900 candidates for first exercise physiology textbook listed in Table 1 also include Combe s 1843 text The Principles of Physiology Applied to the Preservation of Health, and to the Improvement of Physical and Mental Education; Hitchcock and Hitchcock s Elementary Anatomy and Physiology for Colleges, Academies, and Other Schools (1860); Kolb s 1887 German monograph, translated into English in 1893 as Physiology of Sport; and the 1898 Martin text, The Human Body. An Account of Its Structure and Activities and the Conditions of Its Healthy Working.

[^12]:    ${ }^{n}$ Personal communication to F. Katch, June 13, 1995, from Dr. strand regarding his professional background. Recipient of five honorary doctorate degrees (Universit de Grenoble, 1968; University of Jyv skyl, 1971; Institut Superieur dEducation Physique, Universit Libre de Bruxelles, 1987; Loughborough University of Technology, 1991; Aristoteles University of Thessaloniki, 1992). strand is an honorary Fellow of nine international societies, a Fellow of the American Association for the Advancement of Science (for outstanding career contributions to understanding of the physiology of muscular work and applications of this understanding), and has received many awards and prizes for his outstanding scientific achievements, including the ACSM Honor Award in 1973. strand served on a committee for awarding the Nobel Prize in physiology or medicine from 1977 to 1988 and is coauthor with Kaare Rodahl of Textbook of Work Physiology, third edition, 1986 (translated into Chinese, French, Italian, Japanese, Korean, Portuguese, and Spanish). His English publications number about 200 (including book chapters, proceedings, a history of Scandinavian scientists in exercise physiology, ${ }^{3}$ and monographs), and he has given invited lectures in approximately 50 countries and 150 different cities outside of Sweden. His classic 1974 pamphlet Health and Fitness has an estimated distribution of 15 to 20 million copies (about 3 million copies in Sweden) mffortunately, all without personal royalty!

[^13]:    ${ }^{o}$ There are many excellent sources of information about the history of science and medicine, including the following: Bettman O. A Pictorial History of Medicine. Springfield, IL: Charles C Thomas, 1956; Clendening L. Source Book of Medical History. New York: Dover Publications/Henry Schuman, 1960; Coleman W. Biology in the Nineteenth Century. New York: Cambridge University Press, 1977; Franklin K. A Short History of Physiology, 2nd ed. London: Staples Press, 1949; Fye WB, The Development of American Physiology. Scientific Medicine in the Nineteenth Century. Baltimore: Johns Hopkins University Press, 1987; Guthrie D. A History of Medicine. London: T. Nelson \& Sons, 1945; Haskins T. Science and Enlightenment. New York: Cambridge University Press, 1985; Holmes FL. Lavoisier and the Chemistry of Life. Madison: University of Wisconsin Press, 1985; Knight B. Discovering the Human Body. London: Bloomsbury Books; Lesch JE. Science and Medicine in France. The Emergence of Experimental Physiology, 1790 1855. Cambridge, MA: Harvard University Press, 1984; Vertinsky PA. The Eternally Wounded Woman: Women, Exercise, and Doctors in the Late Nineteenth Century. Urbana: University of Illinois Press; Walker K. The Story of Medicine. London: Arrow Books, 1954.

[^14]:    ${ }^{a}$ The diets total cholesterol content is less than 200 mg , and total calcium equals 1242 mg .

[^15]:    - 44\% Meat, fish, poultry, eggs
    - 24\% Dairy
    - 7\% Fruits, vegetables
    - 5\% Beans, peas, nuts
    $\square 1 \%$ Fats, oils

[^16]:    
     individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.
    
     Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001). These reports may be accessed via www.nap.edu/catalog/dri.
    Copyright by the National Academy of Sciences. Reprinted with permission.

[^17]:    Svetkey LP, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. Arch Intern Med 1999;159:285.

[^18]:    From Brodney S, et al. Nutrient intake of physically fit and unfit men and women. Med Sci Sports Exerc 2001;33:459.
    BMI, body mass index; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; RE, retinol equivalents;
    $\mathrm{AE}, \alpha$-tocopherol units.
    ${ }^{a}$ Significant difference between low and moderate fit, $P<.05$.
    ${ }^{b}$ Significant difference between low and high fit, $P<.05$.
    ${ }^{\text {c }}$ Significant difference between moderate and high fit, $P<.05$.

[^19]:    Figure 6.11 Glycolysis: a series of 10 enzymatically controlled chemical reactions create two molecules of pyruvate from the anaerobic breakdown of glucose. Lactate forms when NADH oxidation does not keep pace with its formation in glycolysis. Enzymes colored yellow/purple play a key regulatory role in these metabolic reactions.

[^20]:    From Zuntz N. Ueber die Bedeutung der verschiedenen N hrstoffe als Erzeuger der Muskelkraft. Arch Gesamte Physiol, Bonn, Germany: 1901; LXXXIII:557 571; Pfl gers Arch Physiol,1901;83:557.

[^21]:    Data from Passmore R, Durnin JVGA. Human energy expenditure. Physiol Rev 1955;35:801.
    ${ }^{a}$ How to use the table: A $120-\mathrm{lb}(54-\mathrm{kg})$ person who walks at $3.0 \mathrm{mph}\left(4.83 \mathrm{~km} \cdot \mathrm{~h}^{-1}\right)$ expends $3.6 \mathrm{kCal} \cdot \mathrm{min}^{-1}$. This person expends 216 kCal in a 60 -minute walk $(3.6 \times 60)$.

[^22]:    Immediate energy system (ATP-PCr)
    -Short-term energy system (Glycolysis)
    Long-term energy system (Aerobic)

[^23]:    $\square$ Trained $\square$ Untrained

[^24]:    Adapted from McArdle WD, et al. Comparison of continuous and discontinuous treadmill and bicycle tests for max $\mathrm{VO}_{2}$. Med Sci Sports $1973 ; 5: 156$. ${ }^{a}$ Values are means $\pm$ standard deviations.

[^25]:    From George JD, et al. Non-exercise $\mathrm{VO}_{2 \max }$ estimation for physically active college students. Med Sci Sports Exerc 1997;29:415.

[^26]:    From Mahler DA, et al. Ventilatory responses at rest and during exercise in marathon runners. J Appl Physiol 1982;52:388.
    ${ }^{a}$ All differences not statistically significant.

[^27]:    ST, stature (height) in centimeters; A, age in years.

[^28]:    ${ }^{a}$ At 760 mm Hg ambient air pressure.
    ${ }^{b}$ Includes $0.93 \%$ argon and other trace rare gases.

[^29]:    From Rode A, Shephard RJ. The influence of cigarette smoking upon the oxygen cost of breathing in near-maximal exercise. Med Sci Sports Exerc 1971;3:51.
    ${ }^{a}$ The implication of the negative cost of $\mathrm{V}_{\mathrm{E}}$ in this subject is that the added dead space reduces the cost of the normal exercise ventilation.

[^30]:    Values are averages for seven subjects. Data from Freedson PF, et al. Intraarterial blood pressure during free weight and hydraulic resistive exercise. Med Sci Sports Exerc 1984;16:131 and unpublished data from the Human Performance Laboratory, Department of Exercise Science, University of Massachusetts, Amherst, MA.
    ${ }^{a}$ Open glottis (no Valsalva maneuver); average of two trials; contraction time, 2 to 3 seconds; arm position that of bench-press exercise, with hands slightly above chest.
    ${ }^{b}$ The weight lifted was either 25 or $50 \%$ of previously determined isometric maximum action.
    ${ }^{c}$ Performed on Hydra-Fitness chest-press apparatus at dial setting 3 (slow) and 5 (fast) for 20 seconds of repeated maximal actions.

[^31]:    Systolic blood pressure Diastolic blood pressure

[^32]:    $\left\lceil\right.$ Arterial $\mathrm{O}_{2}$ capacity $\square$ Arterial $\mathrm{O}_{2}$ content
    $\square$ Mixed-venous $\mathrm{O}_{2}$ content

[^33]:    - Exercise training improved $\dot{\mathrm{V}} \mathrm{O}_{2 \text { max }}$ (particularly for the E-trained leg) and lowered heart rate and blood lactate in submaximal exercise only when exercising with a trained leg.

[^34]:    ${ }^{a}$ Data represent an average computed from individual studies as cited in the following sources: McArdle WD, et al. Essentials of exercise physiology. 3rd ed. Lippincott Williams \& Wilkins, 2006, and Wilber RL, Moffatt RJ. Physiological and biochemical consequences of detraining in aerobically trained individuals. J Strength Cond Res 1994;8:110. Note that a change for heart rate represents a decline in functional capacity. Omitted values for trained and detrained excluded in original sources.
    ${ }^{b}$ Short term, 3 weeks or less in primarily aerobically trained individuals.
    ${ }^{c}$ Longer term, 3 to 12 weeks in primarily aerobically trained individuals. NS, not statistically significant.

[^35]:    ${ }^{a}$ In some cases, approximate values are used. In all cases, the trained values represent data from endurance athletes. Caution is advised in assuming that the percentage differences between trained and untrained necessarily results from training because genetic factors exert a strong influence on many of these factors.
    ${ }^{b}$ Percentage by which the value for the trained differs from the corresponding value for the untrained.

[^36]:    From Morganroth J, et al. Comparative left-ventricular dimensions in trained athletes. Ann Intern Med 1975;82:521.
    ${ }^{a}$ LVID, left-ventricular internal dimension at end diastole; LVV, left-ventricular volume; SV, stroke volume; LV wall, posterobasal left-ventricular wall thickness; Septum, ventricular septal thickness; LV mass, left-ventricular mass.
    ${ }^{b}$ Range.
    NR, Values not reported.

[^37]:    Modified from Rowell LB. Circulation. Med Sci Sports 1969;1:15.

[^38]:    ECC, eccentric; CON, concentric; Nov, novice; Int, Intermediate; Adv, advanced; SJ, single-joint; MJ, multiple-joint; ex., exercises; HI, high intensity; LI, low intensity; 1RM, 1-repetition maximum; PER, periodized; VH, very heavy; L-MH, light-to-moderately heavy; S, slow; M, moderate; US, unintentionally slow; F, fast, MR, moderate repetitions; HR, high repetitions.
    From ACSM position stand on: Progression models in resistance training for healthy adults. Med Sci Sports Exerc 2002;34:364.

[^39]:    From Byrnes WC. Muscle soreness following resistance exercise with and without eccentric muscle actions. Res Q Exerc Sport 1985;56:283.
    ${ }^{a}$ All differences between groups were statistically significant.
    $\mathrm{X}=$ mean

[^40]:    ${ }^{a}$ Not truly listed as an herb; usually listed as a supplement.
    From Fetrow C, Avila JR. Professionals handbook of complementary \& alternative medicines. Springhouse, PA: Springhouse Corporation, 1999; and Schuyler W, et al. The natural pharmacy. 2nd ed. New York: Three Rivers Press. Imprint of Crown Publishing Group, 1999.

[^41]:    Ivy J, Portman R. Nutrient timing: the future of sports nutrition. New Jersey: Basic Health Publications, 2004.

    Crigg PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exerc

[^42]:    Data from product labels and manufacturers and Nation Soft Drink Association.
    ${ }^{a}$ Brewing tea or coffee for longer periods slightly increases the caffeine content.
    ${ }^{b}$ Prescription, 1 oz or 30 mL .

[^43]:    From Wilkes D. et al. Effects of induced metabolic alkalosis on 800-m racing time. Med Sci Sports Exerc 1983;15:277.
    ${ }^{a}$ Preexercise values significantly higher than pretreatment values.
    ${ }^{b}$ Alkalosis values significantly higher than placebo and control values after exercise.
    ${ }^{c}$ Alkalosis time significantly faster than control and placebo times.

[^44]:    From Roberston RJ, et al. Effect of induced erythrocythemia on hypoxia tolerance during exercise. J Appl Physiol 1982;53:490.
    ${ }^{a}$ Hematocrit expressed as the percentage (\%) of $100 \mathrm{~mL}(1 \mathrm{dL})$ of whole blood occupied by red blood cells.
    ${ }^{b}$ Difference statistically significant.

[^45]:    $\square$ Normal climbing $\square$ Everest data (max exercise) $\square$ Himalayan expd. 1960/61 (max exercise)

[^46]:    $\square$ Steady-rate $\mathrm{VO}_{2}$ at 100-W power output

[^47]:    ${ }^{a} \mathrm{TDB}$, temperature of dry bulb thermometer
    From Montain SJ, et al. Exercise-associated hyponatremia: Quantitative analysis for understanding the aetiology. Br J Sports Med. 2006;40:98.

[^48]:    $2 \mathrm{mmol} \cdot \mathrm{L}^{-1}\left\lceil 26 \mathrm{mmol} \cdot \mathrm{L}^{-1} \square 52 \mathrm{mmol} \cdot \mathrm{L}^{-1} \square 100 \mathrm{mmol} \cdot \mathrm{L}^{-1}\right.$

[^49]:    $\square$ Skylab $4 \square$ Skylab $3 \square$ Skylab $2 \square$ Shuttle, SLS
    Shuttle (Inflight), LMS

[^50]:    From Katch VL, Freedson PS. Body size and shape: derivation of the HAT frame-size model. Am J Clin Nutr 1982;36:669.

[^51]:    Adapted from De Garay, et al. Genetic and anthropological studies of Olympic athletes. New York: Academic Press, 1974; and Hirata K. Physique and age of Tokyo Olympic champions. J Sports Med Phys Fitness 1966;6:207.
    ${ }^{a}$ Calculated by Behnkes method: LBM (lean body mass) $=\mathrm{h}^{2} \times 0.204$, where $\mathrm{h}=$ stature, dm (see reference 2).
    ${ }^{b}$ Body fat $(\%)=($ Body mass - LBM $) /$ Body mass $\times 100$.
    ${ }^{c}$ Error resulting from specific prediction equation as percentage body fat cannot reach zero or a negative value.

[^52]:    ${ }^{a}$ Grouping according to Wilmore JH, Haskel WL. Body composition and endurance capacity of professional football players. J Appl Physiol 1972;33:564.
    ${ }^{b}$ Data from Wickkiser JD, Kelly JM. The body composition of a college football team. Med Sci Sports 1975;7:199.
    ${ }^{c}$ UMass data from Coach Robert Stull and F Katch, University of Massachusetts. Data collected during spring practice, 1985; \%fat by densitometry.
    ${ }^{d}$ USC data from Dr. Robert Girandola, University of Southern California, Los Angeles, 1978, 1993.
    ${ }^{e}$ Data courtesy of Dr. Kristin Steumple, Department of Exercise and Sport Science, Gettysburg College, Gettysburg,
    PA, 2000.
    ${ }^{f}$ Data from Wilmore JH, et al. Football pros strengthsand CV weaknesseharted. Phys Sportsmed 1976;4:45.
    ${ }^{g}$ Data from Dr. A. R. Behnke.
    ${ }^{h}$ Data from Katch FI, Katch, VL. Body composition of the Dallas Cowboys and New York Jets football teams, unpublished, 1978.

[^53]:    Scholarly theses on this subject began to appear in the late 16 th century, with the first monographs published in the 18th century. The values of dietary restriction, increasing exercise, and reducing the amount of sleep were identified early in medical history dating at least from the time of Hippocrates. These concepts were often framed in a manner that implied a moral

[^54]:    From Klem MI, et al. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. Am J Clin Nutr 1997;66:239.

[^55]:    From Broeder CE, et al. Assessing body composition before and after resistance or endurance training. Med Sci Sports Exerc 1997;29:705.
    ${ }^{a}$ Significant difference between pre- and posttest measurements ( $p<0.05$ ).
    All values means $\pm$ SD.

[^56]:    From Milesis CA, et al. Effects of different durations of physical training on cardiorespiratory function, body composition, and serum lipids. Res Q 1976;47:716.

[^57]:    From Tipton CM. Making and maintaining weight for interscholastic wrestling. Gatorade Sports Science Exchange. 1990;2(22).
    ${ }^{a}$ Lohman TG. Skinfolds and body density and their relationship to body frames: a review. Hum Biol 1981;53:181.
    ${ }^{b}$ Katch FI, McArdle WD. Prediction of body density from simple anthropometric measurements in college-age men and women. Hum Biol 1973;145:445.
    ${ }^{\text {cBehnke AR, Wilmore JH. Evaluation and regulation of body build and composition. Englewood Cliffs, NJ: Prentice Hall, } 1974 .}$
    ${ }^{d}$ Thorland W, et al. New equations for prediction of a minimal weight in high school wrestlers. Med Sci Sports Exerc 1989;21:S72.

[^58]:    Clinical Areas
    Cardiovascular Diseases and Disorders
    Pulmonary Diseases and Disorders
    Neuromuscular Diseases and Disorders
    Metabolic Diseases and Disorders
    Immunologic and Hematologic Diseases
    Disorders
    Orthopedic Diseases and Disorders
    Aging
    Cognitive and Emotional Disorders

[^59]:    Modified from Clausen JP, et al. Physical training in the management of coronary artery disease. Circulation 1969;40:143.
    ${ }^{a}$ Intraarterial catheter.

[^60]:    Modified from Franklin BA, et al. ACSM s guidelines for exercise testing and prescription. 8th ed. Baltimore: Lippincott Williams \& Wilkins, 2008.
    ${ }^{a}$ Risk factors: family history of heart disease; cigarette smoking; hypertension; hypercholesterolemia; impaired fasting glucose; obesity; sedentary lifestyle.
    ${ }^{b} \mathrm{HDL}>60 \mathrm{mg} \cdot \mathrm{dL}^{-1}$ (subtract 1 risk factor from the sum of other risk factors because high HDL decreases CHD risk).
     fatigue or shortness of breath with mild activity.

[^61]:    Onset of angina or angina-like symptoms
    Significant drop of 20 mm Hg in systolic blood pressure or failure of systolic blood pressure to rise with an increase in exercise intensity
    Excessive rise in blood pressure: systolic pressure $>260 \mathrm{~mm} \mathrm{Hg}$ or diastolic pressure $>115 \mathrm{~mm} \mathrm{Hg}$
    Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
    Failure of heart rate to increase with increasing exercise intensity
    Noticeable change in heart rhythm
    Subject requests to stop
    Physical or verbal manifestations of severe fatigue Failure of testing equipment
    Early-onset horizontal or downsloping S T segment depression or elevation ( $>4 \mathrm{~mm}$ )
    Increasing ventricular ectopy; multiform PVCs
    Sustained supraventricular tachycardia

[^62]:    From Franklin BA, et al. ACSM s guidelines for exercise testing and prescription. 8th ed. Baltimore: Lippincott Williams \& Wilkins, 2008.
    ${ }^{a}$ Direct physician supervision of GXT.
    ${ }^{b}$ Complications defined as the occurrence of serious arrhythmias during exercise testing (i.e., ventricular fibrillation, ventricular tachycardia, or bradycardia) that mandated immediate medical treatment (cardioversion, use of intravenous drugs, or closed-chest compression).

    1. Atterhog JH, et al. Am Heart J 1979;98:572.
    2. Cahalin LP, et al. J Cardiopulm Rehabil 1987;7:269.
    3. Blessey RL. Exercise Standards and Malpractice Reporter 1989;3:69.
    4. DeBrusk RF. Exercise Standards and Malpractice Reporter 1988;2:65.
    5. Franklin BA, et al. Chest 1997;111:262.
    6. Gibbons L, et al. Circulation 1989;80:846.
    7. Knight JA, et al. Am J Cardiol 1995;75:390.
    8. Lem V, et al. Heart Lung 1985;14:280.
    9. Rochmis P, Blackburn H. JAMA 217:1971;1061.
    10. Scherer D, Kaltenbach M. Dtsch Med Wochenschr 1979;33:1161.
    11. Stuart RJ Jr, Ellestad MH. Chest 1980;77:94.
    12. Young, et al. Circulation 1984;70:184.
[^63]:    ${ }^{a}$ Collagen, the most plentiful structural protein, accounts for about one-fourth of the bodys protein. In essence, it forms molecular cables that strengthen the tendons and plentiful, resilient sheets that support the skin and internal organs. This simple protein, composed of three chains wound together in a tight triple helix, contains more than 1400 amino acids in each chain. Collagen forms from a repeated sequence of three amino acids; every third amino acid is glycine, a small amino acid that fits perfectly inside the helix. Many of the remaining positions in the chain are filled by two amino acids, proline and hydroxyproline, the latter a modified version of proline. Hydroxyproline formation involves modifying normal proline amino acids after building the collagen. The reaction requires vitamin C to assist in the addition of oxygen. Unfortunately, vitamin C deficiency slows hydroxyproline production and stops new collagen construction, ultimately causing scurvy. When heated, collagens triple helix unwinds and the chains separate. When the denatured mass of tangled chains cools down, it soaks up the surrounding water like a sponge to form gelatin commonly used in cooking.

