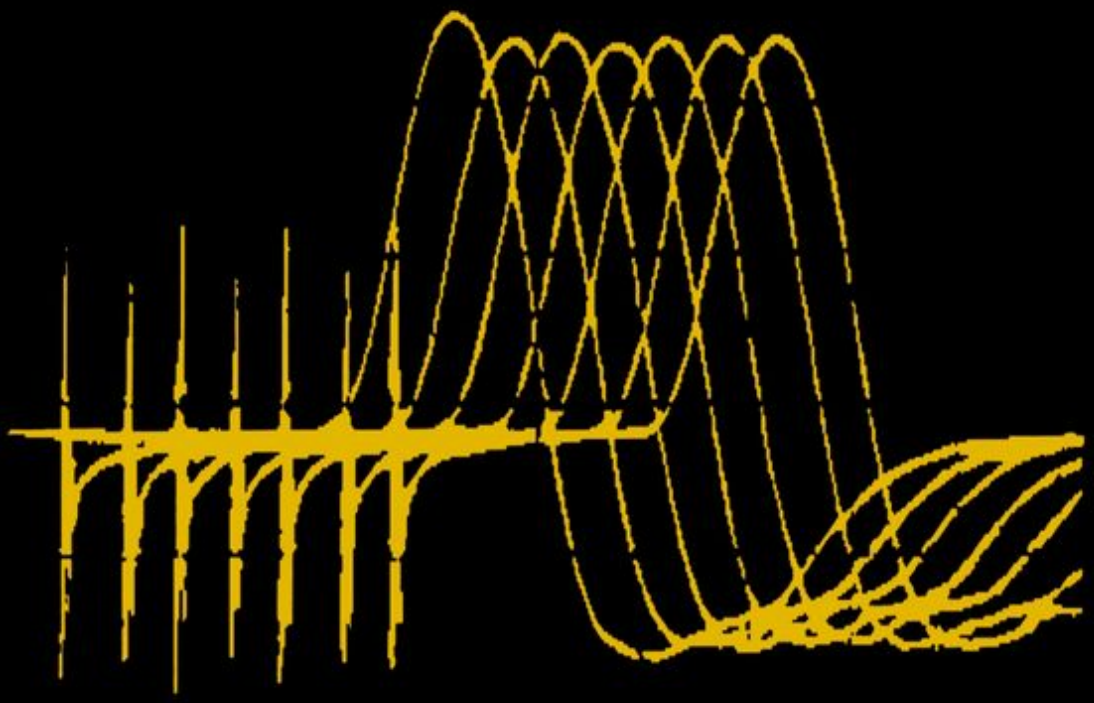
ELECTRODIAGNOSIS

IN DISEASES OF

NERVE AND MUSCLE

PRINCIPLES AND PRACTICE

FOURTH EDITION



JUN KIMURA

Advance Praise for *Electrodiagnosis in Diseases of Nerve and Muscle, Fourth Edition*

The new edition of this classic text will be welcomed not only by trainees in electrodiagnostic medicine but by established physicians who seek a comprehensive and up-to-date account of the specialty by one of its masters. Jun Kimura—a former editor-in-chief of the journal *Muscle and Neve* and a past president of the International Federation of Clinical Neurophysiology—has made seminal personal contributions to the field and is recognized widely as an authority on electromyography and electrodiagnosis. His experience over many years as a physician, investigator, and teacher has been distilled to produce this outstanding, comprehensive new edition. The volume, which incorporates the advances of the years, will serve as a terrific informational resource as well as facilitating daily practice for both new and established specialists. It is a mine of information.

Michael J. Aminoff, MD, DSc, FRCP, Distinguished Professor and Executive Vice Chair, Department of Neurology, University of California, San Francisco, CA

This Fourth Edition of *Electrodiagnosis in Diseases of Nerve and Muscle* by Jun Kimura lives up to all expectations—updating a classic reference that has been the "go-to" resource for a generation of electromyographers and neuromuscular clinicians the past thirty years. Major sections have been revised, new material included, outdated references removed, and the text streamlined to emphasis current concepts and practice. The clearly written and well-illustrated descriptions of the electrodiagnostic evaluation and expected results in health and disease are both practical and comprehensive, making the book appropriate for trainees and veteran electromyographers alike. This resource is a worthy companion of every physician who evaluates patients with suspected neuromuscular disorders. It is a resource to be read and consulted on a regular basis, not one that will collect dust on the owner's bookshelf.

James W. Albers, MD, PhD, Emeritus Professor of Neurology, University of Michigan Health System, Ann Arbor, Michigan

This edition of Kimura is the most complete, authoritative, up-to-date, and readable text on electrodiagnosis available today. It is a multi-layered resource that will serve not only as a primer for the EMG beginner, but also as a reference text for the experienced electrodiagnostic consultant.

Kerry Levin MD, Chairman, Department of Neurology, Director, Neuromuscular Center Cleveland Clinic

Great News—Jun Kimura's *Electrodiagnosis in Diseases of Nerve and Muscle—Principles and Practice* Fourth Edition is out. Even though several decades have past since this book was first conceived it remains the Gold-Standard in the discipline and no text on the subject has out-performed this bible. A text-book of this scope today, is rarely written by a single authority, but much of the success of the previous editions have been due to Professor Kimura's unique ability to cover essentials in ways few others can. His knowledge of the subject is vast, and as the years have gone by, like a good wine, details and controversies have matured.

A new and welcome feature of the 4th Edition is the creation of a CD. This adds important practical value to the book, allowing readers to watch and listen to various types of normal and abnormal EMG activities. A valuable tool for those preparing for Certification in EMG.

Some 5000 new references were reviewed in the preparation of the new edition selecting the pertinent and up-to-date information. The 4th Edition, describes several new techniques that have emerged since the previous edition, with expanded coverage of topics crucial to theory and practice of EMG. New to the 4th edition is a section on intra-operative monitoring, studies for the pediatric and geriatric populations and data analysis and reporting. All of which should help facilitate daily practice.

Kimura's text remains an essential for all those practicing electromyography. Jun Kimura has expertise in Neurology, Physiology and Engineering and all Neurologists, Neurosurgeons, Phsyiatrists, Orthopedic and Hand Surgeons and medical students, even if not running an EMG laboratory will do well to read this book. Without it their medical education is lacking and limited.

Andrew Eisen MD., FRCPC, Professor Emeritus Neurology, University of British Columbia, Vancouver, BC, Canada

The pleasant surprise as I reviewed this fourth edition was the substantial amount of change in organization of sections and chapters, in addition to updates of the material. Age-related information, both pediatric/development and geriatric/aging are now co-located. Similarly late responses now follow the nerve conduction chapters, rather than being lumped into Special Techniques with pediatrics. Throughout this manuscript, Jun Kimura has updated his elegantly written textbook, and it is still the most readable in the field. Whether your interest is the secrets of volume conduction or the basics of median nerve testing, this book belongs on your desk. As a bonus, the consistent chapter structure and thorough indexing makes easy work of finding specific details of interest.

William S. Pease, MD, Ernest W. Johnson Professor, Physical Medicine and Rehabilitation,
The Ohio State University Wexner Medical Center , Dodd Hall Rehabilitation Hospital, Columbus, OH

ELECTRODIAGNOSIS IN DISEASES OF NERVE AND MUSCLE

Principles and Practice

FOURTH EDITION

JUN KIMURA, MD
PROFESSOR EMERITUS
DEPARTMENT OF NEUROLOGY
KYOTO UNIVERSITY
KYOTO, JAPAN

and

PROFESSOR
DIVISION OF CLINICAL ELECTROPHYSIOLOGY
DEPARTMENT OF NEUROLOGY
UNIVERSITY OF IOWA COLLEGE OF MEDICINE
IOWA CITY, IA, USA

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To Leslie Miya

As requested by my wife, Junko, for the courage and grace shown by the youngest of our five granddaughters in a heroic battle with leukemia, which we hope she will overcome.

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Preface and Acknowledgments

PREPARATION FOR this revision began in 2001 soon after the completion of the third edition delivered in haste during an uninvited encounter with the law. To consolidate the voluminous text, the goal intended but unmet at that time, I have now deleted old or impractical concepts and removed outdated references not directly related to current practice. I have then updated the contents based on some 5000 new articles selected for information pertinent to the day-to-day clinical studies, which turned into a slow and tedious process. Fortunately, I had sufficient time to streamline the manuscript for the sake of brevity, especially with the completion of my tenure for the World Federation of Neurology and after the end of the malicious prosecution, which I had to endure for some time as mentioned in the preface of the last edition. Incredible as it may sound, a totally unforeseen turn of events involving the corrupt public office surfaced in 2004, leading to a confession, which finally substantiated our claim. I take heart in the belief that justice, though blindfolded, will eventually prevail and truth always sets you free.

Although the basic premises remain in electrophysiologic problem solving, advanced technology has brought considerable modifications in the way we practice this discipline. A number of new techniques emerged necessitating an expanded coverage of the areas considered crucial in theory or practice as they relate to electrodiagnostic medicine. I have also added brief chapters on intraoperative monitoring, studies for the pediatric and geriatric populations, and data analysis and reporting, which should help facilitate daily practice. New for this edition, the book now comes with a DVD for waveform reproduction, which we successfully tried in the production of a Japanese counterpart of this volume published last year. I wish to thank Dr. Nobuo Kohara, a friend of mine in Kyoto, who created the tape and Mr. Hitoshi Sano of Nihon Kohden, Inc., who

modified it for the use in this edition. I wish also to acknowledge Igakushoin, Inc. for allowing me to reproduce some of the waveforms used in their publication.

I have rewritten, in their entirety, the chapters on principles of nerve conduction studies; the F wave and A wave; other techniques to assess nerve function; facts, fallacies, and fancies of nerve stimulation technique; somatosensory and motor evoked potentials; and all of the clinical sections. The remaining chapters also underwent a complete overhaul not only to reflect current understanding based on careful review of new papers but also to delete some old, now discarded techniques. I have reduced the coverage of special procedures no longer routinely conducted such as provocative studies of neuromuscular transmission. Although I omitted most old articles unless they describe a classic contribution, an ample inclusion of new references should enable interested readers to consult the original sources. The use of common abbreviations as listed in the title page of each chapter should help improve the readability while, at the same time, consolidating sentences. I have tabulated normative data used in our laboratory in Appendix 1 at the end of the book together with myotomes useful for needle studies and height – minimum, mean, and maximum F-wave latency nomograms to allow quick access to the reference values during busy practice.

Throughout the preparation of this revision, I had the good fortune to work in the Division of Clinical Neurophysiology, directed by Dr. Thoru Yamada, and the Department of Neurology, headed by Dr. Robert L. Rodnitzky, who, together with Drs. Torage Shivapour, Jon Tippin, and Eric Dyken, encouraged my venture ever since the publication of the first edition in 1983. Dr. George Richerson, who joined the department as the new chair in 2010, supported my endeavor, allowing me to work at my own pace so that I may devote myself to writing. I enjoyed a most flexible time schedule thanks to Dr. Edward Aul, the director of the EMG Laboratory, Dr. Andrea Swenson, who ran the neuromuscular clinic, and Drs. Jim Worrell, Joe Chen, and Heather Bingham, who filled in regularly to help with the clinical work. David Walker, MSEE, provided the Appendix 2 on electronics, updating the references, and Pete Seaba, MSEE, gave helpful advice. I am indebted to our Chief Technologist, Sheila Mennen, who typed time and time again the voluminous manuscripts not only for this but also for all previous editions dating back some 30 years. Leigha Rios assembled all new references and filed them in order, and, last but not least, Wendy Sebetka proofed every page of the manuscript, in between their busy schedule as electrodiagnostic technologists.

After returning to Iowa, I kept close contact with former colleagues in Kyoto who specialize in clinical electrophysiology : Drs. Hiroshi Shibasaki, Ryuji Kaji, Nobuo Kohara, Takashi Nagamine, Hiroyuki Nodera, and Takahiro Mezaki among others, jointly contributed many new research insights useful for this revision. I owe special thanks to Ichiro Akiguchi for his support during my transition from Kyoto to Iowa. Machiko Miyamoto, with her daughter Maya, kept the Uji office in order for processing necessary literature as the only assistant proficient in English, and Kayoko Morii took care of my secretarial needs in Japan. I wish to thank Mr. Craig Panner at Oxford University Press, who encouraged me to initiate this revision and Susan Lee, Karen Kwak and Leslie Anglin, who guided me with patience and perseverance. I acknowledge the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and its Nomenclature Committee, who granted permission to reprint the AAEM Glossary of Terms in Electrodiagnostic Medicine (2001) as Appendix 4.

In concluding, I wish to update my account on our household, which in the earlier editions triggered many kind commentaries. We now have an empty nest as our three sons have left home to build their own. The third generation comprises three boys and five girls residing in San Francisco, Madison, and Iowa City, where we also have our home. Junko, my wife, periodically visits all five posts, including my frequent retreat in Kyoto, for various household chores and babysitting, thus her self-imposed nickname, "international cleaning lady." The book, dedicated to Leslie on her behalf, attests to our appreciation for her skills in affectionately

maintaining law and order not only at home but also abroad for the growing family. I endorse her conviction that we must endow the royalties of the book to our grandchildren, who represent our new hopes and fresh aspirations. Having exhausted all my resources, I will find it difficult to pursue another project for a while. But on this sunny winter day, when we wrap up the current endeavor, the future can wait.

Jun Kimura, MD
Iowa City, IA

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Foreword for the First Edition

I FOUND particular pleasure in preparing this foreword to the work of a colleague whose professional development and scientific accomplishments I have followed very closely indeed for some twenty years.

Dr. Kimura, very early after his training in neurology, expressed an interest in clinical electrophysiology. His energy and talents led to full-time assignment and responsibility for the development and application of electrodiagnostic techniques in our laboratory of electromyography and then to direction of the Division of Clinical Electrophysiology.

From his early assignment, Dr. Kimura has exploited the possibilities for the applications of clinical electrophysiologic techniques to their apparent limits, which, however, seem to continually advance to the benefit of us all. This volume is based on very extensive personal experience with application of all of the now recognized procedures.

The beginner will be able to follow this discipline from its historical roots to the latest techniques with the advantage of an explanatory background of the clinical, physiologic, anatomic, and pathologic foundations of the methods and their interpretation. The instrumentation, so essential to any success in application of techniques, is further described and explained. The more experienced diagnostician will both appreciate and profit from this pragmatic, well-organized, and authoritative source with its important bibliographic references; the beginner will find it a bible.

There are few areas in electrodiagnosis that Dr. Kimura does not address from his own extensive experience, backed by clinical and pathologic confirmation. The sections on the blink reflex and the F wave reflect his own pioneering work. He has closely followed the application of new techniques to the study of disease of the central nervous system by evoked cerebral potentials from

the beginning. These sections reflect a substantial personal experience in establishment of standards and in interpretation of changes in disease.

So important are the findings of electrodiagnostic methods that the clinical neurologist must himself be an expert in their interpretation. Preferably he should perform tests on his own patients or closely supervise such tests. Only in this way can he best derive the data that he needs or direct the examination in progress to secure important information as unexpected findings appear. To acquire the knowledge to guide him either in supervised training or in self-teaching, he needs first an excellent and comprehensive guide such as this text by Dr. Kimura.

Dr. Kimura is justifiably regarded as a leader in clinical electrophysiology both nationally and internationally. Those of us who profit from daily contact with him should be pardoned for our pride in this substantial and authoritative work.

Maurice W. Van Allen, MD

Preface for the First Edition

THIS BOOK grew out of my personal experience in working with fellows and residents in our electromyography laboratory. It is intended for clinicians who perform electrodiagnostic procedures as an extension of their clinical examination. As such, it emphasizes the electrical findings in the context of the clinical disorder. Although the choice of material has been oriented toward neurology, I have attempted to present facts useful to practicing electromyographers regardless of their clinical disciplines. I hope that the book will also prove to be of value to neurologists and physiatrists who are interested in neuromuscular disorders and to others who regularly request electrodiagnostic tests as an integral part of their clinical practice.

The book is divided into seven parts and three appendices. Part 1 provides an overview of basic anatomy and physiology of the neuromuscular system. Nerve conduction studies, tests of neuromuscular transmission, and conventional and single-fiber electromyography are described in the next three parts. Part 5 covers supplemental methods designed to test less accessible regions of the nervous system. The last two parts are devoted to clinical discussion. The appendices consist of the historical review, electronics and instrumentation, and a glossary of terms.

The selection of technique is necessarily influenced by the special interest of the author. Thus, in Part 5, the blink reflex, F wave, H reflex, and somatosensory evoked potential have been given more emphasis than is customary in other texts. I hope that I am not overestimating their practical importance and that these newer techniques will soon find their way into routine clinical practice. This is, of course, not to de-emphasize the conventional methods, which I hope are adequately covered in this text.

The ample space allocated for clinical discussion in Parts 6 and 7 reflects my personal conviction that clinical acumen is a prerequisite for meangingful electrophysiologic evaluations. Numerous references are provided to document the statements made in the text. I hope that use of these references will promote interest and research in the field of electrodiagnosis.

J. K.

Acknowledgments for the First Edition

I CAME from the Island of the Rising Sun, where English is not the native language. It was thus with trepidation that I undertook the task of writing an English text. Although its completion gives me personal pride and satisfaction, I hasten to acknowledge that the goal could not have been achieved without help from others.

Dr. M. W. Van Allen has provided me with more than a kind foreword. I wish to thank him for his initial encouragement and continued support and advice. He was one of the first to do electromyography in Iowa. During my early years of training I had the pleasure of using his battery-operated amplifier and a homemade loudspeaker (which worked only in his presence). I am indebted to Dr. A. L. Sahs, who initiated me into the field of clinical neurology, and Dr. J. R. Knot, who taught me clinical neurophysiology. I am grateful to Drs. T. Yamada and E. Shivapour for attending the busy service of the Division of Clinical Electrophysiology while I devoted myself to writing. Dr. Yamada also gave me most valuable assistance in preparing the section on central somatosensory evoked potentials, which includes many of his original contributions. Drs. R. L. Rodnitzky, E. P. Bosch, J. T. Wilkinson, A. M. Brugger, F. O. Walker, and H. C. Chui read the manuscript and gave most helpful advice. Peter J. Seaba, M.S.E.E., and D. David Walker, M.S.E.E., our electrical engineers, contributed Appendix 2 and reviewed the text.

My special thanks go to the technicians and secretaries of the Division of Clinical Electrophysiology. Sheila R. Mermen, the senior technician of our electromyography laboratory, typed (and retyped time and time again) all the manuscript with devotion and dedication. Deborah A. Gevock, Cheri L. Doggett, Joanne M. Colter, Lauri Longnecker, Jane Austin, Sharon S. Rath, Lori A. Garwood, and Allen L. Frauenholtz have all given me valuable technical or secretarial assistance. Linda C. Godfrey and her staff in the

Medical Graphics Department have been most helpful in preparing illustrations.

I owe my gratitude to Mr. Robert H. Craven, Sr., Mr. Robert H. Craven, Jr., Dr. Sylvia K. Fields, Miss Agnes A. Hunt, Ms. Sally Burke, Miss Lenoire Brown, Mrs. Christine H. Young, and two anonymous reviewers of the F. A. Davis Company for their interest and invaluable guidance. A number of previously published figures and tables have been reproduced with permission from the publishers and authors. I wish to express my sincere appreciation for their courtesy. The sources are acknowledged in the legends. The Glossary of Terms Commonly Used in Electromyography of the American Association of Electromyography and Electrodiagnosis is reprinted in its entirety as Appendix 3, with kind permission from the Association and the members of the Nomenclature Committee.

My sons asked if the book might be dedicated to them for having kept mostly, though not always, quiet during my long hours of writing at home. However, the honor went to their mother instead, a decision enthusiastically approved by the children, in appreciation for her effort to keep peace at home. In concluding the acknowledgment, my heart goes to the members of my family in Nagoya and those of my wife's in Takayama, who have given us kind and warm support throughout our prolonged stay abroad. The credit is certainly theirs for my venture finally coming to fruition.

J. K.

Contents

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PART I

Basics of Electrodiagnosis

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1

Anatomic Basis for Localization

Abbreviations: ALS—amyotrophic lateral sclerosis, EMG—electromyography

1. INTRODUCTION

Electrodiagnosis, as an extension of the neurologic evaluation, employs the same anatomic principles of localization as clinical examination, searching for evidence of motor and sensory compromise (Fig. 1-1). Neurophysiologic studies supplement the history and physical examination, adding precision, detail, and objectivity. These studies delineate a variety of pathologic changes that may otherwise escape detection, particularly in atrophic, deeply situated, or paretic muscles. Specialized techniques provide means to test the neuromuscular junction, which tends to defy clinical assessment. Electrical studies also allow quantitative measures of reflexes and other central phenomena, which help explore complex neural circuits and determine the integrity of the sensory and motor function.

Meaningful analysis of electrophysiologic findings demands an adequate knowledge on precise location of skeletal muscles and peripheral nerves for accurate placement of the electrodes. The first part of this chapter contains a review of peripheral neuroanatomy important for conducting electrodiagnostic studies. A

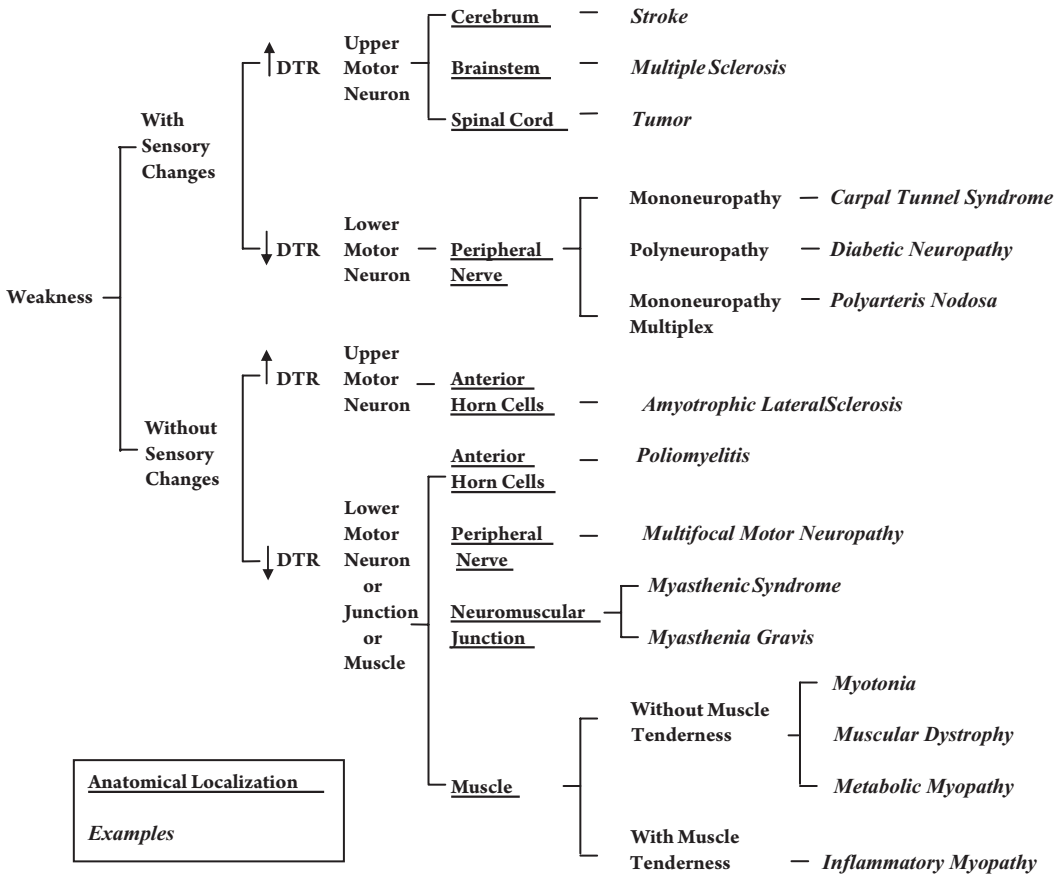

FIGURE 1-1 Simplified diagram illustrating the differential diagnosis of weakness, with a major division into those with and without sensory abnormalities. Patients having sensory symptoms must have involvement of the nervous system rather than muscle or neuromuscular junction. Disease of the upper motor neurons characteristically shows increased stretch reflexes, whereas diseases of the lower motor neurons show decreased stretch reflexes. Patients without sensory disturbance may still have a nervous system disease, especially if associated with hyperreflexia, as in amyotrophic lateral sclerosis. Most, however, have hyporeflexia, as seen in patients with anterior horn cell lesions, diseases of neuromuscular junction, or primary muscle disorders.

concise summary of clinically useful information serves as a framework for the rest of the text. Despite the recognized importance of muscle and nerve anatomy, written descriptions render the subject needlessly dry and intimidating. The schematic illustrations used in this chapter facilitate discussion to compensate for this inherent difficulty at the risk of oversimplification.

The official names for anatomical structures do change over time[14]. An internationally accepted single source, entitled Terminologia Anatomica[6], now proposes "fibular nerve" as the preferred term for an alternative name "peroneal nerve." Similarly, the peroneus longus and brevis will evolve into the fibularis longus and brevis. Temptation to join the bandwagon notwithstanding, I have opted to stick with the traditional names for now until such time "fibular nerve palsy" does not sound so strange to relate to a foot drop. The same holds true for the muscle names extensor digitorum communis and extensor indicis proprius, although I have no objection to the proposed omission of "communis" and "proprius" for the sake of brevity.

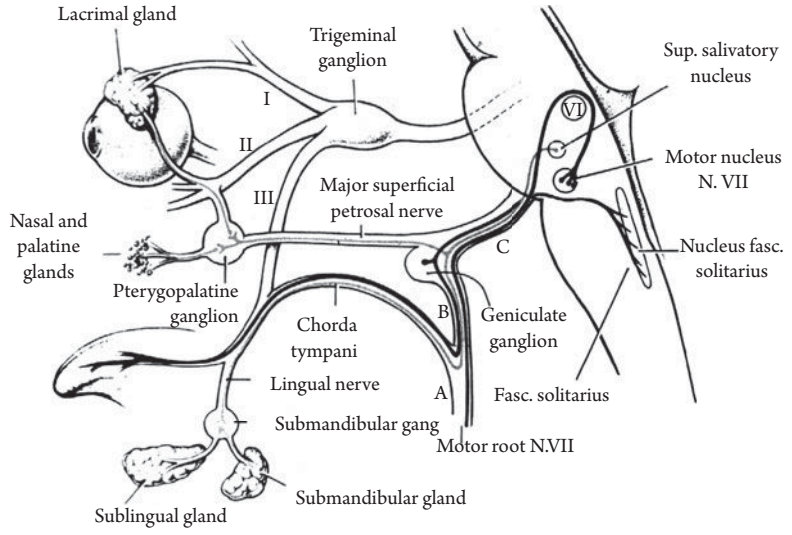

FIGURE 1-2 Functional components of the facial nerve and the three major divisions of the trigeminal nerve. The facial nerve (N VII) consists of the portion at the stylomastoid foramen (A), middle segment distal to the geniculate ganglion (B), and a more proximal segment that includes extrapontine and intrapontine pathways (C). (From Carpenter[2] with permission.)

2. CRANIAL NERVES

Of the 12 cranial nerves, 9 innervate voluntary muscle (see Appendix Table 1-1). The oculomotor, trochlear, and abducens nerves control the movement of the eyes. The trigeminal nerve innervates the muscles of mastication, and the facial nerve, muscles of mimetic expression. The glossopharyngeal and vagal nerves and the cranial root of the accessory nerve supply the laryngeal muscles, and the hypoglossal nerve, the tongue. The spinal root of the accessory nerve innervates the sternocleidomastoid and upper portion of the trapezius. Of these, the nerves most commonly tested in electromyography (EMG) include the trigeminal, facial, and accessory nerves.

Trigeminal Nerve

The trigeminal nerve subserves all superficial sensation to the face and buccal and nasal mucosa. The ophthalmic and maxillary divisions supply sensation to the upper and middle parts of the face, whereas the mandibular division gives off motor fibers to the muscles of mastication; masseters, temporalis, and pterygoids, and sensory fibers to the lower portion of the face (Fig. 1-2). The first-order neurons, concerned primarily with tactile sensation, have their cell bodies in the gasserian ganglion. Their proximal branches enter the lateral portion of the pons and ascend to reach the main sensory nucleus. Those fibers transmitting pain and temperature sensation also have cell bodies in the gasserian ganglion. Upon entering the pons, their fibers descend to reach the spinal nucleus of the trigeminal nerve.

The first-order afferents, subserving proprioception from the muscles of mastication, have their cell bodies in the mesencephalic nucleus. They make monosynaptic connection with the motor nucleus located in the mid pons, medial to the main sensory nucleus. This pathway provides the anatomic substrate for the masseter reflex (see Chapter 9-3). The first component of the blink reflex, or R1, probably follows a disynaptic connection from the main sensory nucleus to the ipsilateral facial nucleus (see Chapter 8-3). The pathway for the second component, or R2, relayed through polysynaptic connections, include the ipsilateral spinal nucleus, multiple interneurons, and the facial nuclei on both sides (see Fig. 8-1 in Chapter 8).

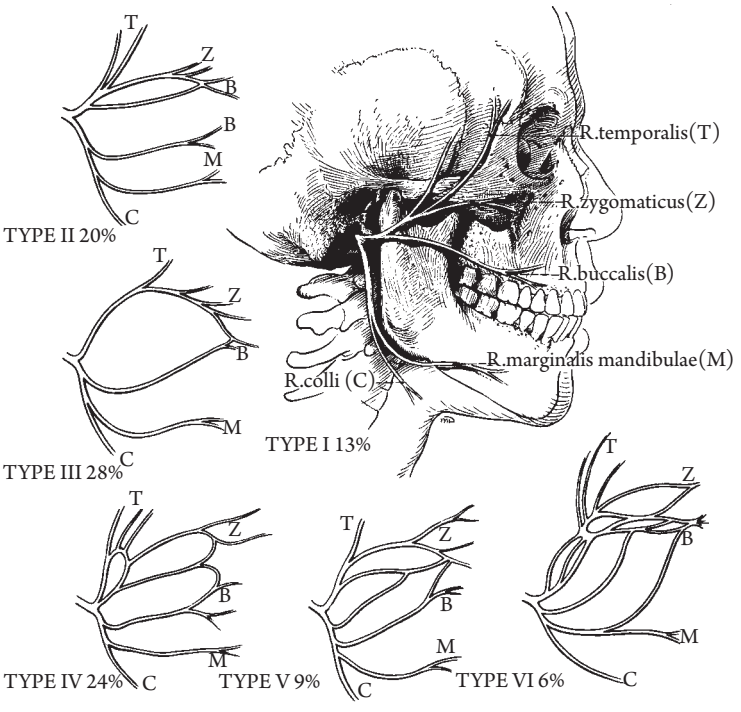

FIGURE 1-3 Major types of facial nerve branching and intercommunication with percentage occurrence of each pattern in 350 recordings. (From Anson[1] with permission.)

Facial Nerve

The facial nerve extends from the nucleus to the distal trunk in four arbitrarily subdivided segments (Fig. 1-2). The central component, or the intrapontine portion, initially courses posteriorly to loop around the sixth nerve nucleus. Its elongated passage makes it vulnerable to various pontine lesions, which cause a peripheral, rather than central, type of facial palsy. The facial nerve complex exits the brainstem ventrolaterally at the caudal pons, a common site of compression by acoustic neuromas or other cerebellopontine angle masses. After traversing the subarachnoid space, the facial nerve enters the internal auditory meatus, beginning the longest and most complex intraosseous course of any nerve in the body. Within this segment lies the site of lesion in Bell's palsy. Upon exiting the skull through the stylomastoid foramen, the facial nerve penetrates the superficial and deep lobes of the parotid gland, where it branches, with some variation, into five distal segments (Fig. 1-3).

Accessory Nerve

The cranial accessory nerve has the cell bodies in the nucleus ambiguus. The fibers join the vagus nerve and together distribute to the striated muscles of the pharynx and larynx. Thus, despite the traditional name, the cranial portion of the accessory nerve functionally constitutes a part of the vagus nerve. The spinal accessory nerve has its cells of origin in the spinal nucleus located in the first five or six cervical segments of the spinal cord (Figs. 1-4 and 1-5). The fibers ascend in the spinal canal to enter the cranial cavity through the foramen magnum and then descend via the jugular foramen to end in the trapezius and the sternocleidomastoid muscles. These two muscles receive additional nerve supply directly from C2 through C4 roots[8]. The spinal accessory nerve provides the sole motor function, whereas the cervical roots subserve purely proprioceptive sensation (Fig. 1-6). The accessory nucleus consists of several separate portions. Thus, a lesion in the spinal cord may not necessarily affect the entire muscle groups innervated by this nerve.

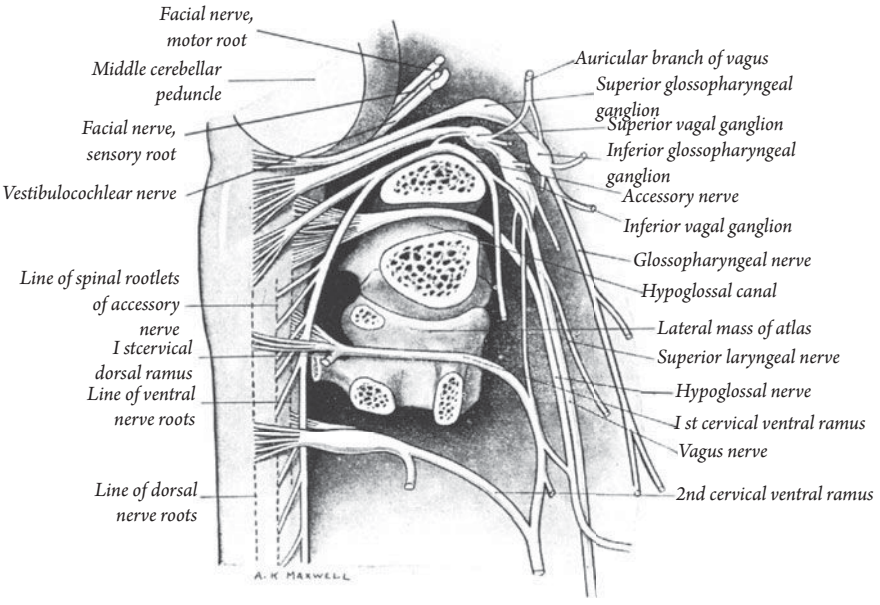

FIGURE 1-4 The last four cranial nerves and the anterior rami of C1 and C2 on the right side viewed from the dorsolateral aspect. Note the division of the accessory nerve into the cranial accessory nerve, which joins the vagal nerve, and the spinal accessory nerve, which supplies the trapezius and sternocleidomastoid muscles. Ventral and dorsal roots join to form a spinal nerve, which then divides into anterior and posterior rami. (From Williams and Warwick[15], with permission.)

This central dissociation could mimic a peripheral lesion affecting individual branches of the nerve.

3. ANTERIOR AND POSTERIOR RAMI

The ventral and dorsal roots, each composed of several rootlets, emerge from the spinal cord carrying motor and sensory fibers (Fig. 1-7). The basic concept places sensory function in dorsal roots, although some afferent nerve fibers also exist in ventral roots[12]. They join to form the spinal nerve that exits from the spinal canal through the respective intervertebral foramina. A small ganglion, the cell bodies of sensory fibers, lies on each dorsal root just proximal to its union with the ventral root but distal to the cessation of the dural sleeve. These spinal nerves, 31 in all on each side, comprise 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal nerve. After passing through the foramina, the spinal nerve branches into two divisions: the anterior and posterior primary rami (Fig 1-7).

The posterior rami supply the posterior part of the skin and the paraspinal muscles, which include the rectus capitis posterior, oblique capitis superior and inferior, semispinalis capitis, splenius capitis, longus capitis, and sacrospinalis. These muscles extend the head, neck, trunk, and pelvis. The anterior rami supply the skin of the anterolateral portion of the trunk and the limbs. They also form the brachial and lumbosacral plexuses, which, in turn, give rise to peripheral nerves in the arms and legs. The anterior rami of the thoracic spinal nerves become 12 pairs of intercostal nerves supplying the intercostal and abdominal muscles. At least two adjoining intercostal nerves innervate each segmental level in both the thoracic and abdominal regions.

The diagnosis of a root lesion depends on identifying abnormalities confined to a single spinal nerve without affecting adjacent higher or lower levels. The posterior rami that supply the paraspinal muscles branch off the spinal nerve just distal to the intervertebral foramen. Hence, denervation found at this level differentiates radiculopathy from more distal lesions of the plexus or

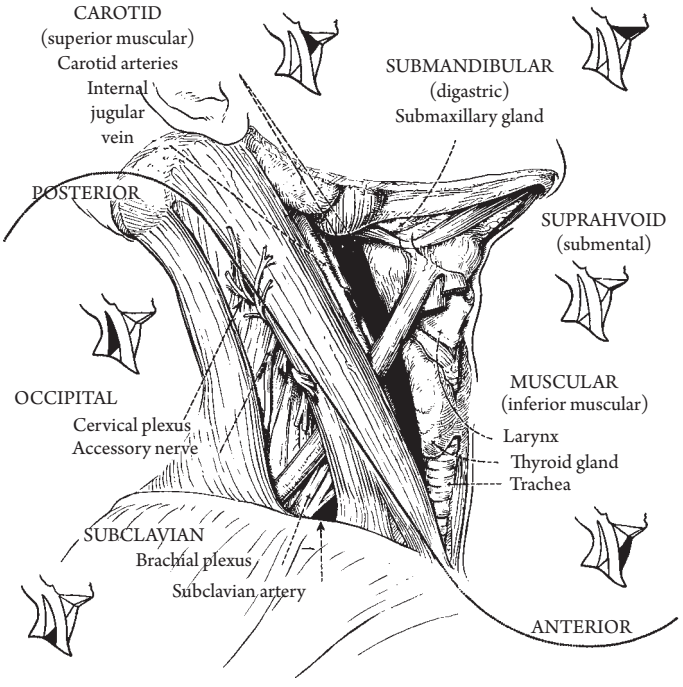

FIGURE 1-5 The sternocleidomastoid divides the field bounded by the trapezius, mandible, midline of neck, and clavicle into anterior and posterior triangles. The obliquely coursing omohyoid further subdivides the posterior triangle into occipital and subclavian triangles. The contents of the occipital and subclavian triangles include the cervical plexus, spinal accessory nerve, and brachial plexus. The spinal accessory nerve becomes relatively superficial in the middle portion of the sternocleidomastoid along its posterior margin, thus making it accessible to surface stimulation. (From Anson[1], with permission.)

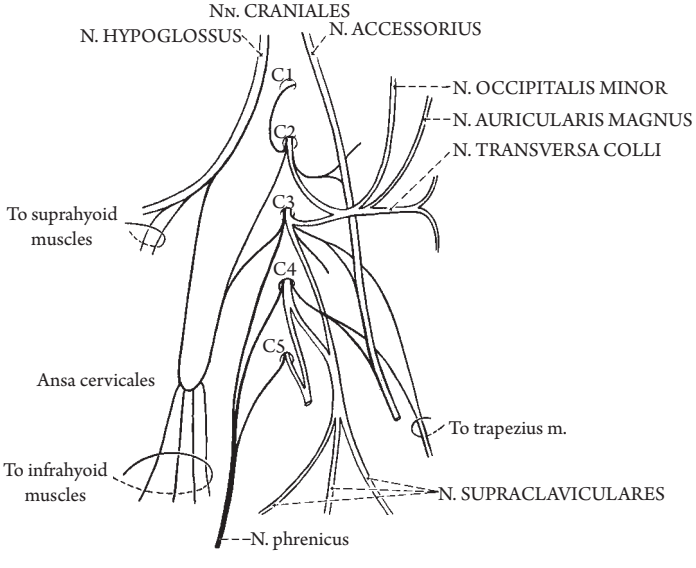

FIGURE 1-6 Anterior rami of the cervical spinal nerves, forming the cervical plexus. Note the phrenic nerve supplying the diaphragm, and the branches from C2, C3, and C4 and the accessory nerve, both innervating the trapezius. (From Anson[1], with permission.)

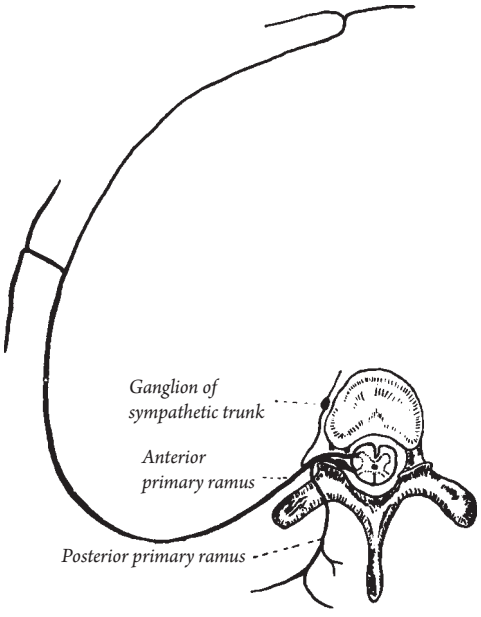

FIGURE 1-7 Ventral and dorsal roots forming the spinal nerve, which divides into the anterior and posterior rami. The sensory ganglion of the dorsal root lies within the respective intervertebral foramen. (From Ranson and Clark[13], with permission.)

peripheral nerve (see Chapter 15-4). The reverse does not necessarily hold, especially in early stages of the disease, when the compressing lesions may only irritate the root without causing structural damage. Similar to the innervation of the intercostal muscles by the anterior rami, the paraspinal muscles receive supplies from multiple posterior rami with substantial overlap. Therefore, the distribution of abnormalities in the limb muscles rather than the paraspinal muscles determines the level of a radicular lesion.

4. CERVICAL AND BRACHIAL PLEXUSES

The anterior rami of the upper four cervical nerves, C1 through C4, form the cervical plexus (Figs. 1-6 and 1-7). It innervates the lateral and anterior flexors of the head, which consist of the rectus capitis lateralis, anterior longus capitis, and anterior longus colli. The brachial plexus, formed by the anterior rami of C5 through T1 spinal nerves, supply the muscles of the upper limb. Occasional variations of innervation include the prefixed brachial plexus with main contributions from C4 through C8, and the postfixed brachial plexus derived primarily from C6 through T2. Appendix Tables 1-1 and 1-2 present a summary of the anatomic relationship between the nerves derived from cervical and brachial plexuses and the muscles of the shoulder, arm, and hand.

Topographic divisions of the brachial plexus include the spinal nerve, trunk, cord, and peripheral nerve (Fig. 1-8). Two nerves originate directly from the spinal nerve before the formation of the trunks: dorsal scapular nerve from C5, innervating levator scapulae and rhomboid, and long thoracic nerve from C5, C6, and C7, supplying serratus anterior. The spinal nerves then combine to give rise to three trunks. The union of C5 and C6 forms the upper trunk, and that of C8 and T1, the lower trunk, whereas C7 alone continues as the middle trunk. Each of the three trunks bifurcates into the anterior and posterior divisions. The posterior cord, the union of all three posterior divisions, gives off the subscapular nerve innervating teres major, thoracodorsal nerve supplying latissimus dorsi, and axillary nerve subserving deltoid and teres minor, and continues as the radial nerve. The anterior divisions of the upper and middle trunks become the lateral cord, which gives rise to the musculocutaneous nerve with its sensory branch, lateral antebrachial cutaneous nerve, and the outer branch of the median nerve. The anterior division of the lower trunk becomes the medial cord, which, in turn, gives off the ulnar nerve, medial antebrachial cutaneous nerve, and the inner branch of the median nerve.

The trunks pass through the supraclavicular fossa under the cervical and scalenus muscles, forming the cords just above the clavicle at the level of the first rib. Accompanied by the subclavian artery, the cords traverse the space known as the thoracic outlet between the first rib and the clavicle. Consequently, injuries above the clavicle affect the trunks, whereas a more distal lesion involves either the cord or the peripheral nerves that emerge from the cords between the clavicle and axilla.

Phrenic Nerve

The phrenic nerve, one of the most important branches of the cervical plexus, arises from C3

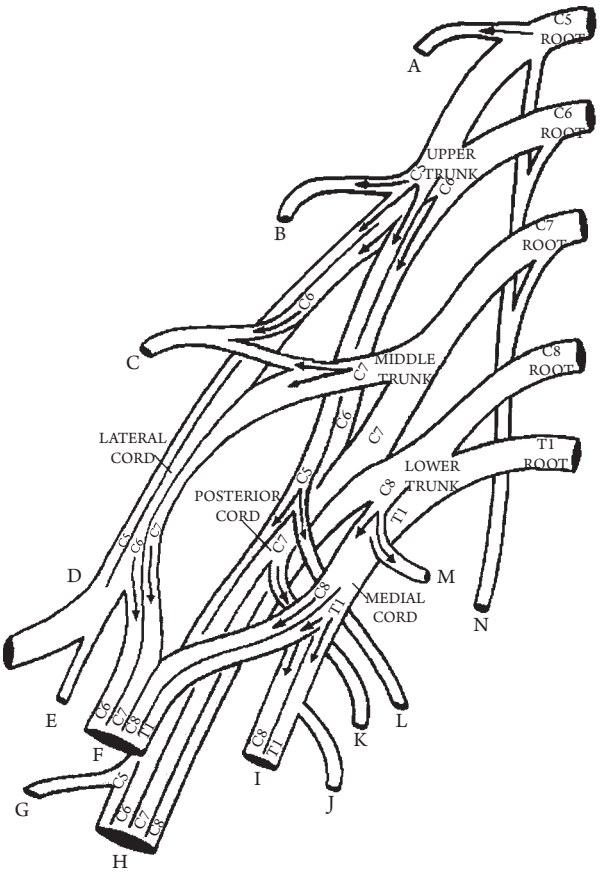

FIGURE 1-8 Anatomy of the brachial plexus with eventual destination of all root components. The brachial plexus gives rise to dorsal scapular (A), suprascapular (B), lateral pectoral (C), musculocutaneous (D), and its sensory branch, lateral antebrachial cutaneous (E), median (F), axillary (G), radial (H), ulnar (I), medial antebrachial cutaneous (J), thoracodorsal (K), subscapular (L), medial pectoral (M), and long thoracic nerves (N). In addition, the radial nerve gives off the posterior antebrachial cutaneous nerve (not shown) at the level of the spiral groove. (Modified from Patten[10].)

and C4 and innervates the ipsilateral hemidiaphragm (see Appendix Table 1-1).

Dorsal Scapular Nerve

The dorsal scapular nerve, derived from C4 and C5 through the most proximal portion of the upper trunk of the brachial plexus, supplies the rhomboid major and minor and a portion of the levator scapulae, which keeps the scapula attached to the posterior chest wall during arm motion. The rhomboid receives innervation only from C5 in contrast to the other shoulder girdle muscles supplied by multiple roots.

Suprascapular Nerve

The suprascapular nerve arises from C5 and C6 through the upper trunk of the brachial plexus. It reaches the upper border of the scapula behind the brachial plexus to enter the suprascapular notch, a possible site of entrapment. The nerve supplies the supraspinatus and infraspinatus (Fig. 1-8).

Upper and Lower Subscapular Nerves

These two nerves arise from C5 and C6 through the upper trunk and the posterior cord. The

upper subscapular nerve enters the upper part of the subscapularis, which it innervates. The lower subscapular nerve supplies the lower part of the subscapularis and the teres major.

Thoracodorsal Nerve

The thoracodorsal nerve, also known as the middle or long subscapular nerve, derives its fibers from C6, C7, and C8 through all three trunks and posterior cord; follows the course of the subscapular artery along the posterior wall of the axilla; and innervates the latissimus dorsi.

Musculocutaneous Nerve

The musculocutaneous nerve originates from the lateral cord of the brachial plexus near the lower border of the pectoralis minor (Fig. 1-9). Its axons, chiefly derived from C5 and C6, reach the biceps, brachialis, and coracobrachialis, with some variations of innervation for the last two muscles. Its terminal sensory branch, called the lateral antebrachial cutaneous nerve, with fibers mainly from the C6 root, supplies the skin over the lateral aspect of the forearm.

Axillary Nerve

The axillary nerve, originating from C5 and C6, arises from the posterior cord as the last branch of the brachial plexus. The nerve traverses a quadrangular space bounded rostrally by the subscapularis anteriorly and teres minor posteriorly, caudally by the teres major, medially by the long head of triceps, and laterally by the humeral

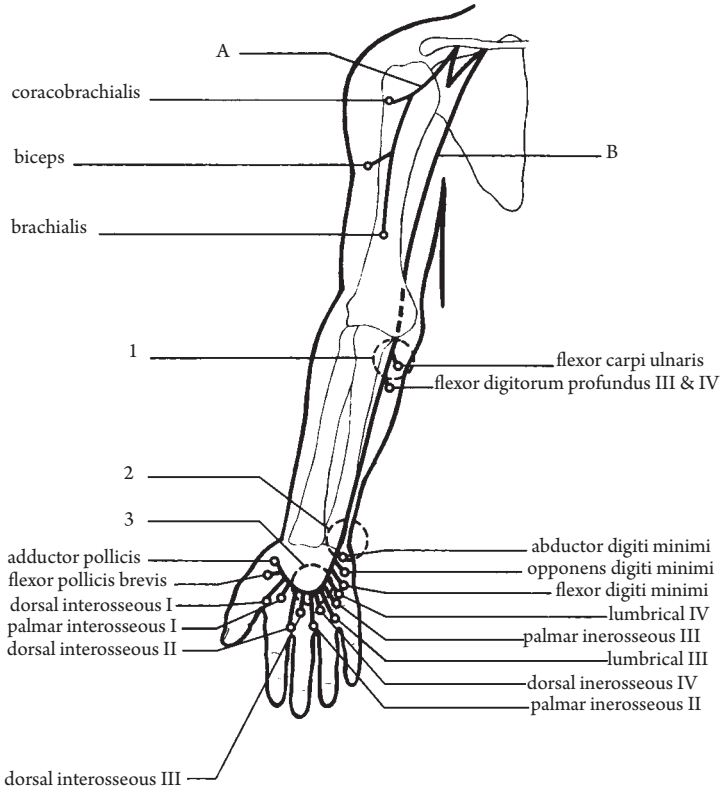

FIGURE 1-9 Musculocutaneous nerve (A) and ulnar nerve (B) and the muscles they supply. The common sites of lesion include ulnar groove and cubital tunnel (1), Guyon's canal (2), and mid palm (3). Except for three forearm muscles, the ulnar nerve supplies only the intrinsic hand muscles. (Modified from: The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System[7].)

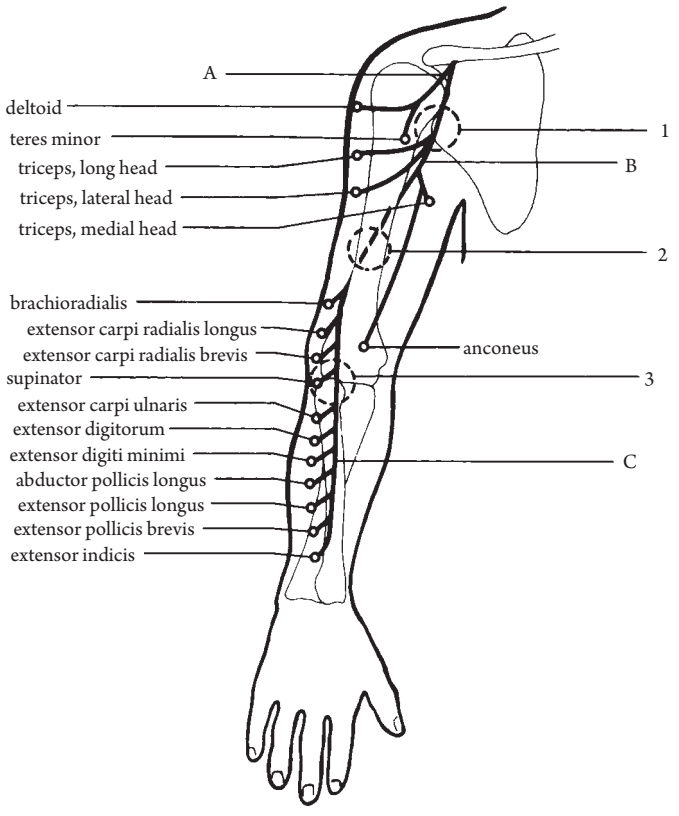

FIGURE 1-10 Axillary nerve (A) and radial nerve (B) with its main terminal branch, posterior interosseus nerve (C) and the muscles they supply. The nerve injury may occur at the axilla (1), spiral groove (2), or the elbow (3) as in the posterior interosseus nerve syndrome. The radial nerve innervates only extensor muscles in the forearm except for brachioradialis, which flexes the elbow. (Modified from: The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System[7].)

surgical neck. Here the nerve divides into two divisions. The anterior division supplies the anterior and middle deltoid, whereas the posterior division subserves the posterior deltoid and teres minor and, as the upper lateral cutaneous nerve, a small area of the skin over the lateral aspect of the shoulder (Fig. 1-10).

5. PRINCIPAL NERVES OF THE UPPER LIMB

Radial Nerve

The radial nerve, as a continuation of the posterior cord, derives its axons from C5 through C8, or all the spinal roots contributing to the brachial plexus (Fig. 1-8). The nerve gives off its supply to the three heads of the triceps and the anconeus, which originates from the lateral epicondyle of the humerus as an extension of the medial head. The radial nerve then enters the spiral groove winding around the humerus posteriorly from the medial to the lateral side (Fig. 1-10). Here, it gives off a sensory branch, posterior antebrachial cutaneous nerve, which innervates the skin of the lateral arm and the dorsal forearm. As the nerve emerges from the spiral groove, it supplies the brachioradialis, the only flexor innervated by the radial nerve and, slightly more distally, the extensor carpi radialis longus. Located lateral to the biceps at the level of the lateral epicondyle, it enters the forearm between the brachialis and brachioradialis.

At this point, it divides into a muscle branch, the posterior interosseus nerve, and a sensory branch, which surfaces in the distal third of the forearm. The muscle branch innervates the

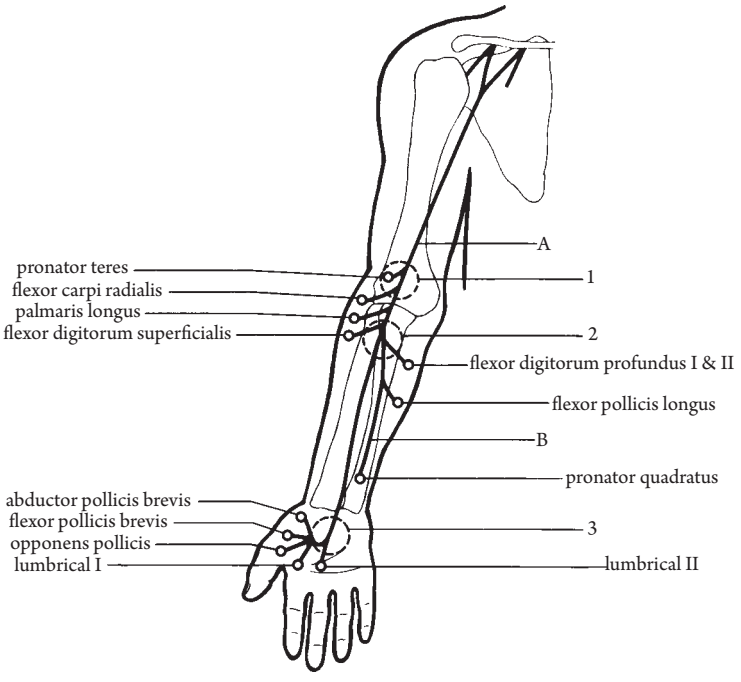

FIGURE 1-11 Median nerve (A) with its branch, anterior interosseus nerve (B), and the muscles they supply. The nerve may undergo compression at the elbow between the two heads of pronator teres (1), or slightly distally (2) as in the anterior interosseus nerve syndrome, or at the palm (3) as in the carpal tunnel syndrome. (Modified from: The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System[7].)

supinator, abductor pollicis longus and all the extensor muscles in the forearm: extensor carpi ulnaris, extensor digitorum communis, extensor digiti minimi, extensor pollicis longus and brevis, and extensor indicis. The sensory fibers, originating from C6 and C7, pass through the upper and middle trunks and the posterior cord. It branches off the main truck about 10 cm above the wrist as the superficial radial nerve, which supplies the dorsum of the hand over the lateral aspect.

Median Nerve

The median nerve arises from the lateral and medial cords of the brachial plexus as a mixed nerve derived from C6 through T1 (Fig. 1-8). It supplies most forearm flexors and the muscles of the thenar eminence. It also subserves sensation to the skin over the lateral aspect of the palm and the dorsal surfaces of the terminal phalanges, along with the volar surfaces of the thumb, index, long finger, and lateral half of the ring finger. The sensory fibers of the index and middle fingers enter C7 through the lateral cord and middle trunk, whereas the skin of the thumb receives fibers mainly from C6 with some contribution from C7 through the lateral cord and upper or middle trunk. The median nerve innervates no muscles in the upper arm (Fig. 1-11). It enters the forearm between the two heads of the pronator teres, which it supplies along with the flexor carpi radialis, palmaris longus, and flexor digitorum superficialis. A pure muscle branch, called the anterior interosseus nerve, innervates the flexor pollicis longus, pronator quadratus, and flexor digitorum profundus I and II. The main median nerve descends the forearm and, after giving off the palmar sensory branch, which innervates the skin over the thenar eminence, passes through the carpal tunnel between the wrist and palm. It supplies lumbricals I and II after giving rise to the recurrent thenar nerve at the distal edge of the carpal ligaments. This muscle branch to the thenar eminence innervates the abductor pollicis brevis, the lateral half of the flexor pollicis brevis, and the opponens pollicis.

Ulnar Nerve

The ulnar nerve, as a continuation of the medial cord of the brachial plexus, derives its fibers from C8 and T1 (Fig. 1-8). It lies in close proximity to the median nerve and brachial artery at the axilla. In this position, the ulnar nerve passes between the biceps and triceps, and then deviates posteriorly at the midportion of the upper arm and becomes superficial behind the medial epicondyle (Fig. 1-9). After entering the forearm, it supplies the flexor carpi ulnaris and flexor digitorum profundus III and IV. It gives rise to the dorsal cutaneous branch of the ulnar nerve, which innervates the skin over the medial aspect of the dorsum of the hand. It then passes along the medial aspect of the wrist to enter the hand, where it gives off two branches. The superficial branch supplies the palmaris brevis and the skin over the medial aspect of the hand, including the hypothenar eminence, the little finger and medial half of the ring finger. The deep muscle branch first innervates the hypothenar muscles, which comprise abductor, opponens, and flexor digiti minimi. It then deviates laterally around the hamate to reach the lateral aspect of the hand, where it reaches the adductor pollicis and medial half of the flexor pollicis brevis. Along its course from hypothenar to thenar eminence, the deep branch also innervates the lumbricals III and IV and all seven interossei: three volar and four dorsal.

General Rules and Anomalies

It takes concerted effort and practice to master the innervation of all the individual upper-limb muscles. Learning certain rules helps broadly categorize them to understand the general pattern of nerve supply (see Appendix Table 1-2). The radial nerve innervates the brachioradialis, triceps, extensor carpi radialis, and, with its main terminal branch, the posterior interosseus nerve, all the extensors in the forearm but none of the intrinsic hand muscles. The radial nerve innervates only the extensors with the exception of brachioradialis, an elbow flexor in neutral or half-pronated position. The nerve subserves all the extensors of the upper limb except for the four lumbricalis, which, innervated by median and ulnar nerves, extend the digits at the interphalangeal joints. The median nerve supplies most flexors in the forearm and pronator teres, which functions with the elbow extended, in addition to the intrinsic hand muscles of the thenar eminence and lumbricals I and II. The anterior interosseus nerve branches off the median nerve trunk in the forearm to innervate the flexor digitorum profundus I and II, flexor pollicis longus, and pronator quadratus, which functions with the elbow flexed. The ulnar nerve, with the exception of the flexor carpi ulnaris and the flexor digitorum profundus III and IV, supplies only the intrinsic hand muscles, including all four dorsal and three volar interossei.

The most common anomaly, called the Martin-Gruber anastomosis, extends a communicating branch from the median to the ulnar nerve in the forearm. The fibers involved in this crossover usually supply the ordinarily ulnar-innervated intrinsic hand muscles. Thus, the anomalous fibers form a portion of the ulnar nerve that, instead of branching off from the medial cord of the brachial plexus, takes an aberrant route distally along with the inner branch of the median nerve before reuniting with the ulnar nerve proper in the distal forearm. Other infrequently seen anomalies include a communication from the ulnar to the median nerve in the forearm and all median or all ulnar hands, in which one or the other nerve supplies all the intrinsic hand muscles. Failure to recognize an anomaly leads to misinterpretation of electrophysiologic data as a common source of error (see Chapter 11-4).

6. LUMBAR PLEXUS AND ITS PRINCIPAL NERVES

The spinal cord ends at the level of the L1 to L2 intervertebral space as the preconus, or L5 and S1, and the conus medullaris, or S2 through S5 cord segments. The fibers of the cauda equina, formed by the lumbar and sacral roots, assume a downward direction from the conus toward their respective exit foramina. The fibrous filum terminale interna extends from the lowermost end of the spinal cord to the bottom of the dural sac at the level of the S2 vertebra. Appendix Table 1-3 summarizes the nerves derived from the lumbar plexus and the muscles they innervate.

The anterior rami of the first three lumbar spinal nerves, originating from the L1, L2, and L3 and part of L4, unite to form the lumbar plexus within the psoas major muscle (Figs. 1-12 through 1-14). The iliohypogastric and ilioinguinal nerves arise from L1 and supply the skin of the hypogastric region and medial thigh. The genitofemoral nerve, derived from L1 and L2, innervates the cremasteric muscle and the skin of the scrotum or labia major. The lateral femoral cutaneous nerve, originating from L2 and L3, leaves the psoas muscle laterally to supply the lateral and anterior thigh. The anterior rami of L2 through L4 form two divisions. The anterior divisions join to form the obturator nerve, which exits the psoas muscle medially to innervate the adductor muscles of the thigh. The posterior divisions give rise to the femoral nerve, which leaves the psoas muscle laterally. It then descends under the iliacus fascia to reach the femoral triangle beneath the inguinal ligament. In addition to these muscle branches, it also gives off sensory branches, intermediate and medial cutaneous nerves, and saphenous nerve.

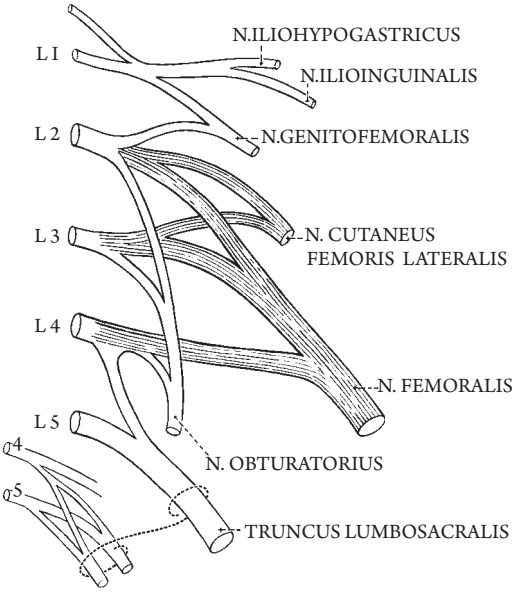

FIGURE 1-12 Anterior rami of the lumbar spinal nerve forming the lumbar plexus, with the major nerves derived from this plexus. The shaded portion indicates the dorsal divisions. (From Anson[1], with permission.)

Iliohypogastric Nerve

The iliohypogastric nerve originates from L1 and supplies the skin of the upper buttock and hypogastric region.

Ilioinguinal Nerve

The ilioinguinal nerve, arising from L1, supplies the skin over the upper and medial part of the thigh, root of the penis, and upper part of the scrotum or labia major. It also innervates the transversalis and internal oblique muscles. The nerve follows the basic pattern of an intercostal nerve, winding around the inner side of the trunk to the medial anterior iliac spine.

Genitofemoral Nerve

The genitofemoral nerve, arising from L1 and L2, branches into lumboinguinal and external spermatic nerves. The lumboinguinal nerve supplies the skin over the femoral triangle. The external spermatic nerve innervates the cremasteric muscle and skin of the inner aspect of the upper thigh and scrotum or labium.

Lateral Femoral Cutaneous Nerve

The lateral femoral cutaneous nerve, the first sensory branch of the lumbar plexus, receives fibers from L2 and L3. It emerges from the lateral border of the psoas major muscle and runs forward, coursing along the brim of the pelvis to the lateral end of the inguinal ligament. The nerve reaches the upper thigh after passing through a tunnel formed by the lateral attachment of the inguinal ligament and the anterior superior iliac spine. About 12 cm below its exit from the tunnel, the nerve gives off an anterior branch, which supplies the skin over the lateral and anterior surface of the thigh, and a posterior branch, which innervates the lateral and posterior portion of the thigh.

Femoral Nerve

The femoral nerve, formed near the vertebral canal, arises from the posterior division of L2

to L4 anterior rami (Figs. 1-12 and 1-15). The nerve reaches the front of the leg passing along the lateral edge of the psoas muscle, which it supplies together with the iliacus. It then exits the pelvis under the inguinal ligament just lateral to the femoral artery and vein. Its sensory branches supply the skin of the anterior thigh and medial aspect of the calf. The muscle branch innervates the pectineus and the sartorius as well as the quadriceps femoris, which consists of the rectus femoris, vastus lateralis, vastus intermedius, and vastus medialis. The iliacus and psoas, or iliopsoas, flex the thigh at the hip, the quadriceps femoris extends the leg at the knee, the sartorius flexes the leg and the thigh, and the pectineus flexes the thigh.

Saphenous Nerve

The saphenous nerve, the largest and longest sensory branch of the femoral nerve, receives the maximum innervation from L3 and L4[1] and supplies the skin over the medial aspect of the thigh, leg and foot. It accompanies the femoral artery in the femoral triangle then descends medially under the sartorius muscle. At the lower thigh, the nerve gives off the infrapatellar branch that supplies the medial aspect of the knee. The main terminal branch descends along the medial aspect of the leg accompanied by the long saphenous vein. It passes just anterior to the medial malleolus supplying the medial side of the foot.

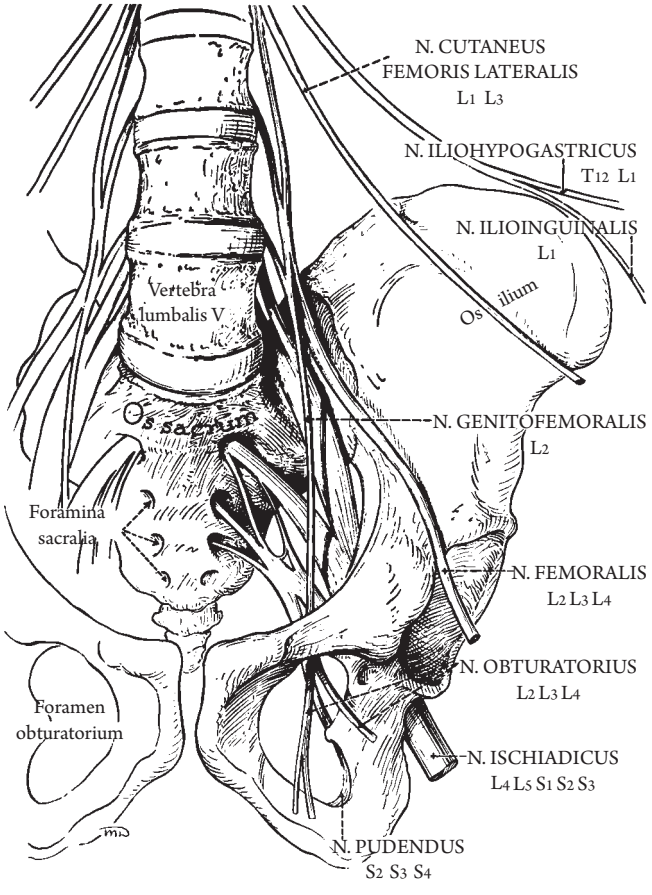

FIGURE 1-13 Lumbosacral plexus and the courses of the femoral, obturator, and sciatic nerves. (From Anson[1], with permission.)

Obturator Nerve

The obturator nerve arises from the anterior divisions of L2 to L4 anterior rami (Fig. 1-15). Formed within the psoas muscle, it enters the pelvis immediately anterior to the sacroiliac joint, passes through the obturator canal, and gives off two branches. The anterior branch supplies the adductor longus and brevis and the gracilis. The posterior branch innervates the obturator externus and half of the adductor magnus muscle. The sensory fibers supply the skin of the upper thigh over the medial aspect and send anastomoses to the saphenous nerve.

7. SACRAL PLEXUS AND ITS PRINCIPAL NERVES

The sacral plexus arises from L5, S1, and S2 in front of the sacroiliac joint (Figs. 1-13 and 1-14). Designation as the lumbosacral plexus implies an interconnection between the sacral and lumbar plexus. Common anomalous derivations include a prefixed pattern with a major contribution of L4 to the sacral plexus or postfixed form with L5 supplying mainly the lumbar plexus. The sacral plexus gives rise to the superior gluteal nerve, derived from L4, L5, and S1, and the inferior gluteal nerve, which arises from L5, S1, and S2. The sciatic nerve, the largest nerve in the body, arises from L4 through S2. After giving off branches to the hamstring muscles, it divides into the tibial and common peroneal nerves. Appendix Table 1-3 summarizes the nerves derived from the sacral plexus and the muscles that they innervate.

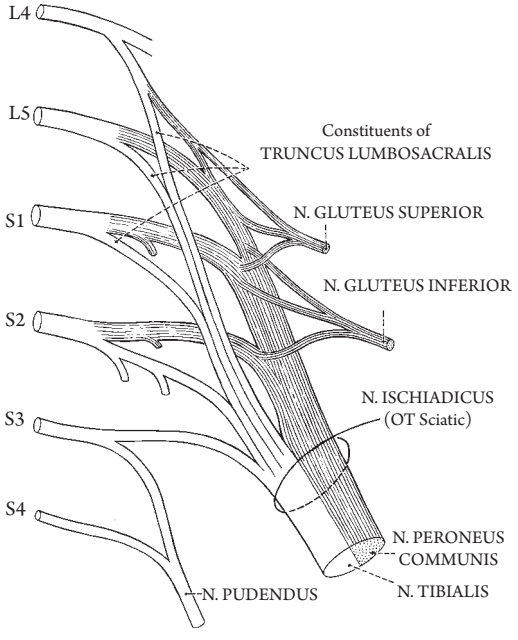

FIGURE 1-14 Anterior rami of the lumbosacral spinal nerve forming the sacral plexus with the major nerves derived from this plexus. The shaded portion indicates the dorsal divisions. (From Anson[1], with permission.)

Superior and Inferior Gluteal Nerves

The superior gluteal nerve innervates the gluteus medius and minimus and the tensor fascia lata, which together abduct and rotate the thigh internally. The inferior gluteal nerve supplies the gluteus maximus, which extends, abducts, and externally rotates the thigh.

Sciatic Nerve

The union of L4 to S2 gives rise to the sciatic nerve, which leaves the pelvis through the greater sciatic foramen (Figs. 1-14 and 1-16). This longest and largest nerve consists of the peroneal and tibial portion derived, respectively, from posterior and anterior division of the anterior rami. These two components eventually bifurcate in the lower third of the thigh to form the common peroneal and tibial nerves or, in the older terminology, anterior and posterior tibial nerves. In the posterior aspect of the thigh, the tibial component of the sciatic trunk gives off a series of short branches to innervate the bulk of the hamstring muscles, the long head of biceps femoris, semitendinosus, and semimembranosus. The peroneal component supplies the short head of biceps femoris above the knee, the muscle important to evaluate in assessing a foot drop. The adductor magnus, primarily supplied by the obturator nerve, also receives partial innervation from the sciatic trunk.

Common Peroneal Nerve

The common peroneal nerve, or fibular nerve, according to the new nomenclature [6,14], arises as

an extension of the lateral popliteal nerve, which branches off laterally from the sciatic trunk in the popliteal fossa (Fig. 1-15). It consists of fibers derived from L4, L5, and S1. Immediately after its origin, the nerve becomes superficial as it winds around the head of the fibula laterally. After entering the leg at this position, it gives off a small recurrent nerve that supplies sensation to the patella and then bifurcates into the superficial and deep peroneal nerves.

The superficial peroneal nerve, also known as the musculocutaneous nerve, supplies the peroneus longus and brevis, which plantar flex and evert the foot. After descending between the peroneal muscles, it divides into medial and intermediate dorsal cutaneous nerves. These sensory branches pass anterior to the extensor retinaculum and supply the anterolateral aspect of the lower half of the leg and the dorsum of the foot and toes.

The deep peroneal nerve innervates the muscles that dorsiflex and evert the foot. These muscles include tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus tertius, and extensor digitorum brevis, the only peroneal nerve innerated muscle below the ankle. An anomalous communicating branch called the accessory deep peroneal nerve may arise from the superficial peroneal nerve at the knee to innervate the lateral portion of the extensor digitorum brevis

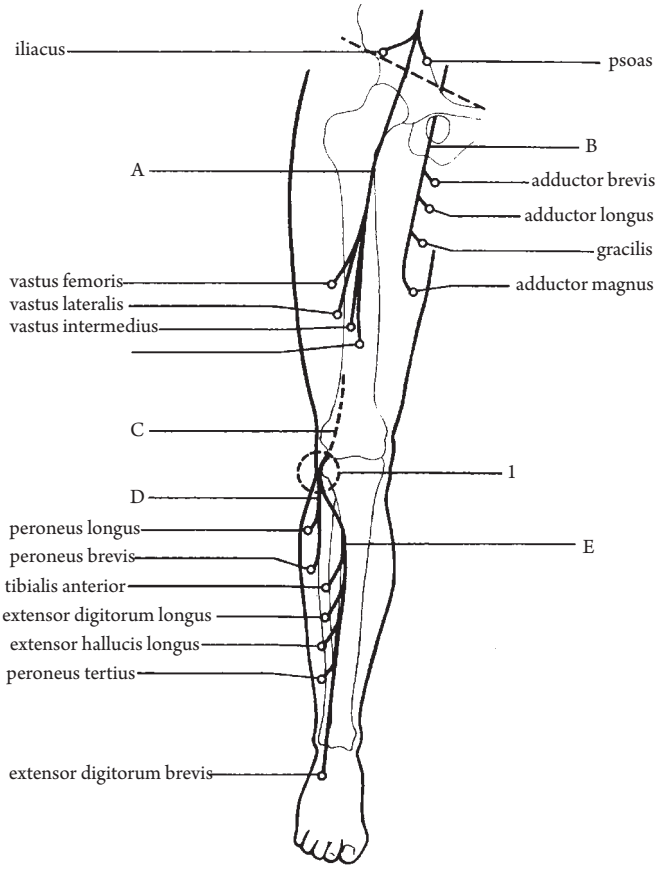

FIGURE 1-15 Femoral nerve (A), obturator nerve (B), and common peroneal nerve (C) branching into superficial (D) and deep peroneal nerve (E) and the muscles they supply. The compression of the peroneal nerve commonly occurs at the fibular head (1). The superficial peroneal nerve innervates only two muscles, which evert and plantar flex the foot. Except for extensor digitorum brevis in the foot, the deep peroneal nerve supplies only leg muscles, which dorsiflex the foot and toes. (Modified from: The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System[7].)

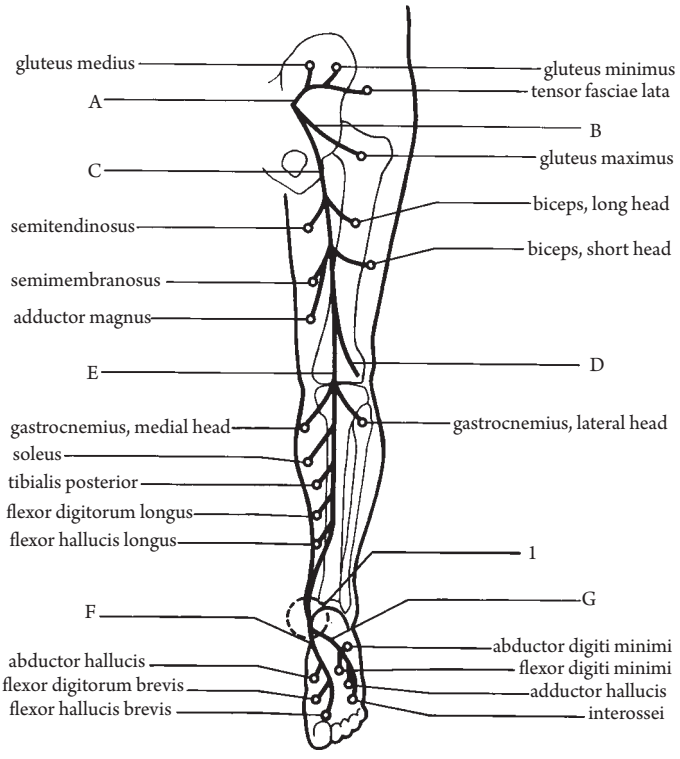

FIGURE 1-16 Superior gluteal nerve (A), inferior gluteal nerve (B), sciatic nerve trunk (C), and the muscles they supply. The sciatic nerve bifurcates to form the common peroneal nerve (D) and the tibial nerve (E). The tibial nerve in turn gives rise to the medial (F) and lateral plantar nerve (G). The tibial nerve supplies all the intrinsic foot muscles derived from S1 and S2 except for extensor digitorum brevis derived from L5 through the peroneal nerve. The compression of the tibial nerve may occur at the medial malleolus in the tarsal tunnel (1). (Modified from: The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System[7].)

(see Chapter 11-4). The deep peroneal nerve also supplies the skin over a small, wedge-shaped area between the first and second toes.

Tibial Nerve

The tibial nerve arises as an extension of the medial popliteal nerve that separates from the sciatic nerve in the popliteal fossa (Fig. 1-16). After giving off branches to the medial and lateral heads of the gastrocnemius and soleus, it supplies the tibialis posterior, flexor digitorum longus, and flexor hallucis longus in the leg. The nerve enters the foot passing through the space between the medial malleolus and the flexor retinaculum. Here it splits into medial and lateral plantar nerves after giving off a small calcaneal nerve (Fig. 1-17), a sensory branch that supplies medial sole[9]. This bifurcation occurs within 1 cm of the malleolar-calcaneal axis in 90% of the feet[4].

The medial plantar nerve accompanies the medial plantar artery, which serves as the landmark to locate the nerve just below the medial malleolus. Its muscle branches innervate the abductor hallucis, flexor digitorum brevis, and flexor hallucis brevis. Its sensory fibers supply the anterior two-thirds of the medial aspect of the sole and the plantar skin of the first three toes and part of the fourth toe. The lateral plantar nerve gives rise to its first branch, inferior calcaneal nerve, or Baxter's nerve, which heads inferiorly and then anteriorly in front of the calcaneus, sending sensory fibers to its periosteum before innervating the abductor digiti minimi[3]. The main trunk of the nerve also winds around the heel to the lateral side of the sole to innervate the flexor digiti

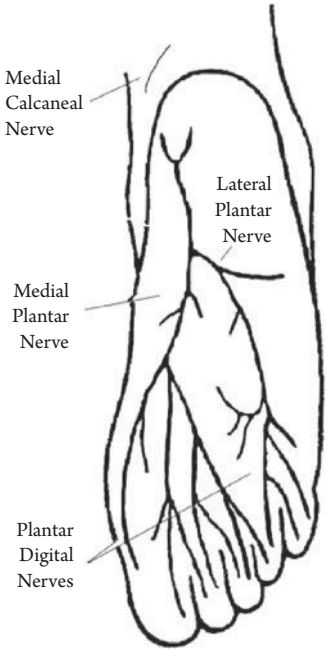

FIGURE 1-17 The tibial nerve, after entering the foot behind the medial malleolus, gives off a small calcaneal nerve, a sensory branch, which supplies the medial sole, before splitting into medial and lateral plantar nerves.

minimi. It supplies the skin over the lateral aspect of the sole, the little toe, and the lateral half of the fourth toe.

Sural Nerve

The sural nerve originates from the union of the medial sural cutaneous branch of the tibial nerve and the sural communicating branch of the common peroneal nerve. It arises below the popliteal space, descends between the two bellies of the gastrocnemius, winds behind the lateral malleolus, and reaches the dorsum of the little toe. It receives maximum innervation from S1, with the remainder coming from L5 or S2[11], and supplies the skin over the posterolateral aspect of the distal leg and lateral aspect of the foot. As one of the few readily accessible sensory nerves in the lower limbs, the sural nerve offers an ideal site for biopsy, especially because its removal induces only minimal sensory deficits. A fascicular biopsy of the sural nerve allows in vitro recording of nerve action potentials (see Chapter 4-4). This procedure provides an interesting opportunity to correlate the data not only with the histologic findings of the biopsy specimen but also with the in vivo conduction characteristics[5].

Pudendal Nerve

The pudendal nerve, derived from S2 to S4 as the direct continuation of the lower band of the sacral plexus, leaves the pelvis via the greater sciatic foramen below the piriformis to enter the gluteal region. It then crosses the spine of the ischium and re-enters the pelvis through the lesser sciatic foramen before passing into the pudendal canal on the lateral wall of the ischiorectal fossa. After giving off the inferior rectal nerve, it divides into two terminal branches: the perineal nerve and dorsal nerve of the penis or clitoris.

The inferior rectal nerve, which may arise directly from the sacral plexus, pierces the medial wall of the pudendal canal and supplies the external anal sphincter and the skin around the anus. The perineal nerve runs forward with the perineal artery, dividing into posterior scrotal or labial nerve and muscular branches that supply the anterior portion of the levator ani, sphincter ani externus, and sphincter urethrae. The muscles of the pelvic floor, the levator ani in particular, also receive direct innervation from branches of S3 and S4. The dorsal nerve of the penis supplies the corpus cavernosum penis and provides sensation to the dorsum of the penis or clitoris.

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2

Electrical Properties of Nerve and Muscle

Abbreviations: CMAP—compound muscle action potential, E1—active electrode, E2—reference electrode, Ek—equilibrium potential, EMG—electromyography, F—number of coulombs per mole of charge, MUP—motor unit potential, Pna, Pk, and Pcl—permeability of sodium, potassium, and chloride ions, R—gas constant, SEP—somtosensory evoked potential, SNAP—sensory nerve action potential, T—absolute temperature, Wc—chemical work, We—electrical work, Zk—variance of ion

1. INTRODUCTION

The nervous system conveys information by means of action potentials, which, under physiologic conditions, originate in the cell body or axon terminal and propagate along the nerve fibers. An electrophysiologic study takes advantage of such neural impulses activated artificially by electrical stimuli applied at certain points of the nerve. Motor conduction studies depend on recording a muscle action potential elicited by stimulation of the mixed nerve, whereas sensory studies use either mixed or sensory nerve action potentials (SNAPs). Electromyography (EMG) permits analysis of electrical properties in the skeletal muscle at rest and during voluntary contraction. Thus, understanding the electrical properties of nerve and muscle constitutes a prerequisite for a proper interpretation of electrodiagnostic data in the clinical domain.

Despite different anatomic substrates subserving electrical impulses, the same basic membrane physiology applies to both nerve and muscle. Excitability of the tissues reflects the magnitude of the transmembrane potential in a steady state. When stimulated electrically or by other means, the cell membrane undergoes an intensity-dependent depolarization. If the change reaches a critical level, called threshold, it generates an action potential, which then propagates across the membrane. Ion channel defects play an important role in the pathogenesis of many neuromuscular disorders such as myotonia and periodic paralysis.[17] In contrast to intracellular recording in animal experiments, clinical electrodiagnostic procedures analyze extracellular

Table 2-1 Ionic Concentration of Cells in Mammalian Muscle

	EXTRACELLULAR (mmol/1)	INTRACELLULAR (mmol/l)	EQUILIBRIUM POTENTIAL (mV)
Cations			
Na^+	145	12	+66
K^+	4	155	97
Others	5	—	
Anions			
Cl^-	120	4	–90
HCO^-_3	27	8	–32
Others	7	155	
Potential	0 mV	–90 mV	

(Modified from Patton[20])

potentials by surface or needle electrodes. Here the interstitial tissues act as a volume conductor, where the position of the recording electrode relative to the generator source dictates the size and waveform of the recorded potentials.

2. TRANSMEMBRANE POTENTIAL

Understanding membrane physiology at the cellular level forms the basis for electrophysiologic examination in the clinical domain. This section deals with the ionic concentration of cell plasma and its role in maintaining transmembrane potentials. The next sections summarize the basic physiology of the propagating action potential recorded through volume conductors. The following comments cover only the fundamental principles relevant to clinical electrophysiology. Subsequent section (see Chapter 4-3) further elaborates on these points.

Ionic Concentration of Cells

The muscle membrane constitutes the boundary between intracellular fluid in cell cytoplasm and extracellular interstitial fluids. Both contain approximately equal numbers of ions dissolved in water but differ in two major aspects. First, an electrical potential exists across the cell membrane, with a relative negativity inside the cell as compared to outside. This steady transmembrane potential measures approximately –90 mV in human skeletal muscle cells, but it varies from one tissue to another, ranging from –20 mV to –100 mV. Second, intracellular fluid has a much higher concentration of potassium and lower concentration of sodium and chloride ions relative to the extracellular fluid (Table 2-1).

Nernst Equation

In the steady state, the influx of an ion precisely counters the efflux, maintaining an equilibrium. Thus, various factors that determine the direction and the rate of the ionic flow together must exert a balanced force. Measuring the ionic concentration, therefore, allows a calculation of the equilibrium potential, that is, the transmembrane potential theoretically required to establish such a balance (Fig. 2-1).

In the case of potassium, for example, the ionic difference tends to push it from inside to outside the cell, reflecting the higher concentration inside. This force per mole of potassium, or its chemical work (Wc), increases in proportion to the logarithm of the ratio between internal and

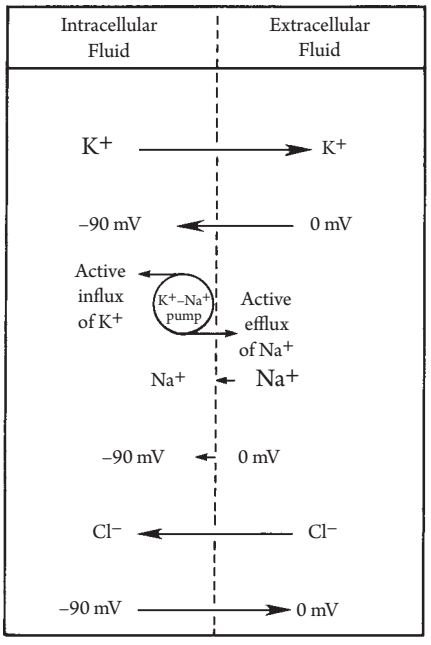

FIGURE 2-1 Simplified scheme of active and passive fluxes of potassium (K^+), sodium (Na^+), and chloride (Cl^-) in the steady state with driving force on each ion shown by vectors. For potassium, the efflux along the concentration gradient equals the influx caused by the electrical force plus the active influx by the sodium-potassium pump. For sodium, electrical and chemical gradient produces only a small influx because of membrane resistence. This inward current by persistent sodium channel equals the active efflux by the sodium-potassium pump. For chloride, the concentration gradient almost exactly counters the electrical force. The ratio of sodium and potassium exchange by a common electrogenic pump averages 3:2, making the inside more negative, although this diagram illustrates a neutral pump with a ratio of 1:1.

external concentration of potassium, $(K^+)i$ and $(K^+)o$, according to the equation,

$$Wc = RT \log(e)\ (K^+)i/(K^+)o$$

where R represents the universal gas constant; T, the absolute temperature; i, inside; o, outside; and log (e), natural logarithm.

The energy required to counter this force must come from the negative equilibrium potential (Ek) pulling the positively charged potassium from outside to inside the cell. This force per mole of potassium, or the electrical work (We), increases in proportion to the transmembrane voltage Ek, according to the equation,

$$We = Zk\ F\ Ek$$

where F represents the number of coulombs per mole of charge and Zk, the valence of the ion.

In the steady state, the sum of these two energies, Wc and We, must equal zero, as they represent forces with opposite vectors. Therefore,

$$Zk\ F\ Ek + RT \log(e)\ (K^+)i/(K^+)o = 0$$

Thus, the Nernst equation provides the theoretical potassium equilibrium potential Ek as follows:

$$Ek = -(RT/ZkF) \log(e)\ (K^+)i/(K^+)o$$

The same equation applies to calculate the sodium and chloride equilibrium potentials, Ena and Ec1, as follows:

$$Ena = -(RT/Zna\ F) \log(e)\ (Na^+)i/(Na^+)o$$

and

$$Ecl = -(RT/ZclF) \log(e)\ (Cl^-)i/(Cl^-)o$$

Table 2-1 shows the values of Ek (–97mV), Ena (+66mV), and Ecl (–90 mV) determined on the basis of their ionic concentrations. These compare with the actual transmembrane potential (–90 mV) in the example under consideration. Thus, ionic concentration and transmembrane potential alone can maintain chloride ions in perfect balance. To keep potassium and sodium in equilibrium at transmembrane potentials of –90 mV, therefore, other factors must exert a substantial influence on ionic movements. These include selective permeability of the cell membrane to certain ions and the energy-dependent sodium-potassium pump.

Sodium-Potassium Pump

An energy-dependent process, known as the sodium-potassium pump, transports sodium outward in exchange for the inward movement

of potassium. Although Figure 2-1 depicts a neutral pump that exchanges one sodium ion for every potassium ion actively transported inward, the actual ratio of sodium and potassium exchange averages 3:2 in most tissues. Such an imbalanced arrangement, called an electrogenic sodium-potassium pump, directly contributes to the membrane potential but only minimally compared with much greater changes associated with altered membrane permeability.

In the case of potassium, the active transport of potassium by this energy-dependent pump explains the small discrepancy between Ek (–97 mV) and Em (–90 mV). Here, the forces pulling potassium from outside to inside the cell consist of the potential difference (–90 mV) and the active potassium transport (approximately equivalent to –7 mV). Together they counter almost exactly the concentration gradient pushing potassium from inside to outside the cell.

In the case of sodium, both the concentration gradient and potential difference (–90 mV) pull the ion from outside to inside the cell. Nonetheless, this cation remains in equilibrium because of its impermeability through a mechanical barrier imposed by the structure of the cell membrane. Its active transport by the energy-dependent pump from inside to outside counters the small amount of sodium that does leak inward through a small number of persistent sodium channels, which remain open at resting membrane potential.

Goldman-Hodgkin-Katz Equation

The Nernst equation closely predicts the membrane potential for highly diffusible chloride and potassium ions. It does not fit well with much less permeable sodium ions because it ignores its relative membrane permeability. The addition of this factor leads to the more comprehensive Goldman-Hodgkin-Katz formula, which incorporates the concentration gradients and membrane permeabilities of all ions.

$$Em = (RT/F)\log(e)\ \frac{Pna\,(Na^{+}o) + Pk(K^{+}o) - - - + Pcl(Cl^{-}i)}{Pna\,(Na^{+}i) + Pk(K^{+}i) - - - - + Pcl(Cl^{-}o)}$$

where Pna, Pk. and Pcl represent the permeabilities of respective ions.

According to this equation, the concentration gradient of the most permeable ions dictates the transmembrane potentials. In the resting membrane with a very high Pk relative to a negligible Pna, the Goldman-Hodgkin-Katz equation would approximate the Nernst equation using the potassium concentration gradient. The transmembrane potentials calculated using either equation range from –80 to –90 mV. Conversely, the Goldman-Hodgkin-Katz potential would nearly equal the Nernst potential for sodium, with a negligible Pk relative to a high Pna. In this situation, seen with the opening of sodium channels by critical depolarization, the calculated membrane potentials range from +50 to +70 mV. This reversal of polarity in fact characterizes the generation of an action potential as outlined in the next section.

3. GENERAL CHARACTERISTICS OF AN ACTION POTENTIAL

Generation of an action potential consists of two phases: subthreshold and threshold. Subthreshold activation produces a graded response or a self-limiting local potential in transmembrane potential that diminishes with distance (see Chapter 10–4). With a threshold depolarization of 15 to 25 mV, the membrane potential, –90 mV at rest, reaches –65 to –75 mV, or the critical level to open the sodium channel. This in turn induces an action potential in an all-or-none fashion or the same maximal response regardless of the kind or magnitude of the stimulus (Fig. 2-2).

All-or-None Response

In the living cell, a voltage-sensitive molecular structure regulates the conductance of sodium and potassium ions across the membrane. One set of channels controls the movement of sodium ions and another set, potassium ions, depending on the transmembrane potential. When open, they provide adequate pathways for that specific ion to cross the membrane. In the resting stage, potassium ions move freely through potassium channels kept open at this transmembrane

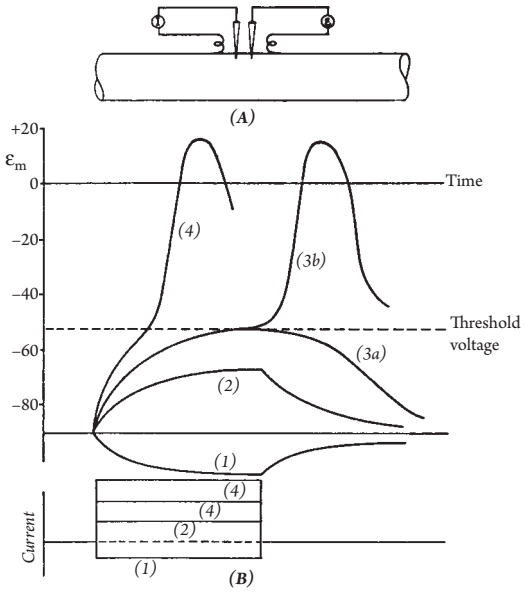

FIGURE 2-2 Schematic diagram of graded responses after subthreshold stimuli and generation of action potentials after suprathreshold stimuli. Experimental arrangement shows intracellular stimulation (I) and recording electrodes (E) on top (***A***) and polarity, strength, and duration of a constant current on bottom (***B***): Hyperpolarizing (1) and subthreshold depolarizing current (2) induce nonpropagating local response. Current of just threshold strength will produce either local change (3a) or an action potential (3b). Suprathreshold stimulation (4) also generates an action potential but with a more rapid time course of depolarization. (From Woodbury, [29] with permission.)

potential. In contrast, sodium ions move very little as only a small number of noninactivating sodium channels remain open, which accounts for some persistent inward current.[26] An externally applied current for nerve stimulation will depolarize the nerve under the cathode, or negative pole, inducing negativity outside the axon, thus making the inside relatively more positive. When depolarization reaches a critical level with intracellular potential shifting from –90 to –70 mV, for example, voltage-dependent sodium channels open, giving rise to a 500-fold increase in sodium permeability, which initiates the sequence of events leading to nerve excitation. In short, nerve stimulation accomplishes its objective by opening the voltage-dependent sodium channels.

This intrinsic property of nerve and muscle underlies the all-or-none response: regardless of the nature of the stimulus, the same action potential occurs as long as depolarization reaches the critical level. The increased conductance or permeability allows sodium ions to enter the cell seeking a new steady state. Sodium entry further depolarizes the cell, which in turn accelerates inward movement of this ion. Because of this regenerative sequence, an action potential develops explosively to its full size. The dramatic change in sodium permeability during this process results in a reversal of membrane potential from –80 or –90 mV to +20 or +30 mV. In other words, a switch from the potassium to the sodium equilibrium constitutes the generation of an action potential. A negative spike recorded extracellularly reflects this intracellular shift of the membrane potential from negative to positive.

In a depolarized membrane, permeability to potassium ions also increases as a result of a molecular change, but only after a delay of about 1 millisecond. At about the same time, the increased permeability to sodium falls again to near the resting value with closure or inactivation of sodium channels. Inactivated sodium channels fail to open for a few milliseconds even with depolarization above the critical level, constituting the refractory period (see Chapter 10-3). This inactivation of sodium conductance, together with increased potassium permeability, results in rapid recovery of the cell membrane from depolarization. After the potential falls precipitously toward the resting level, the opening of slow potassium channels induce further increase in potassium conductance. This, together with activation of electrogenic sodium potassium pump to restore the altered ionic concentration, hyperpolarizes the membrane, which then returns slowly to the resting value, completing the cycle of repolarization. The amount of sodium influx and potassium efflux during the course of an action potential changes the concentration gradients of these two ions very little. Abnormal, repetitive impulse firing arising from incomplete inactivation of sodium channels may characterize several neuromuscular disorders such as myotonias and neuropathic pain syndromes.[12]

Although repolarization primarily results from a delayed increase in potassium conductance in squid giant axon, this may not apply to mammalian peripheral or central myelinated axons.[28] Voltage clamp experiments indicate abundant sodium channels with minimum potassium conductance at the nodes of Ranvier in the mammalian peripheral myelinated axons or dorsal column axons.[21] In contrast, potassium channels abound all along the internodes, although paranodal regions also contain some sodium conductance. Theoretically, the availability of potassium conductance facilitates repolarization, but at a cost of prolonging the refractory period. In mammalian fibers, the absence of potassium channels at the node of Ranvier, combined with the fast inactivation of sodium conductance, tends to shorten the refractory period, thus allowing an increased rate of firing (see Chapter 10–3). In contrast to the ordinary inward sodium current, which inactivates in 1 to 2 ms, some voltage-sensitive channels seen in motoneuron dendrites, for example, stay open as long as the membrane potential remains above threshold, thus, the name persistent inward currents.[8]

Local Current

An action potential initiated at one point on the cell membrane renders the inside of the cell positive in that local region, reflecting elevated sodium conductance. Intracellular current then flows from the active area to the adjacent, negatively charged, inactive region. A return flow through the extracellular fluid from the inactive to active region completes the current. In other words, a current enters the cell at the site of depolarization, that is, sink, and passes out to adjacent regions of the polarized membrane, that is, source (Fig. 2-3). This local current tends to depolarize the inactive regions on both sides of the active area. When depolarization reaches the threshold, an action potential occurs, giving rise to a new local current further distally and proximally. Thus, an impulse, once generated in the nerve axon, propagates in both directions from the original site of depolarization, initiating orthodromic as well as antidromic volleys of the action potential (see Fig. 4-3 in Chapter 4).

After-Potential

In an extracellular recording, an action potential consists of an initial negative spike of about 1 millisecond duration, representing the intracellular positive spike of depolarization, and two subsequent negative, or depolarizing, and positive, or hyperpolarizing, after-potentials (Fig. 2–4). The first phase results from sustained internodal positivity and the extracellular accumulation of potassium ions, which tends to depolarize the cell after the generation of an action potential. The negative after-potential, an externally negative deflection grafted onto the declining phase of the negative spike, therefore, corresponds to a supernormal period of excitability. The second phase reflects the elevated potassium conductance at the end of the action potential, which tends to hyperpolarize the cell. In addition, an increased rate of the electrogenic sodium-potassium pump to counter the internal sodium accumulation also induces the same effect by removing three sodium ions in exchange for two potassium ions for a net gain of internal negativity (see Chapter 10–3). The positive after-potential, a prolonged externally positive deflection, therefore, signals a subnormal period of excitability.

4. VOLUME CONDUCTION AND WAVEFORM

Diphasic Recording of Action Potential

A pair of electrodes placed on the surface of a nerve or muscle at rest registers no difference of potential between them. If, in the tissue activated at one end, the propagating action potential reaches the nearest, or active, electrode (E1), then E1 registers the external negativity relative to the distant, or reference, electrode (E2), which remains neutral. This results in an upward deflection of the tracing according to the convention of clinical electrophysiology. With further passage of the action potential, the trace returns to the baseline at the point where the depolarized zone affects E1 and E2 equally. When the action potential moves further away from E1 and toward E2, E2 becomes negative relative to E1, or E1

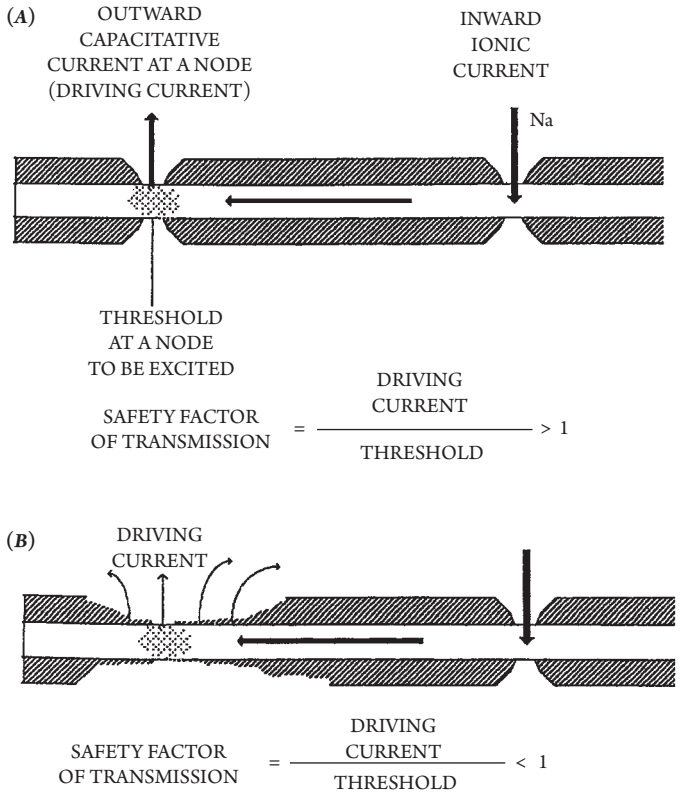

FIGURE 2-3 Classical view of normal conduction (***A***) and demyelinative conduction block (***B***). For successful conduction through a node of Ranvier, safety factor of transmission defined as the ratio of action current available at the node to threshold current must exceed unity. In contrast to normal myelinated nerves (***A***) with a factor of 10 or more, the action current destined for the node dissipates through paranode in demyelinated nerves (***B***) as a consequence of increased capacitance and decreased resistance. It now takes longer to charge the next nodal membrane to threshold, prolonging internodal conduction time. This provides the basis of conduction slowing in a demyelinated nerve fiber. The conduction time, around 20 μs in normal fibers, may reach up to 50 μs or more in demyelinated fibers. As demyelination progresses, the current becomes insufficient to reach the threshold, causing conduction block. (Modified from Kaji[11])

becomes positive relative to E2. Therefore, the trace now shows a downward deflection according to the convention. It then returns to the baseline as the nerve activity becomes too distant to affect the electrical field near the recording electrodes. This produces a diphasic action potential (Fig. 2-5).

Effect of Volume Conduction

The earlier discussion dealt with a directly recorded action potential in animal experiments with no external conduction medium intervening between the pickup electrodes and the nerve or muscle. During a clinical study, however, connective tissue and interstitial fluid act as a volume conductor surrounding the generator sources. Here, an electrical field spreads from a source represented as a dipole, or a pair of positive and negative charges. In a volume conductor, currents move along an infinite number of pathways between the positive and negative ends of the dipole with the greatest number of charges passing per unit time through a unit area along the straight path.

The current flow decreases in proportion to the square of the distance from the generator source. Thus, the effect of the dipole gives rise to

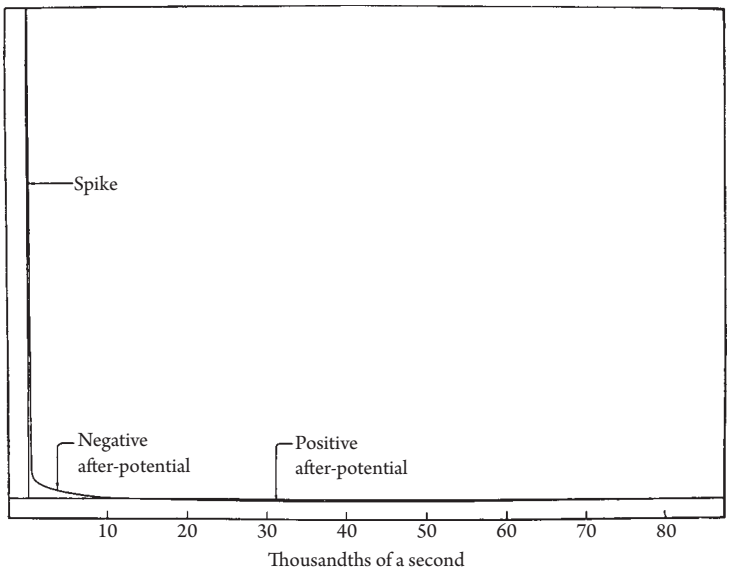

FIGURE 2-4 Diagrammatic representation of an action potential in A fibers of the cat with the negative spike and negative and positive after-potentials (as seen from outside the cell) drawn in their correct relative size and true relationships. (From Gasser[6] with permission.)

a voltage difference between the active recording electrode in the area of high current density and a reference electrode at a distance. Whether the electrode records positive or negative potentials depends on its spatial orientation to the opposing charges of the dipole. For example, an active electrode located at a point equidistant from the positive and negative charges registers no potential. The factors that together determine the amplitude of a recorded potential at a given electrode include charge density, or the net charge per unit area, surface areas of the dipole, and its proximity to the recording electrode.

The solid angle approximation pertains to analyzing an action potential recorded through a volume conductor. This theory states that the solid angle subtended by an object equals the area of its surface divided by the squared distance from a specific point to the surface. The resting transmembrane potential consists of a series of dipoles arranged with positive charges on the outer surface and negative charges on the inner surface. Thus, it increases in proportion to the size of the polarized membrane viewed by the electrode and decreases with the distance between the electrode and the membrane. Solid angle approximation closely predicts the potential derived from a dipole layer (Fig. 2-6). The propagating action potential, visualized as a positively charged wave front, or leading dipole, represents depolarization at the cross section of the nerve at which the transmembrane potential reverses. A negatively charged wave front, or trailing dipole, follows, signaling the repolarization of the activated zone.

Analysis of Triphasic Waveform

Analyzing waveforms plays an important role in the assessment of nerve and muscle action potentials. A sequence of potential changes arises as two sufficiently close wave fronts travel in the volume conductor from left to right (Fig. 2-7). This results in a positive-negative-positive triphasic wave as the moving fronts of the leading and trailing dipoles, representing depolarization and repolarization, approach, reach, and finally pass beyond the point of the recording electrode. Thus, an orthodromic sensory action potential from a deeply situated nerve gives rise to a triphasic waveform in surface recording. The potentials originating in the region near the electrode, however, lack the initial positivity in the absence of an approaching volley. A compound muscle action potential (CMAP), therefore, appears

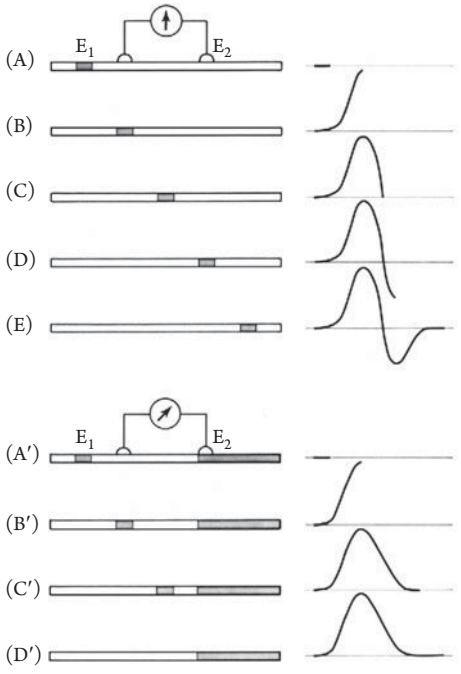

FIGURE 2-5 Diphasic (top) and monophasic recording (bottom) of an action potential represented by the shaded area, which shows surface negativity from depolarization. As the impulse propagates from left to right in the top series, the two electrodes see no potential difference in (a), (c), or (e). Relative to the reference electrode (E2), the active electrode (E1) becomes negative in (b) and positive in (d), resulting in a diphasic potential. In the bottom, the darkened area on the right indicates a killed end with permanent depolarization, with surface negativity making E1 positive relative to E2 in (a′), (c′), and (d′). In (b′), E1 and E2 see no potential difference, causing upward deflection from the positive baseline to 0 potential.

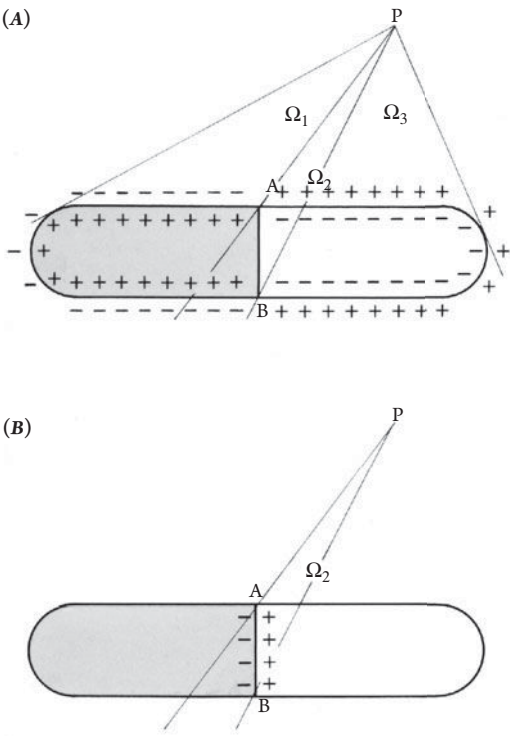

FIGURE 2-6 Potential recorded at P from a cell with active (dark area) and inactive region. In (***A***), total solid angle consists of Ω(1), Ω(2), and Ω(3). Potential at P subtending solid angles Ω(1) and Ω(3) equals zero as, in each, the nearer and farther membranes form a set of dipoles of equal magnitude but opposite polarity. In Ω(2), however, cancellation fails because these two dipoles show the same polarity at the site of depolarization. In (***B***), charges of the nearer and farther membranes subtending solid angle Ω(2) appear, as approximation, on the axial section through a cylindrical cell. A dipole sheet equal in area to the cross section then represents the onset of depolarization traveling along the cell from left to right with positive poles in advance, which the recording electrode at P sees as an approaching face of positivity. (Adapted from Patton[19]).

as a negative-positive diphasic waveform when recorded with the active electrode near the end-plate region where the volley of muscle action potential initiates. In contrast, a pair of electrodes placed away from the activated muscle registers a positive-negative diphasic potential indicating that the impulse approaches but does not reach the recording site.

The number of triphasic potentials generated by individual muscle fibers summates to give rise to a motor unit potential (MUP) recorded in EMG (see Chapter 13-5). The waveform of the recorded potential varies with the location of the recording tip relative to the source of the muscle potential.[4,25,27] Thus, the same motor unit shows multiple profiles depending on the site of the exploring needle. Moving the recording electrode short distances away from the muscle fibers increases the rise time or the time interval between the positive and negative peak of MUP, which, therefore, gives an important clue in

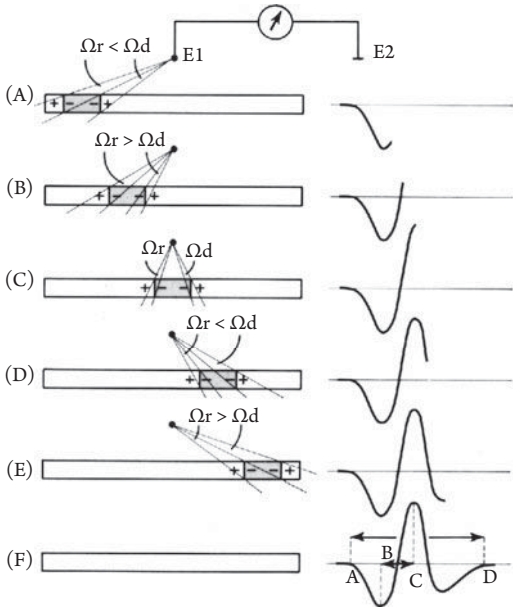

FIGURE 2-7 Triphasic potential characterized by amplitude, duration (A–D), and rise time (B–C). A pair of wave fronts of opposite polarity represents depolarization and repolarization. The action potential travels from left to right in a volume conductor with the recording electrode (E1) near the active region and reference electrode (E2) on a remote inactive point. As shown in (a), E1 initially sees the positivity of the first dipole, which subtends a greater solid angle (Ωd) than the second dipole of negative front (Ωr). In (b), this relationship reverses with gradual diminution of Ωd compared with Ωr, as the active region approaches E1. In (c), the maximal negativity signals the arrival of the impulse directly under E1, which now sees only negative ends of the two dipoles. In (d), the negativity declines as E1 begins to register the positive end of the second dipole. In (e), the polarity reverses again as Ωr exceeds Ωd. In (f), the trace returns to the baseline when the active region moves further away. The last positive phase, though smaller in amplitude, lasts longer than the first, indicating a slower time course of repolarization.

determining proximity of the needle to the generator source. The amplitude of an MUP does not serve for this purpose because its reduction may also result from abnormally small muscle fibers or low fiber density.

According to the volume conductor theory, the location of the needle dictates the waveform of recorded potentials. Thus, depending on the spacial relationship, the same single fiber discharge may appear as initially positive triphasic fibrillation potential, initially negative biphasic endplate spike, or initially positive biphasic positive sharp wave (see Chapter 14-4). An accurate description of the observed potential, therefore, provides clinically useful information. [3,18] Positive sharp waves recorded in the absence of fibrillation potentials may imply subliminal hyperexcitability of single muscle fibers that "spontaneously" fire only with mechanical irritation of the needle. If the tip of a needle damages the muscle membrane blocking a propagating impulse, the recorded potential appears as a positive sharp wave reflecting an approaching positive front without a negative spike, which would normally signal the arrival of the action potential.

Near-Field and Far-Field Potentials

The specific potential recorded under a particular set of conditions depends not only on the location of the recording electrodes relative to the active tissue at any instant in time but also on the physical characteristics of the volume conductor. [2,15–16,19,23] The near- and far-field potentials distinguish two different manifestations of the volume-conducted field.[9] The near field represents recording of a potential as it propagates under a pair of usually closely spaced electrodes placed directly over the path of the impulse. A bipolar recording registers primarily, though not exclusively, the near field from the axonal volley along the course of the nerve. In contrast, the far field implies detection of either a distant nonpropagating discharge or a stationary peak generated by a propagating impulse as a voltage step long before the signal arrives at the recording site. A pair of widely separated electrodes located across the junction of volume conductor preferentially records far-field potential, although one of the electrodes if placed near the passage of the traveling volley may also register near-field potential (see Chapter 19-3).

A far-field derivation has become popular in the study of evoked potentials to detect voltage sources generated at a distance. Original work on short-latency auditory evoked potentials[9] suggested that synaptically activated neurons

in the brainstem gave rise to stationary peaks. Subsequent animal studies emphasized the role of a synchronized volley of action potentials within afferent fiber tracts as their source. Indeed, short sequential segments of the brainstem pathways may each summate in far-field recording, resulting in successive peaks of the recorded potentials.[1] This mechanism by itself, however, does not account for the standing peaks derived from the propagating volleys at certain points along the greater length of the afferent pathway.

Studies using the peripheral sensory nerve conduction as a model documented that stationary peaks can, in fact, result at a junction of the volume conductor solely from the propagating impulse in the absence of synaptic discharge.[13,15–16] Hence, stationary peaks seen in a far-field recording may represent a fixed neural source such as synaptic discharges or, alternatively, a junctional potential registered as the advancing front of axonal depolarization crosses a volume conductor boundary. As for the first of the two possibilities, consider electrocardiographic artifacts seen in an isoelectric electroencephalogram recorded with high gain in a patient with brain death. Here, a large cardiac discharge represents a fixed generator in the chest recorded by distant electrodes placed on the scalp. As for the second, which defies the conventional belief, the new compartment becomes suddenly positive as compared to the old compartment, with the passage of the positive front of the leading dipole across the boundary. Thus, the chamber approached always detects a positive potential initially, although it may revert to negativity as the negative end of the same dipole crosses the partition.

Thus, in short-latency somatosensory evoked potentials (SEPs) of the median[7] or tibial nerve,[22] a voltage step develops between the two compartments when the moving volley encounters a sudden geometric change at the border of the conducting medium.[16] The same principles apply in the analysis of MUP and spontaneous single-fiber discharge.[5] At the time of entry of the impulse, each volume conductor on the opposite side of the boundary, in effect, acts as a lead connecting any points within the respective compartment to the voltage source at the partition.[10,14,24] Consequently, the potential difference remains nearly, though not exactly, the same regardless of the distance between E1 and E2, provided they flank the border between the two conjoining volume conductors. The designation, junctional or boundary potential, differentiates this type of stationary peak from fixed neural generators and helps specify the mechanism of the voltage step generated by the traveling impulse at a specific location (see Chapter 19-3).

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3

Electronic Systems

Abbreviations: AANEM—American Association of Neuromuscular and Electrodiagnostic Medicine, CMAP—compound muscle action potential, CRD—complex repetitive discharge, CRT—cathode ray tube, EMG—electromyography, MUP—motor unit potential, NCS—nerve conduction study, SFEMG—single fiber electromyography

1. INTRODUCTION

The apparatus used in the performance of routine electrodiagnosis includes electrodes, amplifiers, displays, loudspeakers, and data storage devices. Surface electrodes placed on the skin over the target register a summated electrical activity from many muscle or nerve fibers. Needle electrodes inserted closer to the source discriminate single muscle fiber or individual motor unit potentials (MUPs) depending on their recording radius. The electrical and physical characteristics of the electrode dictate the amplitude and other aspects of the recorded potentials under study.

Electromyographers analyze both the visual image of the waveform displayed on the screen and the auditory characteristics of the signals heard through a loudspeaker. The kind of information

desired and the type of activities under study determine the optimal amplifier settings. Digital storage has replaced the traditional devices for permanent recordings such as photographs with Polaroid films, a fiber-optic system with sensitive papers, or a magnetic tape recorder. Amplitude and time calibrations verify the accuracy of the stored signals. This chapter deals with practical aspects of instrumentation, deferring a detailed discussion of electronics to Appendix 2.

2. ELECTRODES

The signals recorded during voluntary muscle contraction depend to a great extent on the type of recording electrodes used. Surface electrodes placed over the muscle summate activities from many motor units. The use of a needle electrode allows recording of an individual MUP during mild muscle contraction. With increased effort, synchronous activities from many adjacent motor units interfere with the identification of single motor units. For routine purposes, clinical electromyographers use standard concentric, bipolar concentric,[2] or monopolar needles.[15] Single fiber electrodes have a leading edge small enough to allow recording of potentials derived from single muscle fibers in isolation.[24] Less commonly used "special purpose" electrodes include multielectrode, flexible wire electrode, and microelectrode placed intracellularly. An electrode lead wire should have a protected pin to prevent inadvertent connection to a power source, causing shocks, burns, or electrocutions.[3]

Preparation of Needle Electrodes

With the advent of less costly disposables, it has now become a common practice to discard needle electrodes after use in each patient. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) recommends this practice to circumvent any concerns of possible transmission of diseases, especially after studying a patient with AIDS, hepatitis, or any other contagious disorders. Jakob-Creutzfeldt disease poses special problems because the transmissible agent responsible for the disease may resist conventional sterilization procedures. Further precaution, therefore, calls for incinerating the used needles and blood-contaminated materials or autoclaving them for 1 hour at 120°C and 15 PSI before disposal.[4]

In reusing needle electrodes, sterilization in boiling water for at least 20 minutes prevents the transmission of infection. Commercially available sterilizers bring the water temperature to 100°C and maintain it without excessive boiling. Only the metal and plastic components of needle electrodes will withstand the time and temperature of steam autoclaving, thus the need to detach non-autoclavable connectors and lead wires before the sterilization procedure. Gas sterilization also suffices, although the chemicals used may damage the plastic, causing defects in insulation. With one terminal of a battery connected to the lead of a monopolar needle and the other terminal to an ammeter with a small exploring metal hook, a current should flow only if the hook also touches the lead. Any current, if registered while exploring the shaft of the needle, indicates defective insulation. An ammeter should register no current if connected to the battery through the two insulated leads of standard or bipolar concentric needles. A current will flow normally with immersion of the needle tip in water, which short-circuits the two lead edges.

Types of Electrodes

Figure 3-1 illustrates electrodes commonly used for nerve conduction studies (NCS) and electromyography (EMG).

SURFACE ELECTRODES

Surface electrodes, square or round metal plates made of platinum or silver, come in different sizes with the average dimension of 1 × 1 cm. The type of recording electrode used influences the characteristic of the evoked potential. A surface electrode serves best for monitoring voluntary muscle contraction during kinesiologic studies, but not for studying an MUP with high-frequency components not detectable by this method. It registers electrical activities nonselectively from a wider region covering the recording radius of some 20 mm compared to selective pickup from a

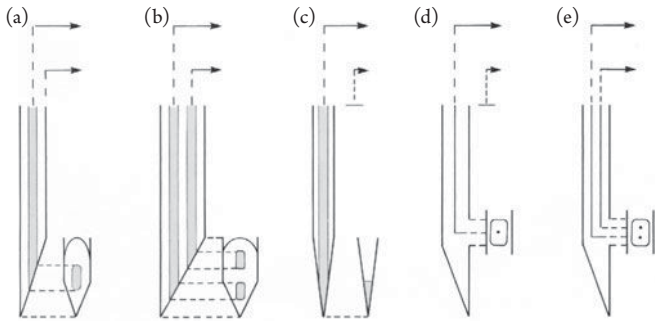

FIGURE 3-1 Schematic illustration of (*a*) standard or coaxial bipolar, (*b*) concentric bipolar, (*c*) monopolar, and (*d* and *e*) single fiber needles. Dimensions vary but the diameters of the outside cannulas shown resemble 26-gauge hypodermic needles (460 μm) for (*a*), (*d*), and (*e*); 23-gauge needle (640 μm) for (*b*); and 28-gauge needle (360 μm) for (*c*). The exposed tip areas measure 150 μm x 600 μm for (*a*), 150 μm x 300 μm with spacing between wires of 200 μm center to center for (*b*), 0.14 mm^2 for (*c*), and 25 μm in diameter for (*d*) and (*e*). A flat skin electrode completes the circuit with unipolar electrodes shown in (*c*) and (*d*). (Modified from Stålberg, and Trontelj and Sanders.[24])

500 μm radius by a needle electrode.[6] Increasing electrode size tends to diminish the amplitude of compound muscle action potential (CMAP) because potentials registered per unit become smaller with greater recording radius.[27] The surface electrode also works well as a stimulating probe or a reference or a ground lead in conjunction with a monopolar needle.

An adhesive tape suffices for application of the electrode to the skin in clinical practice, although the use of collodion improves stability in long-term monitoring. Time-efficient application of disposable adhesive electrodes, though more costly, provides results equal to, if not better than, the usual disc electrodes applied with adhesive tapes.[8] Cleansing the skin with alcohol, scraping the calloused surface, and applying electrolyte cream under the electrode reduces the impedance. Too much paste can form a bridge between the recording (E1) and reference electrodes (E2), cancelling the voltage difference. Steady electrode offset voltage at the interface, not recorded by the amplifier, can give rise to an artifact if movement causes a sudden mechanical change in the metal-electrolyte interface. To reduce this type of potential, some surface electrodes allow most movement to occur between electrolyte and skin rather than at the metal-electrolyte interface. A short circuit between the stimulator and pickup electrodes or ground introduces a large stimulus artifact. Perspiration can act in a similar manner.

STANDARD OR COAXIAL NEEDLE

This electrode, introduced by Adrian and Bronk,[2] has a stainless-steel cannulas similar to hypodermic needles, with a wire in the center of the shaft. The wire, usually made of nichrome, silver, or platinum, measures 0.07 square mm or slightly larger as compared to the external rim of the shaft, 0.46 mm in diameter. The pointed tip of the needle has an oval shape with an exposed area of about 150 μm x 600 μm, and an impedance of around 50 Kohms. The wire and shaft, bare at the tip, form a spheric rather than hemispheric recording territory.[12] The needle, when near the source of electrical activity, registers the potential difference between the wire and the shaft, showing a restricted recording area. The so-called facial concentric needle electrode, 25 mm in length, has the advantage of a smaller needle shaft of 0.3 mm but also has a smaller recording surface of 0.03 square mm, showing slightly different recording characteristics.[7]

In the recording of a single motor unit discharge, only the muscle fibers located within about 500 μm radius from the tip of the needle contribute to the amplitude, and those within 2.5 mm to the duration of the recorded potential.[11] Thus,

although recording characteristics vary from one type of needle to another, the pickup area, in general, constitutes a very small portion of the motor unit territory that extends at least 1 cm in diameter. A separate surface electrode, taped or applied with adhesive, serves as the ground. Disposable concentric needles generally compare reasonably well with reusable electrodes, although electric or physical testing of the leads may not adequately predict their recording characteristics.[21]

BIPOLAR CONCENTRIC NEEDLE

The cannula contains two fine stainless-steel or platinum wires. This electrode, therefore, has a larger diameter than the standard concentric needle embedded with wires of the same size. The electrode registers the potential difference between the two inside wires, with the cannula serving as the ground. The bipolar electrode thus detects potentials from a much smaller volume than the standard needle. The three terminals in the connecting cable consist of two active leads and a ground connection. In this type of recording from a very localized area, only a small number of single muscle fibers contribute as the source for measured amplitude.[19] This restricted recording range provides selectivity but at the risk of disregarding the overall activity of the motor unit. Concentric electrodes tend to detect more spontaneous potentials than monopolar needles, probably because of increased tissue injury[23]

MONOPOLAR NEEDLE

This electrode, made of stainless steel for its mechanical properties, has a fine point insulated except at the distal 0.2 to 0.4 mm. The wire, covered by a Teflon sleeve, has an average diameter of about 0.8 mm. A surface electrode or a second needle in the subcutaneous tissue serves as a reference lead and a separate surface electrode placed on the skin, as a ground. Although electrically less stable, hence noisier than the concentric electrode, its sharp tip causes less pain during insertion.[16,25] The average impedance ranges from 1.4 megohms at 10 Hz to 6.6 Kohms at 10 KHz[28] Presoaking the electrodes with a small concentration of a wetting agent in saline solution reduces the impedance by 6- to 20-fold. This pretreatment improves the resolution of low-amplitude signals. A monopolar needle records voltage changes between the tip of the electrode and the reference. The spatial recording characteristics[18] differ considerably from one type of needle to another. In general, a monopolar needle registers an amplitude twice as large as that of a concentric needle from the same source[13,19,22] although duration and firing rate remain nearly the same.

SINGLE FIBER NEEDLE

Single fiber electromyography (SFEMG) requires an electrode with a much smaller leading edge to record from individual muscle fibers rather than motor units (see Chapter 16-2). A wire, 25 μm in diameter, mounted on the side of a needle, provides the maximal amplitude discrimination between near and distant signals. As in concentric electrodes, single fiber needles may contain two or more wires exposed along the shaft, serving as the leading edge. The most commonly used type has one wire inserted into a cannula with its end bent toward the side of the cannula, a few millimeters behind the tip.[24] The spatial recording characteristics of single fiber needles show specific asymmetries and a greater potential decline with radial distance compared with concentric or monopolar electrodes.[17,24]

MACROELECTRODE

The needle used for macro EMG consists of two recording surfaces, one capable of recording SFEMG from a side port and the other dedicated for territorial pickup with a bare cannula 15 mm in length (see Chapter 16-7). A two-channel system provides SFEMG recording with a 500 Hz low-frequency filter in one channel, and macro EMG recording at a standard EMG setting in the other. The SFEMG side port referenced to the cannula produces single-fiber signals that trigger the oscilloscope sweep. The active cannula electrode with reference to a skin or distant electrode registers electrical activities along its entire length, but only if time-locked to the SFEMG trigger. Simultaneous discharges from

neighboring motor units, not time-locked with the trigger, cancel as background noise during signal averaging.

MULTIELECTRODES

Multielectrodes contain three or more insulated wires, usually 1 x 1 mm in size, exposed through the side of the cannula[10] One of the wires serves as the indifferent electrode and the outside cannula of the electrode, l mm in diameter, as the ground. The separation between the leads along the side of the multielectrode determines the recording radius. The commonly used distances in measuring the motor unit territory include 0.5 mm for myopathy and l.0 mm for neuropathy. The single needle may also contain multiple wires exposed along the shaft.

FLEXIBLE WIRE

A flexible wire, introduced through a hypodermic needle, permits freedom of movement in kinesiologic examination. Some investigators prefer a bipolar electrode made of nylon-coated Evanohm alloy wire, 25 μm in diameter. Although this type of electrode comes in different sizes, the most commonly used has insulated platinum wires 50–100 μm in diameter with the tip bare. A small hole made in the insulation of the wire may serve as a smaller lead-off surface on the order of 10–20 μm. These electrodes, however, lack the rigid standardization required for quantitative studies of action potentials [24]

GLASS MICROELECTRODES

A glass microelectrode, used for intracellular recording, consists of fine glass tubing filled with potassium chloride solution. Because of its extreme fragility, one must use a cannula as a carrier to introduce the electrode through the skin, and a micromanipulator to insert it into the exposed muscle. The electrode has a very fine tip, less than 1 μm in diameter, and consequently a very high impedance on the order of 5 megohms. Therefore, recording from a glass microelectrode calls for amplifiers of exceedingly high input impedance.

3. ELECTRODE AMPLIFIERS

Potentials assessed during electrodiagnostic examinations range in amplitude from microvolts to millivolts. With the oscilloscope display set at 1 V per cm, signals of 1 μV and 1 mV, if amplified 1 million times and 1000 times, respectively, cause a 1 cm deflection. To accomplish this range of sensitivity, the amplifier consists of several stages. One system uses a preamplifier with a gain of 500, followed by several amplifier and attenuator stages to produce a variable gain of 2 to 2000. This arrangement increases the signal-to-noise ratio by allowing major amplification of the signal near the source prior to the emergence of noise that develops in the following circuits. To achieve this goal, the preamplifier must have high input impedance, a low noise level, and a large dynamic range.

Differential Amplifiers

During EMG examination, a major source of interference comes from the coupled potential of the alternating current power line. The magnitude of this field can exceed that of biological potential by a million times. Proper assessment, therefore, depends on selective amplification of the signal without, at the same time, magnifying the noise. Differential amplifiers, therefore, magnify only the voltage difference between the two input terminals rather than the voltage appearing between an input terminal and the ground terminal. This system effectively rejects common mode voltages, which appear between both input terminals and common ground. These include not only power-line interference but also distant muscle action potentials that affect the two recording electrodes equally. A common mode voltage, too large for a perfect balance, overloads the amplifier.

Common Mode Rejection Interference

Inherent imbalance in the electrical system of an amplifier renders rejection of the common mode voltage less than perfect. The rejection ratio specifies the degree of differential amplification between the signal and the common mode voltage. Good differential amplifiers should have rejection

ratios exceeding 100,000, or 100,000 times more amplification of the signal than unwanted potentials. A very high rejection ratio, however, will not guarantee the complete elimination of external interference, for two reasons. First, electromagnetic interference affects the two recording electrodes almost, but not quite, equally depending on their relative positions. Second, inevitably different contact impedances of the two recording electrodes lead to unequal distribution of the same common mode voltage.

Means of Reducing Interference

Other precautions for minimizing electromagnetic interference include reducing and balancing contact impedances of the two electrodes and the use of short, well-shielded electrode cables. The system must effectively ground not only the patient and the bed but also the instrument and, if necessary, the examiner. Major interference may originate from unshielded power cords running to other appliances in the vicinity of the recording instrument. With adequate care, most modern equipment operates well without a shielded room. In the presence of electrical noise uncontrollable by ordinary means, a properly constructed Faraday shield can dramatically reduce the interference. For the best performance, it should enclose the examining room as one continuous conductor grounded at one point. The 50 or 60 Hz filter available in most instruments reduces power-line interference at the expense of distorting the signals under study. Thus, only special situations, such as portable recording in an intensive care unit, may warrant their application, and even then only when all other attempts have failed.

Input Impedance

Analogous to the resistance in a DC circuit, the impedance in an AC circuit determines the current flow for a given alternating voltage source. In this circuit, the needle tip and the input terminal act as a voltage divider in proportion to the respective impedance with a negligible drop across the tissue and electrode wires. Thus, with the impedance equally divided between these two, only one-half of the original potential will appear across the input terminal. Increasing the input impedance of the amplifier from 100 kilohms to hundreds of megohms, a level much higher than that of the electrode tip, would minimize the loss. Higher input impedance also renders the electrical asymmetry of the recording electrodes small, improving the common mode rejection ratio. Large electrode impedances also induce amplifier noise and external interference, although higher values apparently cause no major waveform distortion.[1]

Frequency Response

Most commercially available apparatus have variable high- and low-bandpass filters to adjust frequency response according to the type of potentials under study. Fourier analysis of complex waveforms encountered in electrodiagnosis reveals sine waves of different frequencies as their harmonic constituents. The prominent sine wave frequencies of muscle action potentials, for example, range from 2 Hz to 20 KHz. For clinical studies, the frequency band of the amplifier ideally should cover this range. In the presence of interfering high-pitched noise and DC drift, however, a bandpass extending from 10 Hz to 10 KHz suffices. Filter settings must remain constant in serial studies to avoid alteration of waveform.

High-frequency (low-pass) filters, if set too low, reduce the amplitude of high-frequency components disproportionately. Extending the high-frequency response beyond the band required for proper recording results in an unnecessary increase in background noise. A low-frequency (high-pass) filter, if set too high, distorts the slowly changing potential without enhancing MUP complexity, or turn[9] Here the new waveform approximates the first derivative (rate of change) of the original signal. Extending the frequency response too low causes instability of the baseline, which then shifts slowly in response to changing biopotentials. The analog filters also affect the peak latency of the recorded response because of phase shift. High-frequency filtering increases whereas low-frequency filtering reduces the apparent peak latency. The use of digital filtering, which introduces zero

phase shift, circumvents this problem in clinical assessments.[20]

A square-wave pulse of known amplitude and duration serves as a calibration signal for accurately determining the amplitude and duration of the recorded potentials. The distortion seen in the square pulse results from the effects of high- and low-frequency filters. Its rise time indicates the high-frequency response, and the slope of the flat top, the low-frequency response (see Appendix Figs. 2-18 and 2-20). Other calibration signals include sine waves from the power line and discontinuous waveforms of known frequency and amplitude.

4. VISUAL AND AUDITORY DISPLAYS

Appropriate amplification ensures an optimal display of the waveform for visual analysis. Before the advent of digital processing, the cathode ray tube (CRT) provided an excellent means to trace rapidly changing amplitude against time. Most manufacturers now use digital circuitry to process and store the potentials before displaying them on a monitor. The waveform displayed on the face of the screen depicts the signal voltage changing in time. The vertical axis represents the response amplitude, whereas the horizontal axis shows the units of time. An EMG examination usually uses a free running mode; that is, when the spot reaches the end of the screen, it returns rapidly to the beginning to repeat.

Delay Line

Instead of the free running mode, the horizontal sweep may initiate on command, triggered, for example, by an MUP itself for detailed analysis. In this mode of operation, a given unit recurs successively at the beginning of each sweep, although, by design, only the portion of the waveform following the trigger point appears on the screen. In an analog machine, an electronic delay circumvents this difficulty by storing the recorded MUP for a short period. After a predetermined delay following the onset of a sweep triggered by the real-time potential, the stored signal leaves the delay line for display on the screen. With this arrangement, the potential in question occurs repetitively and in its entirety on the same spot of the screen for precise determination of its amplitude and duration. With digital circuitry, the computer begins displaying data at any desired point prior to the trigger, thus accomplishing the same objective.

Multiple-Channel Recording

Some electrophysiologic instruments have multiple channels to allow simultaneous recording from two or more sets of electrodes. With CRT, two or more channels share a beam from a single gun by switching the point vertically between the base lines of different traces as the beam sweeps horizontally across the screen. This electrical switching takes place so fast that each trace in effects appears to be continuous despite the interruption from one trace to the next.

Storage Oscilloscope

Storage oscilloscopes have a different CRT that retains traces on the face of the screen for several hours. A second electron gun floods the screen to visualize the trace retained as electrostatic charges on a mesh behind the screen. Electrically discharging the mesh can quickly erase the stored pattern. The advent of digital storage and display techniques has made such storage oscilloscopes obsolete.

Loudspeaker

Muscle or nerve action potentials have distinct auditory characteristics when played through a loudspeaker. For clinical analyses, electromyographers depend very heavily on the sounds produced by different kinds of spontaneous or voluntarily activated muscle potentials during EMG. For example, fibrillation potentials sound like "rain on a tin roof" (see Chapter 14-4). Acoustic properties also help distinguish a nearby motor unit with a clear, crisp sound, reflecting a short rise time, from distant units with dull sound (see Chapter 14-5). In fact, an experienced examiner can detect the difference between near and distant units by sound better

than by waveform display. The acoustic cues usually serve as an excellent guide in properly repositioning the needle close to the source of the discharge.

5. ARTIFACTS

Not all electrical potentials registered during electrophysiologic examinations originate in muscle or nerve. Any voltage not attributable to the biologic potential under study represents an artifact, which usually causes a unique discharge pattern on the oscilloscope and distinct sounds through the loudspeaker. Some noises, however, mimic biologic activity so closely that even a trained examiner may have difficulty in identifying them.

Most artifacts unaffected by the position of the recording electrode originate outside the muscle. These include 50 or 60 Hz interference caused by the electrostatic or electromagnetic fields of electrical appliances and other exogenous activities like those induced by a cardiac pacemaker (Fig. 3-2) or transcutaneous stimulator (Fig. 3-3). Improper or inadequate grounding results in electromagnetic interference from the nearby alternating current source. Different generator sources give rise to characteristic, though not specific, patterns for easy identification (Fig. 3-4). Artifacts may also originate in the recording instruments themselves or from a more remote generator such as a hammer drill (Fig. 3-5). A loose connection in one or more parts of the recording circuit may generate electrical activity similar to the muscle action potential. Impedance variability within the muscle tissue may also cause electrical activity depending on the location of the needle tip. These artifacts may mimic the intended signals under study.

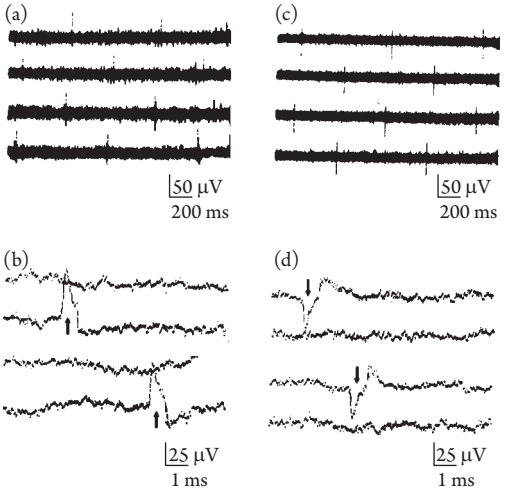

FIGURE 3-2 Artifacts induced by a cardiac pacemaker recorded by a monopolar needle electrode from gluteus medius and (*a* and *b*) paraspinal muscle (*c* and *d*). Note opposite polarity of the sharp discharge in the two recording sites. The interval between the successive impulses of 800 ms corresponds to a discharge frequency of 75 impulses/minute. Trains in (*a*) and (*c*) show continuous recordings from top to bottom, and those in (*b*) and (*d*), interrupted tracings from one sweep to the next.

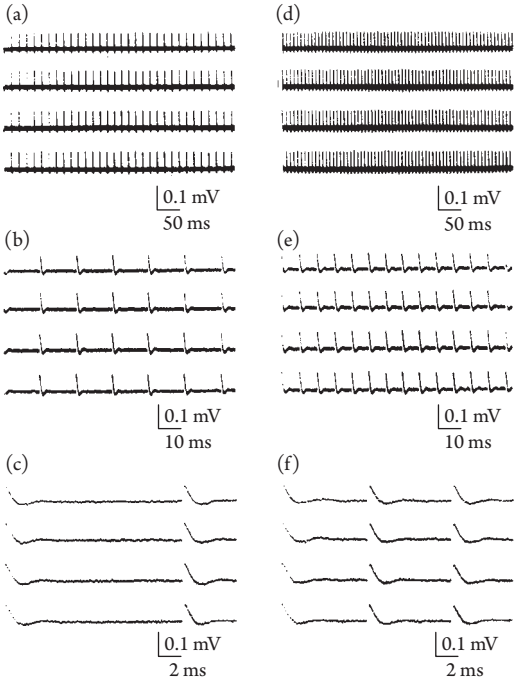

FIGURE 3-3 Artifact induced by a transcutaneous stimulator. The 14 ms interval between the successive impulses (*a*, *b*, and *c*) corresponds to an approximate discharge rate of 70 impulses/second and 7 ms interval (*d*, *e*, and *f*), a faster rate of 140 impulses/second.

Electrode Noise

Potentials may arise from two active metals or the metal-fluid junction at the surface electrode on the skin or needle tip located intramuscularly.

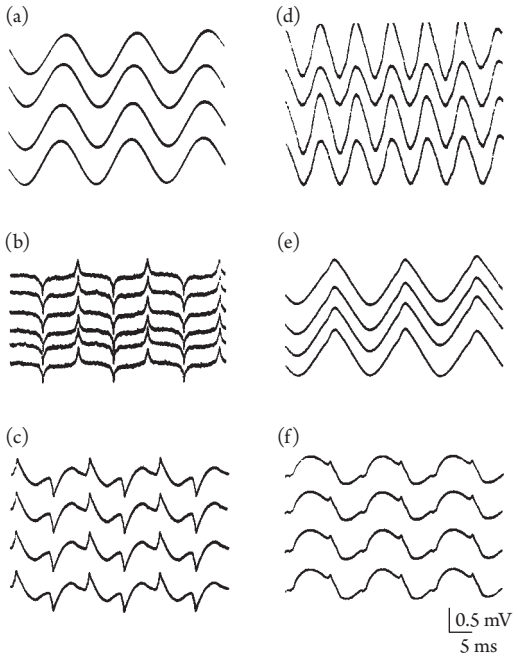

FIGURE 3-4 Various types of interference induced by nearby electrical appliance. They include common 60 Hz alternation (*a*), spikes from high impedance of the recording electrode (*b*), fluorescent light (*c*), 120 Hz pattern from diathermy unit (*d*), and 60 Hz oscillation from heat lamp (*e* and *f*).

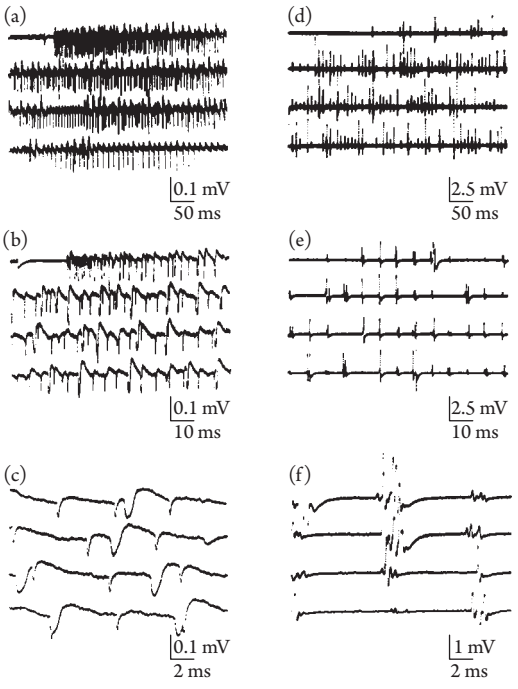

FIGURE 3-5 Effect of hammer drill operated nearby (*a*, *b*, and *c*) and oscillation of the amplifier circuits (*d*, *e*, and *f*) probably induced by an excessively high impedance of the electrode tip. Both superficially resemble complex repetitive discharges, but the recordings with a fast sweep speed (*c* and *f*) uncover a waveform and pattern of recurrence not usually associated with a biologic discharge.

A constant electrode-fluid potential by polarization may distort the signals, whereas changing potentials will result in electrode noise. A small electrode tip, because of its high impedance, causes a greater voltage drop during the passage of current, inducing a greater interference from its polarization. Therefore, the type of metal alters the recording characteristics of the needle electrode much more than those of the surface electrode. The use of relatively inert metals, such as stainless steel or platinum, minimizes such adverse effects.

Amplifier Noise

Electrical noise inherent in an amplifier originates from all components, including the resistors, transistors, and integrated circuits. Noise arising from the thermal agitation of electrons in a resistor increases with the impedance in the input stage. Microphonic noise results from the mechanical vibration of various components. The use of a high-pass filter suppresses low-frequency noise from these and other sources in amplifier circuits. A low-pass filter reduces high-frequency noise, which appears as a thickening of the baseline as it sweeps across the screen accompanied by a hissing noise on the loudspeaker (Fig. 3-6). The level of amplifier noise as perceived on the oscilloscope increases in proportion to the amplifier gain and frequency response. Thus, operating the system at lower gains and with narrower filter band widths substantially reduces this component of noise seen on the screen, often at the expense of distorting the signals under consideration.

Defective Amplifier

By far the most likely cause of recording problems relates to a defect in the three recording

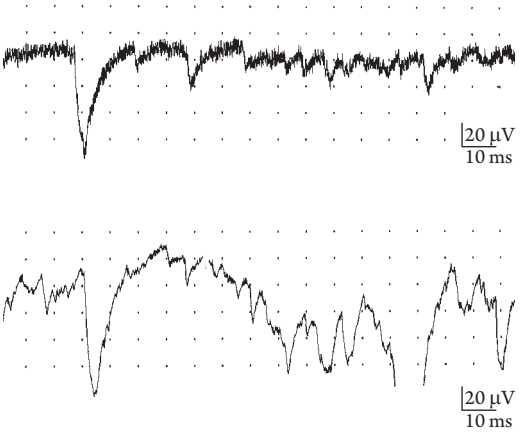

FIGURE 3-6 Amplifier noise superficially resembling positive sharp waves, recorded with a monopolar needle placed in the edematous subcutaneous tissue. The baseline thickness changed abruptly with slight relocation of the needle tip probably altering the impedance, high with the needle in contact with fatty tissue (*top*) and low when located elsewhere (*bottom*).

electrodes or its application. A broken wire induces bizarre and unsuspected artifacts even if the insulating cover appears intact. A partially severed conductor may generate very deceptive movement-induced potentials, which recur with muscle twitch, mimicking stimulus locked evoked signals. Other common causes of artifacts include defective insulation of a monopolar needle or a concentric needle with a short-circuited tip. The use of disposable needles eliminates problems inherent to sterilization, but unused electrodes may manifest similar artifacts, caused by mechanical defects induced during the manufacturing process. These include Teflon retraction, a dull or burred tip, a break in a wire or pin, electrical artifacts, and a bend in the needle shaft.

Movement Artifact

When a patient contracts a muscle, the surface electrode may slide over the skin. This causes a movement artifact primarily because of changing impedance between the surface electrode and the skin. Movement-induced potentials also may result from existing fields near the surface of the skin, particularly those originating from sweat glands. Movement of electrode wires may produce artifacts resembling muscle activity, mostly reflecting changing capacitance. Rubbing the lead of the needle electrode with a finger or cloth sometimes produces friction artifacts from a static charge. Adequate insulation of the needle, ideally with the use of driven shields, reduces this type of interference.

Electrostatic and Electromagnetic Interference

Sources of 50 or 60 Hz interference abound (Fig. 3-4). They include electric fans, lamps, fluorescent lights, CRT screens, electric motors, light dimmers, and even unused power cords plugged into the wall outlets. The use of an ungrounded wheelchair or a metal examining table enhances this type of artifact. Appliances sharing the same circuit with the EMG instrument cause especially noticeable interference. Radio frequency electromagnetic waves can also "carry" alternating current. A strong field from a nearby diathermy apparatus produces a characteristic wave pattern. Federal regulations now restrict the amount of interference that such a unit can render to other equipment. Intermittent power-line load causes transient voltage changes, which in turn give rise to an artifact. In an examining room located near a driveway, auto ignition causes a popping sound. The examiner, if not properly grounded, may act as an antenna by touching the needle.

Bundling or weaving the lead wires of the recording and ground electrodes minimizes the area susceptible to the field of interference. Other simple but effective measures to reduce EMG interference include relocating the wires, patient, or recording apparatus within the room and relative to each other. With power cords near the patient, turning off power to the offending appliance does not necessarily eliminate the artifacts. To minimize the interference from the oscilloscope screen or monitor, the patient and operator should avoid the location near the source. If these simple precautions fail, one may consider, as a last resort, removing all the electrical appliances from the room and shielding the examining area.

Radio and Mobile Phone Interference

High-frequency audio interference may appear from radio broadcasts, television, or radio paging systems. This type of transient artifact may escape detection unless the sounds heard through the loudspeaker alert the examiner. Their elimination may call for relocation or screening of the EMG instrument. An examining room located on the side of the building farthest from transmitting antennas has the least interference. The use of power-line radio frequency filters may minimize the noise caused by power wiring. A mobile phone in use near the laboratory also can give rise to substantial artifacts, which may mimic high-frequency complex repetitive discharges (CRDs)[26]

6. STIMULATORS

Electrical Stimulation Requirements

Electrical stimulation applied with surface electrodes on the skin or through needles inserted subcutaneously induces a current in the fluid surrounding a nerve bundle, depolarizing the nerve under the cathode and hyperpolarizing it under the anode. Increasing the shock intensity to a level slightly above the value just sufficient to elicit a maximal response assures the excitation of all the axons in the nerves. The waveform of stimulus pulse affects the patient's perception of an electrical shock. Monophasic stimulation evokes different responses compared to a biphasic pulse, with a trailing positive phase, which has a stimulating effect[14]

Surface stimulation in the range of 50–500 V drives a current of 5–50 mA, assuming the skin impedance of 10 KΩ. Higher shock intensities can usually, though not always, compensate for a decreased nerve excitability seen in some neuropathic conditions (see Chapter 11-5). Stimulation with subcutaneus needle electrodes, already in good fluid contact and closer to the nerve, uses a much lower intensity for adequate activation. Just a few volts may elicit a response in this case, requiring a much tighter intensity control than surface delivery for consistent and safe practice. The stimulus intensity and duration required for effective depolarization shows an inverse relationship. Thus, within limits, a lower intensity suffices if applied for a longer duration, and vice versa. Generally, patients tolerate a stimulus duration exceeding 2 ms poorly. With durations of less than 50 μs, tissue capacitances limit the rate of rise of the stimulus pulse, which, therefore, may not reach a fully effective level. Commonly used stimulus duration, therefore, ranges from 0.1 to 1.0 ms.

The equipment must also provide a good control over the timing of the stimuli for different purposes of clinical measurements. In performing a paired-shock technique, the first shock with reduced intensity may subliminally excite the neural elements, which then fire with the second shock delivered within a few milliseconds. Some collision techniques use two or three precisely timed stimuli, with individually adjustable intensities, durations, and delays, delivered to the same or to different sets of electrodes. A train of stimulus technique uses many shocks of identical intensity at rapid, adjustable rates of discharge. Such complex stimulus generators must have adequate programmability with fail-safe protection features.

Stimulus Isolation

Electrical stimulators "isolated" from the recording amplifiers and other equipment circuits improve safety and artifact reduction. In such a system, the stimulation circuits have no conductive path to other circuits except through the patient's body. This isolation ensures that stimulus current flows only in the loop provided by the two stimulating electrodes. If the stimulator circuit has any connection to the recording circuit, then the stimulus current divided into additional paths can cause a large stimulus artifact, amplifier overload, or even spurious stimulation at unintended sites. Under conditions of component failure, these additional paths might also conduct hazardous levels of current. Stimulus isolation usually relies on magnetic coupling of energy to the stimulating circuits, although battery-powered stimulators may use optical coupling of the control signal.

Constant Voltage versus Constant Current

A "constant-voltage" stimulator delivers an adjustable voltage across the stimulating electrodes, essentially independent of stimulus current. At a fixed output voltage, the electrode impedance determines the stimulus current level. Increasing the voltage alters the current to achieve a desired level of stimulation. A "constant-current" stimulator delivers an adjustable current through the stimulating electrodes, essentially independent of their impedance. The voltage across the stimulating electrodes adjusts dynamically to maintain a constant stimulus current, providing more consistent stimulus control, especially for techniques that require a train of stimuli or response averaging.

Magnetic Coil Stimulation

Magnetic coil stimulation, more widely used for excitation of the central rather than peripheral nervous system, serves as an alternative means of nerve activation.[5] In this method, an electric current of a primary circuit induces a rapidly changing magnetic field of high intensity, which in turn gives rise to an electric current in the body fluid to cause nerve excitation (see Chapter 20-3). The apparatus consists of a doughnut- or figure 8–shaped coil and a capacitive-discharge power unit, triggered from conventional EMG equipment. Magnetic stimulation can excite the brain noninvasively, with less pain and no need of stimulus electrode application. Inducing a stimulus magnetically requires huge coil currents and high voltages, which cause substantial stimulus artifact in the recording circuits. Uncertainty and variability of stimulation point limits its use for excitation of the peripheral nerve. Specially constructed devices enable closely paired or a train of stimuli, although their routine applications cause some safety concerns. Despite the spreading use of magnetic stimulation for cortical excitation in Europe and Japan, the US Food and Drug Administration has not yet approved its clinical use for brain stimulation, except for as therapy for major depression. The national review board has granted permission for some research applications conducted for the study of central nervous system.

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PART II

Nerve Conduction Studies

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4

Anatomy and Physiology of the Peripheral Nerve and Types of Nerve Pathology

Abbreviations: ACh—acetylcholine, CIDP—chronic inflammatory demyelinative polyneuropathy, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CTS—carpal tunnel syndrome, EMG—electromyography, GBS—Guillain-Barré syndrome, HMSN—hereditary motor sensory neuropathy, HNPP—hereditary neuropathy with susceptibility to pressure palsies, MAG—myelin-associated glycoprotein, MMN—multifocal motor neuropathy, MUP—motor unit potential, NCS—nerve conduction study, SNAP—sensory nerve action potential

1. INTRODUCTION

Histologic techniques have advanced our understanding of peripheral nerve pathology, especially through quantitative analysis of fiber diameter spectrum and single teased fiber preparations. Electrophysiologic methods have made equally important contributions in elucidating the pathophysiology of these disorders.[20] In particular, in vitro recordings of sensory nerve action potentials (SNAPs) from the sural nerve delineated the types of fibers predominantly affected in certain neuropathic processes. These studies also demonstrated the close relationships between histologic and physiologic findings in many disease entities.

Traumatic lesions of the nerve usually result in structural changes in the axon with or without separation of its supporting connective tissue sheath. Nontraumatic disorders of the peripheral nerve may affect the cell body, axon, Schwann cell, connective tissue, or vascular supply singly or in combination. Electrophysiologic abnormalities depend on the kind and degree of nerve damage. Hence, the results of nerve conduction studies (NCSs) closely parallel the structural abnormalities of the nerve. Histologic changes in the nerve and the nature of conduction abnormalities allow subdivision of peripheral nerve lesions into two principal types: axonal degeneration and segmental demyelination. This chapter will deal with the basic anatomy and physiology of the peripheral nerve to discuss types of conduction abnormalities.

2. ANATOMY OF THE PERIPHERAL NERVE

Gross Anatomy

Nerves have a structure of considerable complexity with various features of special relevance to injury and regeneration.[130] Three kinds of connective tissue, endoneurium, perineurium, and epineurium, surround the axons in the nerve trunks (Fig. 4-1). The endoneurium forms the supporting structure found around individual axons within each fascicle. The perineurium consists of collagenous tissue, which binds each fascicle with elastic fibers and mesothelial cells. This layer serves neither as a connective tissue nor as a simple supporting structure; rather, it provides a diffusion barrier to regulate intrafascicular fluid. The epineurium, comprised of collagen tissue, elastic fibers, and fatty tissue, tightly binds individual fascicles together, providing a protective cushion against compression.[130] This outermost layer of supporting structure for the peripheral nerve merges in the dura mater of the spinal roots.[55]

Paucity of endoneurial collagen at the roots as compared with the nerve trunk may explain why some disease processes selectively involve the root. Fascicular groups bound by perineurium remain localized within the nerve for long distances, destined for the same endpoint.[142] Somatotopic clustering of nerve fascicles may explain restricted clinical deficits seen after focal nerve lesions, defying the classic rules of localization.[123,124] The vasa nervorum, located in the epineurium, branch into arterioles and penetrate the perineurium to form capillary anastomoses in the fascicles. The perineurium probably acts as a blood–nerve barrier, but the elucidation of its detailed function needs further study.

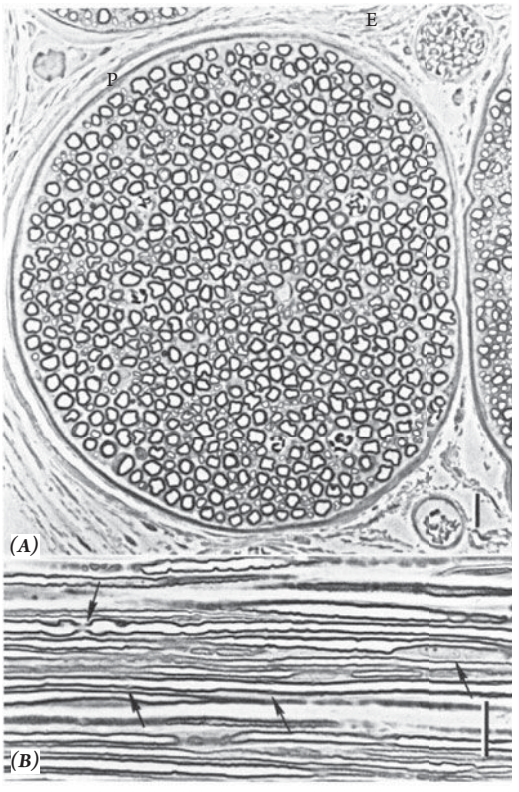

FIGURE 4-1 Transverse (***A***) and longitudinal (***B***) sections of the sciatic nerve shown at low magnification. Vertical scales at lower right represent 20 μm. In (***A***), the epineurium (E) contains vessels, fibroblasts, and collagen. The perineurium (p) surrounds fascicles, whereas endoneurial connective tissue separates individual nerve fibers. The longitudinal section (***B***) includes a node of Ranvier (upper arrow), a Schwann cell nucleus (right arrow), and Schmidt-Lantermann clefts (lower arrows). (From Webster,[148] with permission.)

Myelinated and Unmyelinated Fibers

The nerve trunks contain myelinated and unmyelinated fibers. Certain inherent properties of the axon apparently determine whether myelination will eventually occur. Conversely,

myelinating Schwann cells control the number of neurofilaments and elevate their phosphorylation state in the axon.[91] Transplantation of exogenous Schwan cells may restore normal conduction properties in demyelinated spinal cord in the adult rats.[61] In myelinated fibers, the surface membrane of a Schwann cell, or axolemma, spirals around the axon to form the myelin sheath (Fig. 4-2). Each myelinated axon has its own Schwann cell, which regulates myelin volume and thereby its thickness. The nodes of Ranvier, located at junctions between adjacent Schwann cells, represent uninsulated gaps along the myelinated fiber. In contrast, several unmyelinated axons share a single Schwann cell, which gives rise to many separate processes, each surrounding one axon. Schwann cells may modulate local immune responses by recognizing and presenting antigens.[151]

The spacing of the Schwann cells at the time of myelination determines the internodal distance. As the nerve grows in length, the internodal distance must increase because Schwann cells do not proliferate. Thus, the fibers, if myelinated early, achieve larger diameters and wider spacing between the nodes of Ranvier. This explains

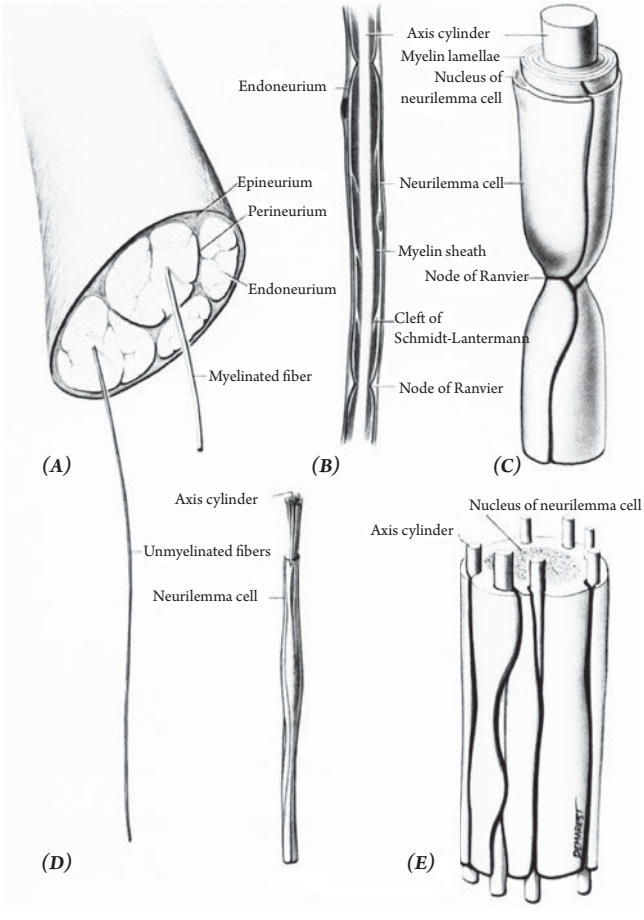

FIGURE 4-2 Fine structures of the peripheral nerve as visualized with the light microscope (***A***, ***B***, and ***D***) and as reconstructed from electron micrographs (***C*** and ***E***). (***A***) The epineurium covers the entire nerve, whereas the perineurium surrounds individual fascicles, and endoneurium, nerve fibers. (***B***) The myelinated fiber consists of axis cylinder, myelin sheath, and Schwann (neurilemma) cells. The myelin sheath abates at the node of Ranvier. (***C***) The Schwann cell produces a helically laminated myelin sheath that wraps around an axon individually. (***D***) Several unmyelinated nerve fibers share one Schwann cell. (***E***) Several axis cylinders of unmyelinated fibers surround the nucleus of the Schwann cell. (From Noback,[100] with permission.)

why the larger diameter fibers have a greater internodal distance. In myelinated fibers, the action potentials propagate from one node of Ranvier to the next with the rate approximately proportional to the fiber diameter. Many other factors play a role. For example, selective deletion of Schwann cell can result in slowed nerve conduction and nodal changes, including sodium channel density.[114] In unmyelinated nerves, conduction velocity varies in proportion to the square root of the fiber diameter. The largest and fastest conducting fibers include the Group IA afferent fibers transmitting proprioceptive, positional, and touch sensations and the α motoneurons. Small myelinated or unmyelinated fibers have pain and temperature sense and autonomic functions. Those found in the human epidermis apparently originate from nerve trunks in the dermis, subserving some sensory function.[72]

Axonal Transport

In the peripheral nervous system, a small cell body with a diameter of 50 to 100 μm regulates axons up to 1 meter in length. A complicated system of axonal transport provides the metabolic needs of the terminal segments. Hence, the axons not only conduct propagating electrical potentials but also actively participate in conveying nutrient and other trophic substances. The velocity of transport varies from several hundred to a few millimeters per day. The majority of particles flows centrifugally, though some seem to move centripetally.

Axonal flow of trophic substances also dictates, at least in part, the histochemical and electrophysiologic properties of the muscle fibers. No substance other than acetylcholine (ACh) seems to transfer across the neuromuscular junction. Therefore, ACh molecules may have a trophic influence on muscle in addition to their role as a neurotransmitter. Separation of the axon from the cell body first results in failure of the neuromuscular junction, followed by axonal degeneration and muscle fiber atrophy.[21] Both the failure of neuromuscular transmission and the degeneration of the nerve terminals proceed faster with distal than with proximal axonotmesis. Similarly, membrane changes in denervated muscles appear more rapidly after nerve injury close to the muscle.[57]

3. PHYSIOLOGY OF NERVE CONDUCTION

Transmembrane Potential

Nerve axons have electrical properties common to all excitable cells (see Chapter 2-2). Measured transmembrane steady state potentials vary from about –20 to –100 mV in different tissues, despite the same basic physiologic mechanisms underlying the phenomenon. A smaller resting membrane polarization in the soma (–70 mV) as compared to the axon (–90 mV) probably reflects a partial depolarization from continuous synaptic influences. As in any excitable element, generation of a nerve action potential consists of two steps: graded subliminal excitation caused by any externally applied stimulus and suprathreshold activation, which results in increased sodium conductance. A local subliminal change in the transmembrane potential rapidly diminishes with distance. In contrast, suprathreshold depolarization produces an all-or-none action potential determined by the inherent nature of the cell membrane irrespective of the type of stimulus applied.

Generation and Propagation of Action Potential

With application of a weak current to a nerve, negative charges from the negative pole, or cathode (so named because it attracts cation), accumulate outside the axon membrane, making the inside of the cell relatively more positive, that is, cathodal depolarization. Under the positive pole, or anode, the negative charges tend to leave the membrane surface, making the inside of the cell relatively more negative, that is, anodal hyperpolarization. The cell plasma resistance together with the membrane conductance and capacitance limits the subliminal local changes of depolarization or hyperpolarization only within a few millimeters from the point of origin. After about 10 to 30 mV of depolarization, the membrane potential reaches the critical level for opening the voltage-dependent sodium channels, leading to the generation of an all-or-none action potential (see Chapter 2-3). Nerve excitability change seen after a single nerve impulse has three phases: the initial refractory

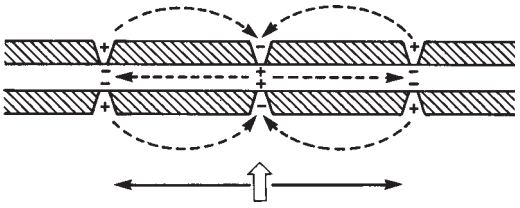

FIGURE 4-3 Saltatory conduction along the myelinated fiber. The myelin sheath effectively insulates the internodal segment with the bare axon at the node of Ranvier, where the current flows between intracellular and extracellular fluid. A local current (dotted arrows) induced by an action potential at one node (open arrow) depolarizes the axis cylinder at the adjacent nodes on either side, transmitting the impulse in both directions (solid arrows). This type of saltatory excitation propagates rapidly as it jumps from one node to the next.

period of a few milliseconds, supernormality lasting 30 ms or so, and subnormality extending up to 100–200 ms (see Chapter 10-3).

An action potential initiated along the course of an axon propagates in both directions from its point of origin (Fig. 4-3). Intracellular current flows from the positively charged active area to the adjacent negatively charged inactive region. An opposing current flows through the extracellular fluid from the inactive to active region, allowing the recording of electric as well as magnetic fields. This local current depolarizes the inactive regions on both sides of the active area. When it attains the critical level, an action potential generated there initiates a new local current further distally and proximally. Hence, the nerve volleys always propagate bidirectionally from the site of external stimulation at one point along the axon. Physiologic impulses originating at the anterior horn cells or sensory terminal travel only orthodromically. In pathologic situations, however, impulses may arise in the midportion of nerve fibers. For example, discharges occur in the middle of the spinal root axons in dystrophic mice, either spontaneously or as a result of ephaptic transmission (cross-talk) from neighboring fibers.[111]

Factors Determining the Conduction Velocity

Various factors affect the time necessary for generating action potentials, which in turn determine the conduction velocity of an axon. Rapid propagation results from (1) faster rates of action potential generation, (2) increased current flow along the axons, (3) lower depolarization thresholds of the cell membrane, and (4) higher temperature. Warming up the body facilitates activation and inactivation of sodium conductance, thereby lowering the amplitude of action potential and increasing its rate of transmission. Conduction velocity increases nearly linearly about 4%–5% per 1°C from 29°C to 38°C. Thus, the change ranges from 1.5 to 3 m/s per°C in a normal nerve conducting at 40 to 60 m/s. Other elements of clinical importance (see Chapter 5-6) include internodal length,[19] variation among different nerves and segments, effect of age, and metabolic factors such as hyperglycemia.

In the myelinated fibers, action potentials occur only at the nodes of Ranvier. This induces a local current that, in effect, jumps from one node to the next, producing saltatory conduction (see Fig. 4-3) instead of the continuous propagation observed in unmyelinated fibers. Myelin normally provides high impedance and low capacitance, preventing leakage current through the internodal membrane to sustain saltatory conduction (see Chapter 2-3). Sodium channels when open at the activated node of Ranvier produce "inward ionic current" or "sink," which subsequently causes "outward capacitative current" or "source" at the next node. This in turn depolarizes the nodal membrane to threshold, thus opening the sodium channels and initiating another cycle of "inward ionic current." An increase in internodal distance allows a longer jump of the action potential but causes greater loss of current through the internodal membrane. Typically, it takes approximately 20 μs for the local current to excite the next node, yielding the conduction velocity of 50 m/s for an internode distance of 1 mm.

The longitudinal resistance of axoplasm tends to inhibit the flow of the local current. The capacitance and conductance of the internodal membrane also have the same effect as the loss of the current before it reaches the next node. This, in turn, makes the time required to depolarize the adjacent nodal membrane longer,

resulting in slower conduction. Both internodal capacitance and conductance decrease with myelin thickness. Thus, for the same axon diameter, conduction velocity increases with myelin thickness up to a certain point. For a fixed total fiber diameter, an increase in axon diameter induces two opposing factors, smaller axoplasmic resistance on the one hand and greater membrane conductance and capacitance reflecting reduced myelin thickness on the other.[143,144] Theoretical considerations indicate that the anatomic characteristics of myelinated fibers fulfill all the conditions required for maximal conduction velocity.

Demyelinated or partially remyelinated segments have an increased internodal capacitance and conductance because of their thin myelin sheath. This leads to a loss of local current by charging the capacitors and by leaking through the internodal membrane before reaching the next node of Ranvier. Failure to activate the next node results in conduction block. If the conduction resolves, the impulse propagates slowly because the dissipated current needs more time to generate an action potential. Thus, demyelinated axons characteristically exhibit conduction failure, decreased velocity, and temporal dispersion. After segmental demyelination, smaller diameter fibers may show continuous rather than saltatory conduction if the demyelinated region has a sufficient number of sodium channels.[12] Reduction in length of the adjacent internodes tends to restore conduction past focally demyelinated zones.[139,145]

Conduction abnormalities do not necessarily imply demyelination. Reduced fiber diameter by focal compression decreases the capacitance of the internodal membrane, which tends to facilitate conduction. Concomitant increases in resistance of the axoplasm, however, more than offset this effect by delaying the flow of the local current to the next node. Most mechanisms known to influence nerve conduction velocity affect the cable properties of the internodal segments. Additionally, altered characteristics of the nodal membrane itself may interfere with generation of the action potential. Conduction failure can also result from toxins or anesthetic agents.[18]

4. TYPES OF NERVE FIBERS

Classification of Nerve Fibers

The compound nerve action potential elicited by supramaximal stimulation consists of several peaks, each representing a group of fibers with a different conduction velocity. Erlanger and Gasser[39] in their original study of the A fibers designated successive peaks using the Greek letters α, β, γ, and δ in order of decreasing velocity. Subsequent studies have revealed two additional components showing a very slow conduction velocity: B and C fibers. The mammalian peripheral nerves contain no B fibers. This designation, therefore, now indicates the preganglionic fibers in mammalian autonomic nerves. The original terminology for various peaks of the A fibers has created some confusion,[86] for example referring to the initial peak as either A-α[47] or A-β,[38] and the subsequent peak, now considered artifact of recording as A-γ.[47] Current practice designates the two peaks in the A potential of cutaneous nerves as A-α and A-δ.

The three types of nerve fibers, A, B, and C, have histologically and electrophysiologically distinctive characteristics (Table 4-1): A fibers, or myelinated somatic axons, either afferent or efferent; B fibers or myelinated efferent preganglionic axons of the autonomic nerves; and C fibers, or unmyelinated efferent postganglionic axons of autonomic nerves and the small afferent axons of the dorsal root and peripheral nerves. As documented in the human median nerve, both myelinated and unmyelinated fibers show intrafascicular segregation by modality rather than random distribution.[56] Two types of afferent input, for example, A-delta and C fibers, may interact at primary afferent level.[150]

Despite histologic resemblance, physiologic characteristics can differentiate B fibers from small A fibers. For instance, the B fibers lack negative after-potentials and consequently a supernormal period of excitability after generation of an action potential. The negative spike lasts more than twice as long in B as in A fibers. The B fibers show smooth compound action

Table 4-1 Types of Nerve Fibers

A fibers: myelinated fibers of somatic nerves

Muscle nerve
- Afferent
  - Group I: 12–21 μm
  - Group II: 6–12 μm
  - Group III: 1–6 μm
  - Group IV: C fiber
- Efferent
  - Alpha motor neuron
  - Gamma motor neuron

Cutaneous nerve
- Afferent
  - Alpha: 6–17 μm
  - Delta: 1–6 μm

B fibers: myelinated preganglionlc fibers of autonomlc nerve

C fibers: unmyelinated fibers of somatic or autonomlc nerve
- sC fibers: efferent postganglionic fibers of autonomlc nerve
- drC fibers: afferent fibers of the dorsal root and peripheral nerve

potentials without discrete peaks, indicating an evenly distributed velocity spectrum. Several C fibers share a single Schwann cell, unlike individually bound A or B fibers. This, and the absence of the myelin sheath, allows histologic identification of the C fibers. Physiologic features include high thresholds of activation, long spike duration, and slow conduction velocity. High-frequency stimulation of cutaneous afferents induces paresthesia attributable to hyperexcitability, followed by hypoesthesia that arises from stimulation-induced refractoriness at the central synaptic relays.

Afferent fibers of the cutaneous nerves show a bimodal diameter distribution, with one component ranging between 6 and 17 μm and the other between 1 and 6 μm, or with the Greek letter designation, A-α and A-δ fibers. The muscle nerves comprise efferent and afferent A fibers. The efferent fibers consist of the axons of α and γ motoneurons. In Lloyd's Roman numeral classification, the afferent fibers consist of Groups I, II, and III, ranging in diameter from 12 to 21 μm, from 6 to 12 μm, and from 1 to 6 μm, and Group IV, representing small pain fibers. In this designation, the A-α fibers of cutaneous nerve correspond in size to Groups I and II, the A-δ fibers to Group III, and the C fibers to Group IV.

Modality Dependency of Nerve Conduction

In cats and primates, muscle afferents transmit impulses at a considerably higher speed than cutaneous afferents, which in turn conduct faster than motor fibers. Thus, conduction characteristics distinguish various fiber populations in mammalian species, as well as in human, where the same relationship also holds, albeit less conspicuously. For example, direct recording from human sural nerves can differentiate A-α and A-δ peaks as shown in in vitro studies.

In Vitro Recording and Fiber Diameter

An in vitro study of the sural nerve action potential complements the quantitative morphometric assessment of the excised nerve.[36] The technique allows comparison between the fiber diameter spectrum and the range of conduction velocities for different components of the SNAP. Some authors caution that the sural nerve may occasionally contain motor fibers.[4] The nerve biopsy consists of dissecting a bundle of several fascicles above the lateral malleolus for a total length of approximately 10 cm.[103] The distal half serves as the specimen for histologic studies and the proximal half for in-vitro electrophysiologic evaluation.

Conduction studies consist of transferring the nerve segment to a sealed chamber filled with 5% carbon dioxide in oxygen and saturated with water vapor. Stimulation at the distal end of the nerve allows recording of SNAP with a pair of wire electrodes placed 20-30 mm proximally.

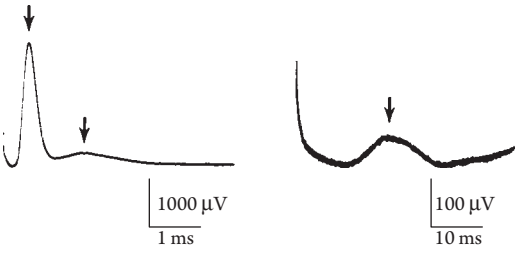

FIGURE 4-4 Compound nerve action potential of a normal sural nerve recorded in vitro from an 11-year-old boy who had an above-knee amputation for osteogenic sarcoma. The arrows from left to right indicate A-α, A-δ, and C components, measuring 2.6 mV, 0.22 mV, and 70 μV in amplitude and 42 m/s, 16 m/s, and 1 m/s in conduction velocity based on the peak latency. (Courtesy of E. Peter Bosch, MD, Mayo Clinic, Scottsdale, AZ.)

A monophasic waveform results with the nerve crushed between the recording electrodes following application of 0.1% procaine at the distal electrode (see Fig. 2-5 in Chapter 2). The potential recorded in vitro consists of three distinct peaks: A-α, A-δ, and C components with an average conduction velocity of 60 m/s, 20 m/s, and 1 to 2 m/s (Fig. 4-4). Each component requires different supramaximal intensity for full activation. The gradual onset of A-δ and C peaks makes accurate calculation of the maximal conduction velocity difficult.

Figure 4-5 shows a fiber diameter histogram for the A-α and A-δ components. Here, the fiber diameter increases from left to right on the abscissa: thus, the first peak on the left corresponds to A-δ and the second smaller peak to A-α fibers. In the opposite arrangement plotting the diameter lessening from left to right, fiber groups appear in order of decreasing conduction velocity, as in the tracings of compound action potentials. In normal fiber groups, fiber diameter histograms show a continuous distribution between the large and small myelinated fibers with no clear separation between the two. Similarly, A-α and A-δ peaks reflect a high concentration of fibers within the continuous spectrum. The largest fibers with a diameter close to 12μm conduct at an approximate rate of 60 m/s, indicating a 5:1 ratio between the two measurements.

Morphologic evaluation of the peripheral nerve must take into account the maturational and age-related changes.[69,136] In one study of 51 normal sural nerve biopsies,[118,122] the fiber diameter histogram changed gradually from unimodal to bimodal distribution between 7 and 13 months. Cross-sectional measurements showed a growth in diameter of the thickest fibers, an increase in peak of the larger fiber group, and separation between the smaller and the larger groups until the beginning of adult life. An increase in total transverse fascicular area, despite a stable number of nerve fibers, indicates decreasing fiber density with age. Determining the internodal length spectra in teased fiber preparation also provides quantitative data in elucidating distribution of histologic abnormalities (Fig. 4-6). Statistical analyses show significant correlations between teased fiber changes and conduction abnormalities affecting both motor and sensory nerves in patients with sensorimotor polyneuropathies.[10]

Analysis of Nerve Action Potentials

The amplitude of a compound action potential, E, recorded over the surface of a nerve increases in proportion to current flow and external resistance. Ohm's Law expresses this as E = IR, where I represents current and R, resistance. Larger nerves have a greater number of fibers that would collectively generate larger currents, with each fiber contributing an approximately equal amount. Nerves with greater cross-sectional areas, however, has a smaller total resistance. Large nerve size, therefore, may have a negligible overall effect on amplitude. In fact, a whole nerve composed of many fascicles does not necessarily give rise to an action potential larger than the one recorded from a single dissected fascicle.[86]

More current flows with an increasing number of the nerve fibers, whereas the resistance falls in proportion to the square diameter of the nerve. Thus, fiber density or the number of fibers per unit of cross-sectional area determines the amplitude of an action potential. The factors that determine the waveform abnormality of a compound action potential include the magnitude of conduction block, diminution of current in individual nerve

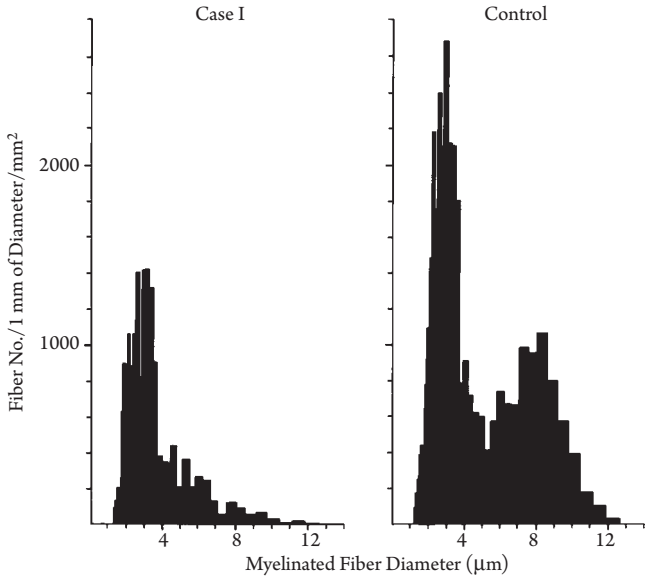

FIGURE 4-5 Myelinated fiber size-frequency histogram plotting the number of fibers with increasing diameter from left to right. The first large peak on the left corresponds to A-δ and the second smaller peak, to A-α. Note a bimodal distribution of myelinated fiber diameter in a normal subject (control). A patient (case 1) with hereditary neuropathy with liability to pressure palsies had an abnormal unimodal pattern with preferential loss of the larger myelinated fibers. (Courtesy of E. Peter Bosch, MD, Mayo Clinic, Scottsdale, AZ.)

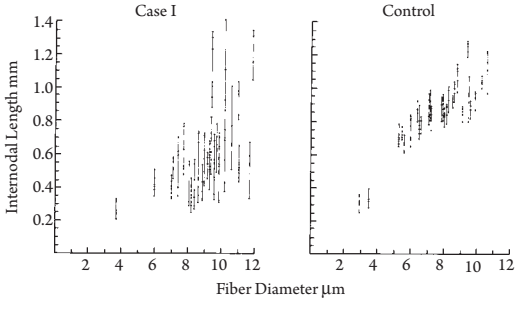

FIGURE 4-6 Internodal length spectra of the same nerves shown in Figure 4-5. Each vertical line indicates internodal lengths measured on a given myelinated fiber. The marked variability of internodal length in the patient reflects the effects of chronic demyelination and remyelination. (Courtesy of E. Peter Bosch, MD, Mayo Clinic, Scottsdale, AZ.)

fibers, and the degree of temporal dispersion. Selective involvement of different groups of fibers results in a major distortion of the recorded potential. In contrast, uniform involvement of all fibers reduces the amplitude with relative preservation of all the components. Hence, waveform analysis of compound nerve action potentials provides a means to assess fiber density and distribution spectrum (see Chapter 11-6).

5. CLASSIFICATION OF NERVE INJURIES

Seddon[120] defined three degrees of nerve injury: neurapraxia, axonotmesis, and neurotmesis. In neurapraxia, or conduction loss without structural change of the axon, recovery takes place within days or weeks following the removal of the cause. The conduction velocity, if initially slowed from demyelination, returns to normal with remyelination. In axonotmesis, the axons lose continuity with subsequent wallerian degeneration along the distal segment. Recovery depends on regeneration of nerve fibers, a process that takes place slowly over months or years at a rate of 1 to 3 mm per day. In neurotmesis, an injury separates the entire nerve, including the supporting connective tissue. Without surgical intervention, regeneration proceeds slowly, resulting in an incomplete and poorly organized repair. This classification, originally proposed for external trauma such as

superficial or penetrating nerve injuries, also applies to entrapment and compression neuropathies such as the carpal tunnel syndrome (CTS) and tardy ulnar palsy.

Neurapraxia and Conduction Failure

The mildest form of nerve block results from local injection of procaine. Tetrodotoxin has similar but more widespread effects over the length of the axon, lowering the conductance of sodium currents at the nodes of Ranvier. A transient loss of circulation with leg crossing, for example, also causes an immediately reversible insult without structural changes of the axon. These short-term changes in nerve conduction probably result from anoxia secondary to ischemia.[68] Paresthesia often accompanies such motor abnormality from ectopic impulses in cutaneous afferents, which tend to show more excitability than motor axons. The difference in their biophysical properties includes more persistent sodium conductance and inward rectification on cutaneous afferents, properties that confer greater protection from impulse-dependent conduction failure but create a greater tendency to ectopic activity.[96]

During transient paralysis, experimentally induced in humans by an inflated cuff around the arm, a complete conduction block usually occurs after 25–30 minutes of compression. Serial stimulation along the course of the nerve reveals normal excitability in the segment distal to such a neurapraxic lesion. In the rat sciatic nerve, a conduction block developed within 10 minutes after femoral artery occlusion, reached a nadir at 45–60 minutes and abated within 24 hours.[109] The initial fall in amplitude accompanied only a mild slowing of conduction, implying a relative preservation of the fast-conducting, large-diameter myelinated fibers. Similarly, a focal compression in humans also affects the slow-conducting, small-diameter fibers first.[133] Intraneural microelectrode recordings show spontaneous activity in the afferent fibers about half a minute after reestablishment of circulation. The perceived paresthesia also suggests ectopic impulses generated along the nerve fibers previously subjected to ischemia.[105]

In most acute compressive neuropathies, such as a Saturday night palsy or crutch palsy of the radial nerve, conduction across the affected segment returns within a few weeks, although weakness could persist for a few months or longer, usually accompanied by demyelination. Similarly the prolonged application of a tourniquet causes sustained conduction block with paranodal demyelination. The degree of compression determines the severity of the initial conduction block, but not the subsequent recovery rate of conduction.[60] In contrast to short-term effects, chronic nerve ischemia induced by a bovine shunt, for example, usually results in axonal degeneration of sensory fibers initially and of motor fibers later.[9] In experimental animals, partial infarction resulted in degeneration of fibers in the center of the nerve with no evidence of selective fiber vulnerability.[108]Hypothermia, by reducing metabolic demands, rescues the nerve from ischemic fiber degeneration.[73]

Although conduction block may result from anoxia secondary to ischemia, studies of experimental acute pressure neuropathy have stressed the importance of mechanical factors [48,107] with the initial displacement of axoplasm and myelin in opposite directions under the edges of the compressed region (Figs. 4-7 and 4-8). Part of one myelin segment invaginates the next with occlusions of the nodal gaps. Demyelination of the stretched portions of myelin follows. A patient with documented pneumatic tourniquet paralysis had severe conduction block of sensory and motor fibers localized to the presumed lower margin of the compression,[11] as in the CTS.[75] A quick recovery of some symptoms following decompression suggests the role of ischemia as

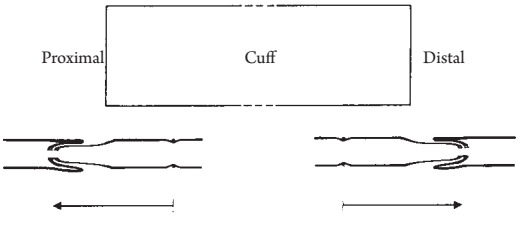

FIGURE 4-7 Diagram showing the direction of displacement at the nodes of Ranvier in relation to the cuff placed to induce a localized mechanical compression in experimental acute pressure neuropathy. Note proximal and distal paranodes invaginated by the adjacent one. (From Ochoa, Fowler, and Gilliatt,[104] with permission.)

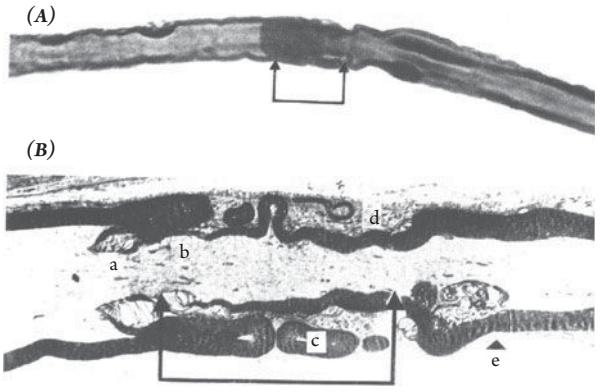

FIGURE 4-8 (***A***) Part of a single teased fiber showing an abnormal node. (***B***) Electron micrograph of nodal region shown in (***A***). a, terminal myelin loops of ensheathing paranode; b, terminal myelin loops of ensheathed paranode; c, myelin fold of ensheathing paranode cut tangentially; d, Schwann cell cytoplasm; e, microvilli indicating site of Schwann cell junction. Large arrows show length of ensheathed paranode (approx. 20 μm). (From Ochoa, Fowler and Gilliatt,[104] with permission.)

an additional factor. Unexpected NCS abnormalities in asymptomatic subjects suggest a high incidence of subclinical entrapment neuropathy. Routine autopsies in patients without known disease of the peripheral nerve also documented unpredicted focal anatomic abnormalities.[99].

Patients with demyelinating neuropathy develop paralysis as a sign of conduction block, not slowed conduction velocity, which in itself causes no clinical symptoms. The paralyzed muscles may show fibrillation potentials and positive sharp waves following a prolonged lack of neural influence, despite the structural integrity of the axons. In one study of 31 patients,[137] 25% developed spontaneous discharges solely on the basis of a conduction block lasting more than 14 days, and 75% as the result of axonal degeneration.

Axonotmesis and Wallerian Degeneration

In this condition, axonal damage of motor fibers results in loss of continuity and wallerian degeneration of the distal segment followed by denervation-induced muscle atrophy (Fig. 4-9).[90] Conduction ceases immediately across the site of nerve injury followed by irreversible loss of excitability, first at the neuromuscular junction, then the nerve segment distal to the site of injury associated with degeneration of the axons.[21] The onset of such change varies among different species but generally not until 4 or 5 days following acute interruption in animal studies. In clinical evaluation, different axons do not necessarily lose excitability simultaneously, showing progressive decline in amplitude over a range of several days (see Fig. 8-3 in Chapter 8). The proximal stump also undergoes relatively mild retrograde changes with nerve conduction abnormalities secondary to the effect of injury as well as collateral sprouting of uninjured axons.[53] Structurally, sodium channels show reorganization not only in the cutaneous afferent cell bodies but also their axons following disconnection of the peripheral target organ.[115] Partial peripheral motor nerve lesions also induce changes in the conduction properties of the remaining, intact motoneurons perhaps associated with compensatory sprouting.[58]

An experimental axotomy in cats caused degeneration of sensory fibers more quickly than motor fibers of similar diameter and reduced the velocities of the fast-conducting fibers at the most rapid rate.[95] This does not seem to hold true in human studies, which often show a loss of muscle potentials a few days before sensory potentials, although the initial failure of the neuromuscular transmission in part accounts for this discrepancy. Permanent axotomy in cats produced by hind-limb ablation results in sequential pathologic alteration of myelinated fibers of the proximal nerve stump, namely, axonal atrophy, myelin wrinkling, nodal lengthening, and internodal demyelination

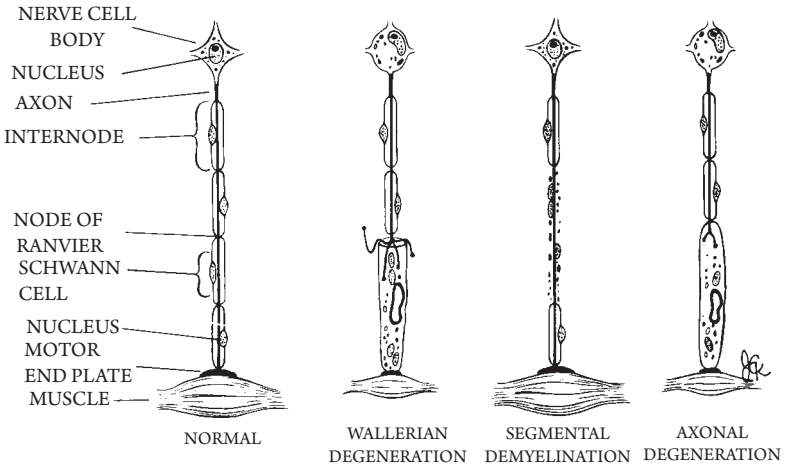

FIGURE 4-9 Schematic representation of nerve axon and myelin sheath. From left to right, normal structures, wallerian degeneration following transection of the fiber, segmental demyelination, and axonal degeneration secondary to disorders of the nerve cell. (From Asbury and Johnson,[6] with permission.)

and remyelination.[35] In the baboon, the muscle response to nerve stimulation disappears 4 or 5 days after nerve section, but an ascending nerve action potential may persist in the segment distal to the section for 2 or 3 more days.[49] Preceding conduction failure, the maximal conduction velocity remains the same whether calculated by the descending motor potential or ascending nerve action potential. Histologically, degeneration develops in the terminal portion of the intramuscular nerve at a time when the proximal parts of the same fibers show relatively little change. This finding seems to counter the view that distal stump undergo dying forward degeneration from the injury site as evidenced by peripheral axonal motor degenereation after spinal cord infarct.[94] The central stump of a transected nerve fiber, though excitable, may show reduction in nerve action potentials and conduction velocity.

Chronic ligation at peripheral nerves initially induces a transient, focal conduction slowing or block at the site of constriction, followed by more protracted distal effects ranging from loss of excitability to slowed conduction.[80] A persistent nerve constriction also results in axonal atrophy and a reduction in motor conduction velocity distal to the ligature. Studies in guinea pigs suggest that atrophic nerve fibers distal to a persistent constriction may become particularly sensitive to local pressure.[121] This experimental finding gave a theoretical rationale for the clinically disputed concept of double crush syndrome (see Chapter 25-5). A tight constriction of the nerve distal to the crush site also adversely influences the process of regeneration as demonstrated in cat studies using special cuff electrodes suitable for repeated studies.[80]

The process of regeneration accompanies the transport of structural proteins newly synthesized in the cell body to the multiple sprouts derived from the parent axon. Once the axon successfully reaches the periphery and reestablishes the physiologic connections, an orderly sequence of maturation takes place and fiber diameter progressively increases. The remaining sprouts that fail to make functional reconnection will eventually degenerate. The Schwann cell basement membrane and the remaining connective tissues, if intact, help the nerve axon to regenerate in an orderly manner along the nerve sheath. The axons grow at a rate of approximately 1 to 3 mm per day, eventually restoring nearly the normal number and size of fibers. Functional recovery, however, remains poor if nerve injury severs the peripheral axon at a proximal site far from their target organs.[51]

Available data lack detailed electrophysiologic information to precisely characterize dying forward conduction abnormalities during wallerian degeneration in humans.[94] In one series, muscle amplitudes fell 50% in 3 to 5 days and abated completely by the

ninth day after injury. Sensory amplitudes declined 50% in 7 days and disappeared by the eleventh day. Shorter distal stumps showed an earlier loss of amplitude.[21] In two cases, serial studies revealed loss of action potentials as early as 185 hours in one case and 168 hours in the other after traumatic transection of the digital nerve. Conduction studies showed a normal velocity during wallerian degeneration prior to the loss of recorded response.[110] During the first few days after nerve injury, studies of distal nerve excitability fail to distinguish axonotmesis from neuropraxia. Finger amputation[117] resulted in permanent retrograde change of the digital nerve as evidenced by a reduction in amplitude of the digital nerve potential. Histologic studies revealed a decrease in axon diameter rather than the number of nerve fibers.[23,25–26] Other types of axonotmesis include nerve injuries caused by injections and tourniquets,[149] sustained high-intensity electric stimulation,[2] and cold injury (see Fig. 5-13 in Chapter 5).[1,63]

Severe compressive neuropathy may at times provide the opportunity to study a single motor axon showing a discrete abnormality.[97] Otherwise, different types of changes coexist in the majority of nerve injuries and neuropathies. Thus, categorizing injuries of a nerve, as opposed to individual nerve fibers, depends on less precise definition. Nonetheless, electrophysiologic studies help elucidate the extent of axonal damage. Nerve stimulation above the site of the lesion reveals a reduced amplitude in proportion to the degree of conduction loss but fails to distinguish neurapraxia from axonotmesis. In either condition, unaffected axons, if present, conduct at a normal velocity across the segment in question. Stimulation of the nerve segment distal to the site of the lesion helps differentiate the two entities, eliciting a small response in axonotmesis after the first few days of injury and a normal response in neuropraxia reflecting axonal integrity. Electromyography (EMG) shows positive sharp waves 1–2 weeks and fibrillation potentials 2–3 weeks after axonotmesis. Rarely, distal nerve inexcitability may develop without frank axonal degeneration after a proximal nerve lesion.[92] In these cases, a quick recovery suggests changes in the number or property of sodium channels as the cause of the initial inexcitability of the distal axons.[37]

Neurotmesis and Nerve Regeneration

Sunderland[129] has proposed three subdivisions of Seddon's neurotmesis. In the first type, the injury damages the axon and surrounding connective tissue, preserving the architecture of the nerve sheath. Unlike the central nervous system pathways,[70] the peripheral nerve regenerates effectively after this type of injury though less completely than in axonotmesis. Misdirected sprouting leads to innervation of muscle fibers previously not supplied by the nerve. The clinical phenomenon of synkinesis probably indicates an antecedent nerve injury of at least this severity.[79, 131] In the second type that involves the nerve sheath as well, the nerve barely maintains the continuity, although it may look grossly intact on inspection. Some poorly oriented regeneration may occur for myelinated as well as unmyelinated axons, usually necessitating surgical intervention, including sensory-motor differentiated nerve repair.[32] The third type represents a complete separation of the nerve with loss of continuity. Surgical repair consists of suturing the stumps, usually with a nerve graft to bridge the gap, and the use of immunosuppression.[40,98] The storage of nerve grafts, if feasible, serves as a possible alternative to conventional method. Sometimes, nerve anastomosis, from spinal accessory nerve to facial nerve, for example, may achieve a better cosmetic and functional outcome.

Despite the advent of microsurgical techniques, functional recovery following peripheral nerve lesion remains inadequate.[89] The poor motor function restoration primarily reflects the limited capacity of injured axons to regenerate across the lesion site and select the appropriate target to reinnervate. Collateral reinnervation of posterior cricoarytenoid muscle by the superior laryngeal nerve after recurrent laryngeal nerve injury in rats also attests to the importance of intramuscular sprouting.[62] The complex factors guide regenerating axons toward appropriate terminations, which include, among others, neurite promoting factors, chemotactic influences, and properties of the extracellular matrix.[119] The average axon diameter in the proximal segment of a transected and reconstructed peripheral

nerve will decrease shortly after the injury and increase again when the regenerating axons make contact with their targets. As some axons reach their target organs and start to mature, others still in search of the destination will abate, retarding the expected maturational increase in compound nerve action potential.[83] In adult cats, conduction velocities recover faster after crushing than after sectioning the mixed nerve, reaching 60%–70% of control values.[45] Studies in rats indicate that afferent activities also undergo major modification after nerve repair by self-anastomosis.[31]

During regeneration, motor axons enter any muscles in an almost random fashion, sometimes even from the homologous contralateral motoneurons.[79,87] Thus, after nerve repair, especially with proximal injury, aberrant reinnervation abounds, accounting for a poor quality of functional restoration (see Fig. 8-15 in Chapter 8).[8,79,127] Proprioceptors and other sensory axons may also reinnervate inappropriate end organs, sometimes giving rise to abnormal connections between sensory and motor fibers.[81] Misdirected axon regrowth, without central adaptation, leads to faulty tactile digit localization.

Regeneration may progress poorly with frequent formation of neuroma and pain associated with spontaneous discharges of nerve impulses.[147] Changes in membrane properties may result from accumulation of sodium channels at injured axonal tips.[37] Their intraneuronal heterogeneity may account for interaction among different populations of sodium channels in cutaneous afferents, one population activating the other, leading to membrane instability.[113] Following re-anastomosis of the nerve, regenerating nerve fibers gradually increase in number and in size over many years, although they regain neither the original number nor diameter.[106] The conduction velocity increases slowly, reaching 60% of the normal value within 4 years[59] and a mean value of 85% after 16 years.[125] Persistent prolongation of the distal latencies suggests the presence of a limited number of fibers distally. Metabolic recoveries of the denervated muscle follow a similar time course as the sequentially tested conduction characteristics of the damaged nerve.[85] Clinical electrophysiology helps evaluate nerve injury and regeneration quantitatively.[34] The force produced by the reinnervated muscle depends on the length of time the muscle remained denervated.[43]

In detailed sequential studies of the median nerve after complete section and suture in three patients,[17] the regeneration took place at an average rate of 1.5 to 2.0 mm per day. The sensory potential, when first recorded 3–4 months after the injury, propagated very slowly at a velocity between 10% and 25% of normal. The conduction velocity increased 3% per month during the first 2 years and 10 times slower thereafter. In the adults, the tactile sensibility returned to normal by 40 months, when the sensory potential showed a normal amplitude but an increased duration, measuring 5 times greater than the control, and conduction velocity reached 65%–75% of normal. In children, the same degree of recovery occurred 13 to 19 months after anastomosis. The sensory potential returned 5 times faster after a compressive nerve lesion than after section and repair. Nerve regeneration after cold injury followed a similar course (see Fig. 5-13 in Chapter 5).

A few studies have dealt with neurophysiologic changes, which characterize the recovery of human peripheral nerves after repair with an autogenous nerve graft.[81,101] In one series,[132,138] motor and sensory NCS showed sustained improvement after sural nerve grafts of the ulnar and median nerves. Two years after surgery, the motor conduction velocity across the graft itself reached, in most cases, 40%–50% of the normal values obtained in the contralateral limb. In 44% of the nerves, a SNAP returned after 18 months, though greatly reduced in amplitude and conduction velocity. In another study based on experience with 67 injured nerves,[33] voluntary motor unit activity returned 7 months after repair and 12 months after grafting. Nerve stimulation elicited a compound muscle action potential (CMAP) by 10 months after suture and 14 months after graft. Motor unit potentials (MUPs) steadily increased in amplitude with time, but sensory fibers showed poor recovery both clinically and electrophysiologically.

Toe-to-digit transplantation provides an excellent model for study of nerve regeneration as it pertains to the donor and recipient nerves. In one series, the transplanted toe achieved 70%–90% recovery for temperature, pinprick, light touch, and vibration, but to a lesser extent for two-point discrimination.[27] The transplanted toe behaved more like a normal toe than a normal finger with regard to current perception threshold.[26] Conduction studies also showed incomplete recovery in toe-to-digit transplantation as compared with digit-to-digit replantation, which resulted in almost complete repair.[27] The factors responsible for different recovery may include time interval from injury to surgery, size mismatch between recipient and donor nerves, retrograde effects on the recipient nerve, and severity of tissue damage. In a study of transplanted autogenous muscles, motor endplate restored its function in about 6 months with myelination of the grafted nerve.[138] Long-term alterations may persist or develop after regenerated axons have established connections with their targets.[14] Electrophysiologic assessments can provide clinically important information about the localization, severity, and pathophysiology of nerve injuries, although available methods permit only inadequate quantitation of regeneration.

6. TYPES OF NEUROPATHIC DISORDERS

The types of conduction abnormalities after nerve injuries described earlier also form the basis of electrophysiologic assessment of other disease processes, either localized as in entrapment syndromes or more widespread as in polyneuropathies. Histologic and electrophysiologic characteristics indicate the presence of three relatively distinct categories of peripheral nerve disorders (Fig. 4-9): (1) wallerian degeneration after focal interruption of axons as in vasculitis; (2) centripetal or dying-back degeneration from metabolic derangement of the neuron or axons, that is, neuronopathy or axonopathy; and (3) segmental demyelination. Of these, wallerian and axonal degeneration cause denervation with reduction in amplitude of compound action potentials, whereas demyelination shows slowed nerve conduction velocities with or without a conduction block.

Axonal Degeneration

This abnormality, in addition to axonal neuropathies, results from injury or mechanical compression of the nerve. Other possible causes include application of toxic substances causing death of the cell body and exposure to vibration.[30] Nerve ischemia, if sufficiently prolonged, also induces axonal degeneration, affecting large myelinated fibers first followed by smaller myelinated fibers and unmyelinated axons.[46] The extent of abnormality varies with location of occlusion.[84] Single-unit recording in dying-back axons has confirmed the earliest failure of impulse generation in the nerve terminal when it still propagates normally throughout the remainder of the axon.[126]

Neuropathies with this type of abnormality include those associated with alcoholism, uremia, polyarteritis nodosa, acute intermittent porphyria, some cases of diabetes and carcinoma, and most cases of toxicity and nutritional deficiency (see Chapter 24). Most axonal neuropathies affect both sensory and motor fibers as exemplified by uremic neuropathies and amyloidosis. Motor abnormalities prevail in acute intermittent porphyria and hereditary motor sensory neuropathy (HMSN) Type II or neuronal type of Charcot-Marie-Tooth disease (CMT). In contrast, sensory changes predominate in the majority of toxic or metabolic polyneuropathies, Friedreich's ataxia, and some cases of carcinomatous neuropathies. Not all the peripheral neuropathies with a distal predominance qualify as truly dying back in type. Selective loss of the perikarya and axons of the longest and largest fibers can produce the same pattern of abnormality.[15] Distally predominant symptoms do not necessarily indicate a distal pathologic process, according to probabilistic models that reproduce a distal sensory deficit on the basis of randomly distributed axonal lesions.[152] In some neuropathies, studies fail to reveal the exact site of the primary damage responsible for axonal degeneration.

In neuropathies secondary to diabetes, alcoholism, carcinoma, or uremia, axonal

degeneration initially involves the most terminal segment of the longest peripheral nerve fibers. Thus, studies show a slower conduction velocity over the same nerve segment if calculated based on latencies to a distal muscle as compared with a proximal muscle.[112] The distal predominance of pathology and its centripetal progression led to the term *dying-back neuropathy*. Less commonly encountered conditions associated with the dying-back phenomenon include thiamine deficiency, triorthocresyl phosphate neuropathy, acute intermittent porphyria, and experimental acrylamide neuropathies. In these conditions, impaired axoplasmic flow initially affects the segment of the nerve furthest from the perikaryon. Thus, primary involvement of the neurons leads to axonal degeneration in the distal segment most removed from the trophic influence of the nerve cell.

Needle EMG reveals normal MUPs that recruit poorly during the acute stage of partial axonal degeneration. To compensate for the loss of axons, remaining units tend to fire rapidly. Fibrillation potentials and positive sharp waves develop in 2–3 weeks after the onset of illness. Axonal degeneration, if mild, affects NCS only minimally, especially in diseases primarily involving the small-diameter axons.[140] More commonly, selective loss of the large, fast-conducting fibers results in reduced amplitude and mild slowing of conduction below the normal range, especially when recorded from distal as opposed to proximal muscles.[115] In these cases, the reduction in size of the CMAP or SNAP shows a correlation to the degree of slowing in nerve conduction.[29,134] The physiologic criteria (see Chapter 5-4) help minimize misclassifying a neuropathy with predominantly axonal loss as demyelinating.[88]

Anterior horn cell diseases can also cause selective loss of the fastest fibers. In poliomyelitis, the motor nerve conduction velocity may fall below the normal value, usually in proportion to the decrease in amplitude. For the same reason, patients with a motoneuron disease have slightly reduced motor conduction velocities. Slower conduction in patients with more severe atrophy may, however, in part reflect lowered temperature of the wasted limbs (see Chapter 5-6).

Segmental Demyelination

Experimental autoimmune neuritis serves as one of the most useful animal models for pathogenetic studies of demyelinative neuropathies.[122,128,135] In animal experiments, demyelination blocks the transmission of nerve impulses through the affected zone as well as dorsal root ganglion.[122] The slowed conduction results primarily from delayed nerve impulses passing through the lesion and not simply from selective block of transmission in the fast-conducting fibers. Experimental conduction block may also result from serum containing anti-GM1 antibodies,[116] affecting sodium channels[41,141] at the nodes of Ranvier, where GM1 abounds.[28] In antiserum-mediated focal demyelination of male Wistar rats, conduction block began between 30 and 60 minutes after injection and peaked within a few hours.[128] Paralysis of the foot muscles persisted until about the seventh day, when low-amplitude, long-latency muscle action potentials returned for the first time. The strength gradually recovered thereafter, reaching a normal level by the sixteenth day. Morphologic studies revealed evidence of remyelination with 2 to 8 myelin lamellae around each axon coincident with the onset of clinical and electrophysiologic recovery. Conduction velocities returned to pre-injection values by the thirty-seventh day, when the myelin layer of remyelinating fibers averaged only about one-third that of control nerves.

The safety factor of transmission, defined as a ratio of the action current available at a node to the threshold current, must exceed unity for successful conduction through a node (see Fig. 2-3 in Chapter 2). In the presence of paranodal or segmental demyelination, the action current dissipates through the adjacent internode as a consequence of increased capacitance and decreased impedance of the demyelinated region. Because it takes longer to charge the next nodal membrane to the threshold, this leakage current prolongs the internodal conduction time, slowing the conduction velocity. Reorganization of sodium channels also plays an important role in the pathophysiology of demyelination.[93,102] Thus, segmental demyelination causes unequivocal reduction of nerve conduction velocity, commonly, though not always, substantially below

the normal range. Axonal degeneration cannot account for this degree of slowing even with selective loss of the fast-conducting fibers leaving only the slow-conducting fibers relatively intact (see Chapter 5-4).

With advanced demyelination the safety factor eventually falls below unity, and the conduction fails because the local current no longer depolarizes the next node of Ranvier beyond threshold. Raising the body temperature quickens the closure of activated sodium channels, which reduces the amplitude of action potentials, further lowering the safety factor. Thus, demyelinated nerves suffer from temperature-induced impulse blocking, which does not affect healthy nerves with a large margin of safety.[22,44] Conversely, administration of 4-aminopyridine, which enhances action potential by blocking potassium channels,[52] partially reverses symptoms in patients with multiple sclerosis,[13] but not in those with inflammatory demyelinating neuropathies.[7]

Normal nerves can transmit impulses at high rates over several hours with the maximal firing frequency of 50 to 70 Hz under physiologic conditions. By contrast, demyelinated nerve fibers may show rate-dependent failure (Fig. 4-10), showing conduction block at higher frequency, causing a rapid fatigue (Fig. 4-11).[64,65,82] Other neuropathies, such as acute streptozotocin-induced diabetes, may show similar rate-dependent conduction abnormalities.[5] With this type of block, information coded in frequencies up to 250 Hz or more may fail in the central nervous system and peripheral sensory nerves. The physiologic factors

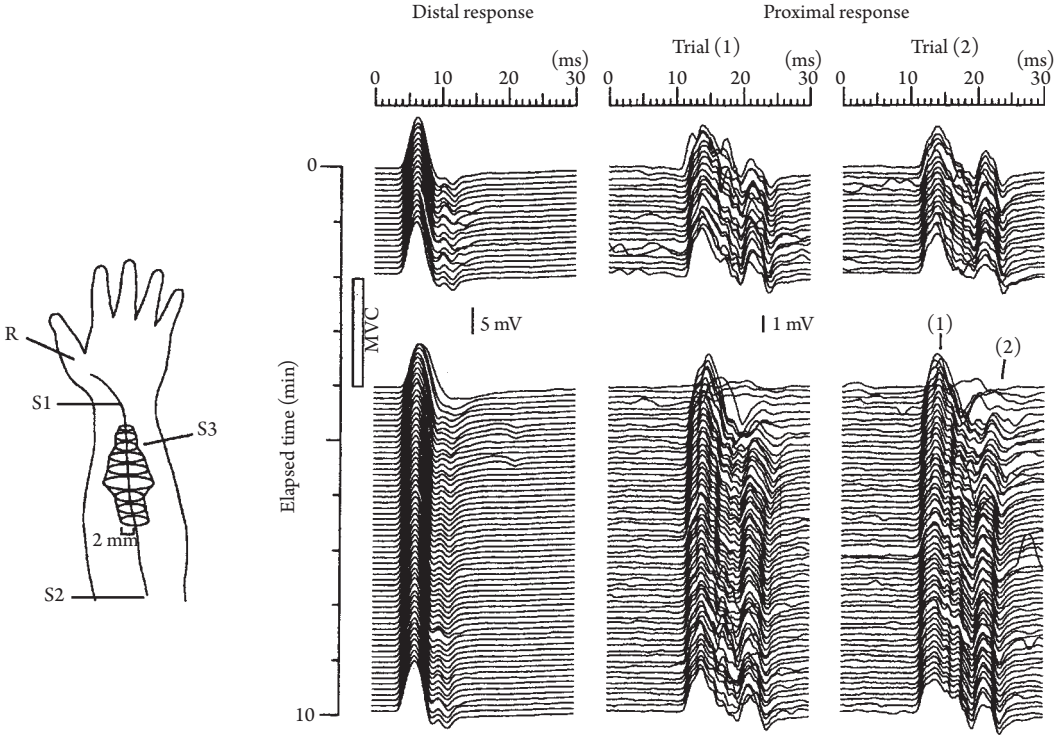

FIGURE 4-10 Serial recordings of distal and proximal responses before and after a 2-minute maximal voluntary contraction in a patient with multifocal motor neuropathy. The illustration on the left shows electrode locations in relation to the extent and size of the lesion, as measured on magnetic resonance imaging (MRI). R, recording site over abductor pollicis brevis; S1, stimulation for distal response; S2, stimulation for proximal response; S3, stimulation for nerve excitability monitoring. The compound muscle action potential waveforms from trial 1 and trial 2 for the proximal responses showed initial reduction in amplitude and subsequent recovery compared to distal responses. The latencies of the second peak (2) returned gradually to the baseline. (From Kaji, Bostock, Kohara, et al.[65])

that dictate the critical frequency for block in demyelinated segment include fiber geometry, sodium-potassium pump activation, and ion channel density.

Demyelinated axons tend to compensate for current dissipation by sustaining action current, thus increasing the influx of sodium into the axon. High sodium concentration in turn activates the electrogenic sodium-potassium pump, which, removing sodium in exchange for potassium at a 3 to 2 ratio, hyperpolarizes the nodal membrane. A raised threshold with hyperpolarization lowers the safety factor below unity in demyelinated segments, especially after high-frequency transmission, leading to a conduction block (see Fig. 2-3 in Chapter 2). Therapeutic strategy in animal models exploits digitalis, which specifically inhibits the sodium-potassium pump, thus circumventing rate-dependent conduction block by pump activation. The use of these agents, however, cannot serve as a general therapeutic approach in humans because of possible cardiac side effects.[66]

Clinical Consequences of Demyelination

The pathophysiology of demyelination and its clinical consequences[64,67,77] include (1) axonal excitability changes and conduction block resulting in clinical weakness and sensory loss; (2) increased desynchronization of volleys causing pathological temporal dispersion of waveforms, loss of reflexes, and reduced sensation; (3) prolonged refractory periods with frequency-dependent conduction block especially at very high firing rates, accounting for reduced strength during maximal voluntary muscle contraction effort; (4) exaggerated hyperpolarization after the passage of impulse, inducing conduction block even at low firing frequencies causing fatigue after mild but sustained effort; and (5) steady, ectopic discharges or sporadic bursts at sites of focal demyelination considered responsible for focal myokymia and spontaneous or mechanically induced paresthesias. A complete conduction block accompanies a major loss of strength, whereas slowing

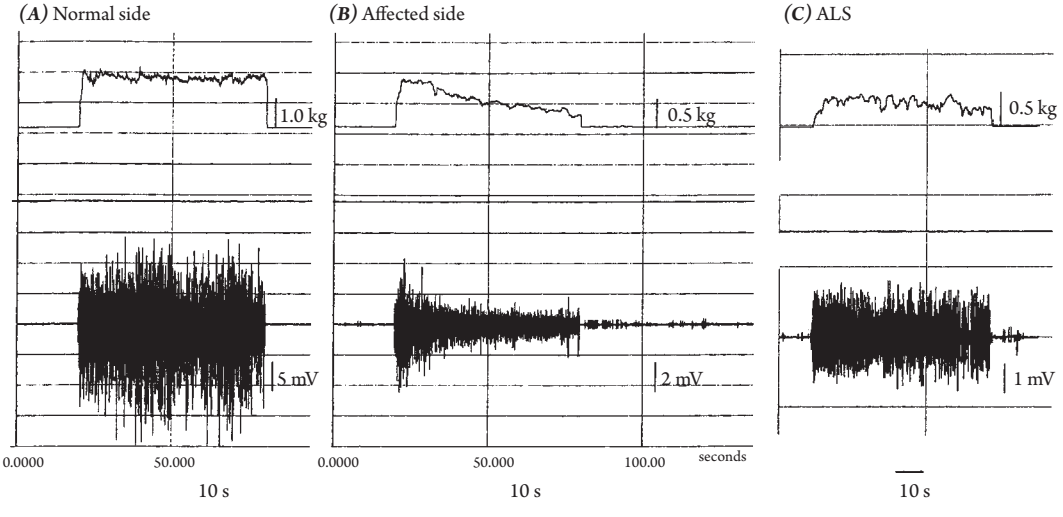

FIGURE 4-11 Force measurement (upper traces) and surface electromyography (EMG) (lower traces) during 1-minute maximal voluntary contraction of the abductor digiti minimi muscle on the normal side (***A***) and the affected side (***B***) in a patient with multifocal motor neuropathy and of the abductor pollicis brevis muscle in a patient with amyotrophic lateral sclerosis (ALS) (***C***). Note the inability to maintain force (i.e., fatigue) and the decline in EMG during the contraction of the affected muscle (***B***), and the development of myokymic discharges after the contraction. The ALS patient had both lower and upper motoneuron signs in the limb tested. (From Kaji, Bostock, Kohora, et al.[65])

of conduction by itself leads to few, if any, clinical symptoms, as long as the impulses arrive at the target organ. A prolonged refractory period for transmission, though helpful as a diagnostic indicator,[50] also causes no symptoms because it does not interface with voluntary discharges firing at 10–50 Hz. Nonetheless, these measures offer potentially important clues to identify demyelination, although similar conduction abnormalities can also result from sodium channel blockage by toxins.[54] Demyelinating diseases of the peripheral nerve (see Chapter 24-3) include the Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), myelomatous polyneuropathy, HMSN Type I or hypertrophic type of CMT, hereditary neuropathy with susceptibility to pressure palsies (HNPP), metachromatic leukodystrophy, Krabbe's leukodystrophy, some cases of diabetic and carcinomatous neuropathies, and diphtheritic polyneuritis, which no longer affect humans very often. Chronic lead intoxication, known to induce segmental demyelination experimentally, shows either normal or only mild conduction abnormalities in human cases.

Demyelinative process affects the nerve throughout its length uniformly in most hereditary neuropathies, delaying conduction at all the nodes of Ranvier. By contrast, acquired demyelination tends to involve certain parts of the nerve with nonuniform slowing of nerve conduction accompanied by conduction block.[42] This finding, however, may also appear as an early sign of reversible injury in ischemic neuropathy.[68] Conventional NCS, basically designed for assessment of the distal segments, may fail to elucidate a more proximal demyelinating lesion.[74] In some cases, the slight loss of fibers or the mild degree of demyelination demonstrated histologically cannot account for the degree of slowing seen in NCS. In diseases affecting smaller fibers out of proportion to the larger fibers, an increased range of conduction velocity broadens the evoked potential by pathological temporal dispersion. Desynchronization of the nerve volley may also result from repetitive discharges at the site of axonal injury after the passage of a single impulse. In EMG studies, an MUP, though normal in amplitude and waveform, recruits poorly, indicating a failure of transmission through demyelinated fibers. Unless damage of the myelin sheath leads to secondary axonal degeneration, EMG reveals little or no evidence of denervation.

In the arbitrary division into axonal and demyelinating types, few cases fall precisely into one group or the other. The mixed category includes neuropathies associated with diabetes, uremia, myeloma, and Friedreich's ataxia. Extensive demyelination may accompany slight axonal degeneration, possibly through inflammatory reaction. Conversely, axonal atrophy proximal to a neuroma or distal to constriction may cause secondary paranodal demyelination in the presence of healthy Schwann cells. Axonal enlargement can also cause secondary demyelination as in hexacarbone intoxication (see Chapter 24-4) and giant axonal neuropathy (see Chapter 24-5). Despite the possibility of mixed abnormalities, the electrophysiologic finding can substantiate demyelinating component even when superimposed upon moderate axonal degeneration.

Conduction abnormalities consistent with demyelination[16,29,88] include reduction of conduction velocity below 70%–80% of the lower limit, prolongation of distal motor or sensory latency and F-wave latency above 120% of the upper limit, and the presence of unequivocal conduction block.[3,71] The lack of these criteria, however, does not necessarily preclude demyelination as absence of evidence constitutes no evidence of absence. For example, a number of patients with GBS may show no major conduction changes during the initial stages. Beyond such a broad classification, electrical studies have limited value in distinguishing one variety of neuropathy from another. In particular, conduction studies and EMG rarely elucidate a specific etiology. Furthermore, routine conduction studies fail to document abnormalities of small-caliber nerve fiber. These limitations notwithstanding, an NCS can provide diagnostically pertinent information, if used judiciously in appropriate clinical contexts.[76,78]

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5

Principles of Nerve Conduction Studies

Abbreviations: AIDP—acute inflammatory demyelinating polyneuropathy, CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, CTS—carpal tunnel syndrome, E1—active electrode, E2—reference electrode, EMG—electromyography, FFP—far-field potential, FWCV—F-wave conduction velocity, MNCV—motor nerve conduction velocity, MUP—motor unit potential, NCS—nerve conduction study, NMT—neuromuscular transmission, SNAP—sensory nerve action potential

1. INTRODUCTION

With steady improvement of recording apparatus, nerve conduction studies (NCSs) have become a simple and reliable test of peripheral nerve function. With adequate standardization, the method now provides a means of not only objectively identifying the lesion but also precisely localizing the site of maximal involvement.[62] Electrical stimulation of the nerve initiates an impulse that travels along motor or sensory nerve fibers. The assessment of conduction characteristics depends on the analysis of compound evoked potentials recorded from the muscle in the study of motor fibers and from the nerve itself in the case of sensory fibers. The same principles apply in all circumstances, although the anatomic course and pattern of innervation dictate the exact technique used for testing a given nerve. Clinical utility of automated devices for simplified NCS waits for further confirmation.[72] In addition to electrical

shocks, used in most clinical studies, other less commonly used modes of stimulation include magnetic (see Chapter 20-4) and tactile stimulation (see Chapter 10-5).[7] Assessment of mechanical characteristics helps delineate contractile properties of the muscle twitch induced by stimulation of the nerve.[47, 120]

2. ELECTRICAL STIMULATION OF THE NERVE

Cathode and Anode

Surface electrodes, usually made of silver plate, come in different sizes, commonly in the range of 0.5 to 1.0 cm in diameter. Stimulating electrodes consist of a cathode, or negative pole, and an anode, or positive pole, so called because they attract cations and anions. As the current flows between them, negative charges that accumulate under the cathode, by making inside the axon relatively more positive than outside, depolarize the nerve or cathodal depolarization. Conversely, positive charges under the anode hyperpolarize the nerve, although not to the extent of blocking the conduction during routine studies.[28] In bipolar stimulation with both electrodes over the nerve trunk, placing the cathode closer to the recording site avoids anodal conduction block, if any. Alternatively, locating the anode away from the nerve trunk also prevents its hyperpolarizing effect. Accurate calculation of conduction velocities depends on proper measurements of the distance between the consecutive cathodal points used to stimulate the nerve at multiple sites. A clear labeling of the stimulating electrodes avoids inadvertent misidentification of the anode for the cathode at one stimulus site, which would lead to an erroneous result.

Types of Stimulators

Most commercially available stimulators provide a probe that mounts the cathode and the anode at a fixed distance, usually 2 to 3 cm apart. The intensity control located in the insulated handle, though bulky, simplifies the operation for a single examiner. The ordinary banana plugs connected by shielded cable also serve well as stimulating electrodes. The use of a large diameter electrode for stimulation lowers current density in the skin, causing less pain, although the exact site of nerve activation becomes uncertain.[136] Some electromyographers prefer a monopolar stimulation with a small cathode placed on the nerve trunk and a large anode over the opposite surface in the same limb. The use of a subcutaneously inserted needle as the cathode reduces the current necessary to excite the nerve compared to surface stimulation. A surface electrode located on the skin nearby or a second needle electrode inserted in the vicinity of the cathode serves as the anode. The maximum current during such stimulation causes neither electric nor heat damage to the tissue.[93]

In constant-voltage stimulators (see Chapter 3-6), current output varies inversely with the impedance of the electrode, skin, and subcutaneous tissues. In constant-current units, the voltage changes according to the impedance to regulate the amount of current that reaches the nerve within certain limits of the skin resistance. Either type suffices for clinical use, provided that the stimulus output has an adequate range to elicit maximal muscle and nerve action potentials in all patients. A constant-current unit serves better for serially assessing the level of shock intensity as a measure of nerve excitability (see Chapter 10-4).

Stimulus Intensity and Possible Risk

The square-wave output usually varies from 0.05 to 2.0 ms in duration and 10 to 500 V in amplitude. Surface stimulation required to fully activate the healthy nerve ranges from 0.1 to 0.5 ms in duration and 100 to 400 V, or 10 to 40 mA assuming a tissue resistance of 10 KΩ, in intensity. This does not necessarily hold in an obese subject with massive subcutaneous tissue, which tends to dissipate the induced current. This accounts for considerable regional variability of average shock intensities used in electrophysiologic assessment (for example, high in Iowa and low in Kyoto). A study of diseased nerves with decreased excitability may call for a maximal output of 400 to 500 V, or 40 to 50 mA, and considerably longer durations up

to 2 ms. Electrical stimulation within the aforementioned intensity range delivered in the limbs or face ordinarily causes no risk even in patients with implanted cardiac devices.[83,116] Any current, if delivered close enough, however, could inhibit a cardiac pacemaker.[117] Special care to safeguard such a case includes placement of proper grounding between the electrically sensitive device and the nerve stimulator located at a sufficiently distant site.[4]

In patients with indwelling cardiac catheters or central venous pressure lines inserted into the heart, all the current may directly reach the cardiac tissue. This possibility makes routine nerve conduction studies contraindicated. Implanted cardioverters and defibrillators also pose safety hazards, usually making electric stimulation near the device unwarranted. Consultation with a cardiologist with special expertise in this area should address feasibility of a nerve conduction study in any patients using such a medical instrument and the need to turn off the system during the procedure. Placing the stimulator at least 6 inches away may minimize the chance of externally triggering the sensor.[87] Electromyographers should always entertain these and other possible problems related to general electrical safety. The patients may not necessarily volunteer their unique risk in this regard unless specifically requested to reveal their medical conditions.

One way to quantify the level of electrical stimuli uses the magnitude of the evoked potential: A threshold stimulus elicits a response in some, but not all, of the axons contained in the nerve. Increasing the duration of stimulation decreases the threshold intensity and prolongs the latency (see Chapter 10-4). A maximal stimulus activates the entire group of axons at or close to its rising edge, independent of its duration. Further increase in shock intensity causes no additional increase in amplitude, although it may shorten the latency, activating the nerve segment away from the cathodal point and closer to the recording electrodes. The current required for maximal stimulation varies greatly from one subject to the next and from one nerve to another in the same individual. A 20% supramaximal stimulus, used conventionally, has intensity 20% greater than the maximal stimulus, which guarantees excitation of all nerve fibers.

If fibers with large diameters have the lowest threshold in humans, as in experimental animals, then a submaximal stimulus should theoretically suffice for determining the onset latency of the fastest conducting fibers. Although this assumption usually holds, especially with sensory nerves,[106] the exact order of excitation also depends on the spatial relationship of various fibers and the stimulating electrode.[53,95] Electrically evoked activation of motor axons in paralyzed muscle may occur in the reversed order proceeding from smaller to larger motor units.[35] Furthermore, in motor conduction studies, the axon terminal, which partially determines the latency of the muscle response, varies in length within a given nerve. Thus, with submaximal stimuli, the onset latency fluctuates considerably from one trial to the next, depending on the excited axons within a nerve. In extreme cases, the first axons excited may in fact have the longest latencies. The use of supramaximal stimuli, which activate all of the axons, circumvents this uncertainty.

Most commercial stimulators can provide a pair of stimuli at variable intervals as well as a train of stimuli of different rates and duration. Ideally, each of paired stimuli should have independent controls of both duration and intensity. A trigger output for the oscilloscope sweep precedes each stimulus by a variable interval to make a clear marking of the stimulus point on the display. In modern equipment, digital processing allows a more exact determination of stimulation time.

Control of Shock Artifact

The control of a stimulus artifact often poses a major technical challenge in nerve conduction studies. Most electrode amplifiers recover from an overloading input in 5 to 10 ms, depending on the amplifier design and the amount of overload. With the stimulus of sufficient magnitude, an overloading artifact interferes with accurate recording of short-latency responses. Better stimulus isolation from the ground through an isolating transformer serves to reduce excessive shock artifact. Not only does this eliminate amplifier overloading, but it also protects the patient from unexpected current leakage (see Chapter 3-6). The use of the transformer, however, makes it difficult to faithfully

preserve the waveform of the original stimulus. A radio-frequency isolation also minimizes stimulus artifacts while maintaining the original shape of the stimulus better than the transformer. Unfortunately, high-frequency stimulus isolation units generally fail to deliver adequate intensity for supramaximal stimulation. Finally, the use of a fast-recovery amplifier minimizes the problem of stimulus artifacts.[138] Even then, optimal recording of short-latency responses calls for adequate reduction of surface spread of stimulus current.

With excessive surface spread, a square pulse of 0.1 ms duration can affect the active electrode for several milliseconds when recording with high sensitivity to register a small signal. Factors causing a large shock artifact include less separation between stimulus and recording sites and greater distance between the active (E1) and reference (E2) electrodes. The use of stimulator leads with no shield can also induce a large artifact, especially if placed near the recording electrodes. Wiping with alcohol helps dry the moist skin surface before the application of the stimulus, which in turn limits surface spread of stimulus current and ensures an optimal recording of short-latency responses. Adequate preparation of the stimulating and recording sites reduces the skin resistance. Surface grease will dissolve if cleaned with ether. Callous skin needs gentle abrasion with a dull knife or fine sandpaper. Rubbing the skin with a cream or solvent of high conductance lowers the impedance between the electrode and the underlying tissue. Theoretically, placement of a ground electrode between the stimulating and recording electrodes diminishes the stimulus artifact. In practice, an alternative location may suffice with the use of a modern fast-recovery amplifier.

3. RECORDING OF MUSCLE AND NERVE POTENTIALS

Surface and Needle Electrodes

Surface electrodes with a larger recording radius serve better than needle electrodes to register the total contributions from all discharging units in assessing a compound muscle action potential (CMAP). Its onset latency indicates the conduction time of the fastest motor fibers, and its amplitude, the number of available motor axons. Averaging technique, though ordinarily unnecessary, may help evaluate markedly atrophic muscles. A needle electrode, despite its small recording radius and inability to register the total muscle activity under study, has its place in identifying the activity from a small muscle when surface recording fails. Its use also improves segregation of a target activity from neighboring discharges after proximal stimulation, which tends to excite unwanted neighboring nerves simultaneously. Single fiber electromyography (EMG) may document minimal conduction abnormality affecting individual nerve axons, which may escape detection by surface recording.[91]

Like motor studies, surface electrodes also suffice for recording sensory and mixed nerve action potentials. Many laboratories now use ring electrodes placed around the proximal and distal interphalangeal joints to record the antidromic sensory potentials from the digital nerves. Individual stimuli usually give rise to sensory nerve action potentials (SNAPs) of sufficient amplitude with careful preparation of the skin before the application of electrodes. Thus, studies of the commonly tested nerves require no averaging except when dealing with pathologically reduced signals. Its routine use to compensate for sloppy recording amounts to a poor excuse for a bad technique. Some electromyographers use needle electrodes placed perpendicular to the nerve to improve the resolution.[132] With this technique, the amplitude of the recorded potential increases by a factor of 2–3 times.[106] The combination of the two effects enhances the signal-to-noise ratio by about 5 times and, when averaging, reduces the time required to reach the same resolution considerably. Measuring SNAP electrical power may improve detection of axonal loss, although its clinical value remains undetermined.[101]

Sweep Speed and Amplifications

The same principles of amplification and display apply to NCS and EMG (see Chapter 3-3). Instead of continuous runs, a prepulse triggers the sweep followed, after a short delay, by the stimulus. This arrangement allows a precise measurement of the time interval between the stimulus and the onset

of the evoked potential. The magnitude of the potential under study dictates the optimal amplifier sensitivity for determination of the recorded response and establishing the normal range.[48] Overamplification results in truncation of the recorded response, whereas underamplification obscures the exact takeoff from the baseline for accurate measurements of the onset latency.

A 1.0 mV muscle action potential, if amplified 1000 times, causes a 1-cm vertical deflection on the oscilloscope at a display setting of 1 V/cm. A much smaller sensory or mixed nerve action potential, on the order of 10 μV, requires a total amplification of about 100,000 times. With such a high gain, the amplifier must have a very low inherent noise level. The use of low-pass filters helps to further reduce such high-frequency interference. The electrode amplifier should provide differential amplification with a signal-to-noise discrimination ratio close to 100,000:1 and an input impedance greater than 1 megohm. It should respond to frequencies of wide bandwidth ranging from 2 Hz to 10 kHz without undue distortion.

Averaging Technique

Conventional techniques fail to detect signals within the expected noise level of the system. Interposing a step-up transformer between the recording electrodes and the amplifier improves the signal-to-noise ratio as does placing the first stage of the amplifier near the electrode site with a remote preamplifier box. The use of digital averaging represents a major improvement over the photographic superimposition and early averaging with its motor-driven switch and multiple storage capacitors. The electronic devices now in use sum consecutive samples of waveforms that are stored digitally after each sweep triggered by repetitive stimulation.

The voltage from noise that has no temporal relationship to stimulation in successive tracings will average close to zero at each time point after stimulus onset. In contrast, signals time-locked to the stimulus will sum at a constant latency and appear as an evoked potential, distinct, within certain limits, from the background noise. Recording a sensory nerve action potential, for example, averaging can virtually eliminate the background noise up to 50 times but not 100 times the signal.[88] Electrical division of the summated potential by the number of trials will provide an average value of the signal under consideration. Here, the degree of enhancement increases in proportion to the square root of the trial number. Thus, four trials give twice as large a response, whereas nine trials give three times the response. In other words, the signal-to-noise ratio improves by a factor of the square root of 2 by doubling the number of trials.

Display and Storage of Recorded Signals

Modern oscilloscopes provide a very stable time base requiring no marking of calibration signals on the second beam. Consequently, a single channel suffices for most routine nerve conduction studies. Dual or multichannel analysis, however, has a distinct advantage in simultaneous recording of related events. The use of an oscilloscope with a digital storage capacity can display a series of responses with a stepwise vertical shift of the baseline. This facilitates the comparison of successively elicited potentials in waveform and latency. Some automatic devices digitally display the latency based on mathematically defined takeoff from the baseline. When necessary, manual positioning of the marker to the desired spot of the waveform improves accuracy. Conversely, any adjustments inconsistent with the overriding definition may induce measurement errors.

4. MOTOR NERVE CONDUCTION

Stimulation and Recording

Motor conduction studies consist of stimulating the nerve at two or more points along its course and recording CMAP (Fig. 5-1) with a pair of surface electrodes for belly-tendon recording with an active lead (E1) placed on the belly of the muscle and an indifferent lead (E2), on the tendon.[69] Depolarization under the cathode results in the generation of a nerve action potential, whereas hyperpolarization under the anode

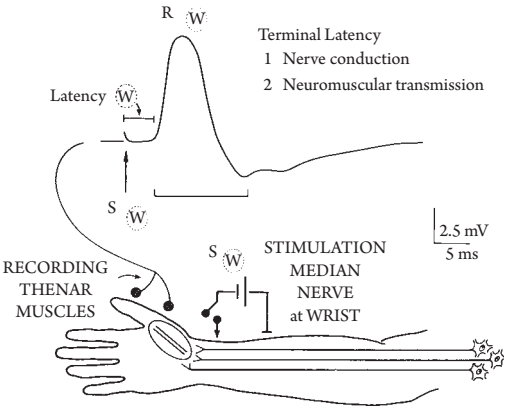

FIGURE 5-1 Compound muscle action potential recorded from the thenar eminence following stimulation of the median nerve at the wrist. The distal or terminal latency includes (1) nerve conduction from the stimulus point to the axon terminal and (2) neuromuscular transmission including the time required for generation and propagation of the muscle action potential after depolarization of the endplate.

tends to block the propagation of the nerve impulse (see Chapter 4-3). Although this poses only theoretical, rather than practical, difficulty in the clinical studies, placing the anode 2–3 cm proximal to the cathode alleviates the concern. With the cathode at the best stimulating site chosen by pulses of moderate intensity, gradual elevation of shock intensity elicits a progressively larger response until it reaches a maximal. The use of a 20% supramaximal intensity activates all the nerve axons innervating the target muscles. Paradoxically, a very high-intensity stimulation, in the range not ordinarily used in the clinical practice, may depolarize the nerve near the anode.[142,144] With stimulation of this type, the shift of the stimulus site from cathode to anode results in erroneous interpretation of measured latencies (see Chapter 11-3).

With belly-tendon recording, the propagating muscle action potential originates under E1 located near the motor point, giving rise to a simple biphasic waveform with an initial negativity (see Chapter 2-4). With inappropriate positioning of the recording electrodes off the motor point, a small positive potential may precede the negative peak. If E1 placed outside the motor point records positivity from one part of muscle and negativity from another, phace cancelation between the two may flatten the initial segment with an apparent delay of onset.[125] This "false" motor point may also result from inadvertent recording from nearby muscles.[6,23] The location of E2 substantially influences the waveform of recorded response,[11,85] especially in the motor conduction study of the ulnar and tibial nerves.[123,127,129,134,147]

The CMAP consists of many motor unit action potentials within the recording radius of the active electrode in the range of 20 mm from the skin surface.[8] A single shock applied to the nerve activates a group of motor units slightly asynchronously because individual nerve axons and muscle fibers differ in length and conduction velocities (see Chapter 11-5). Temporally dispersed impulses result in a degree of phase cancellation depending on the nerve length under study and other multiple factors. The location of the pickup electrodes determines the spacial orientation to the constituent motor units and consequently the pattern of their contribution.[61,69,134] The use of large electrodes tends to reduce the size of CMAP (see Chapter 3-2), although it minimizes the site-induced variability of the recorded potentials.[9]

The usual measurements include (1) latency from the stimulus artifact to the onset of response, defined by either negative or positive deflection from the baseline, (2) amplitude from baseline to negative peak or between negative and positive peaks, and (3) duration from the onset to the first baseline crossing or the final return to the baseline. Electronic integration can provide the area under the waveform, which shows a linear correlation to the product of the amplitude and duration. A latency consists of three components: (1) nerve activation time from application of the stimulus to the generation of action potential, (2) nerve conduction time from the stimulus point to the nerve terminal, and (3) neuromuscular transmission time from the axon terminal to the motor endplate, including the time required for generation of muscle action potential. The onset latency in general measures the fast-conducting motor fibers, although the shortest, but not necessarily fastest, axons may give rise to the initial potential.

Calculation of Conduction Velocity

The motor nerve conduction time equals the latency minus the time for nerve activation, neuromuscular transmission, and the generation of muscle action potential. The latency difference between the two responses elicited by stimulation at two separate points, in effect, excludes these components common to both stimuli. Thus, it represents the time necessary for the nerve impulse to travel from one point of stimulation to the next (Fig. 5-2). Dividing the distance between the stimulus points by the corresponding latency difference derives the conduction velocity. The reliability of results depends on accuracy in determining the length of the nerve segment, estimated with the surface distance along the course of the nerve, and the latency measurements at the two stimulus sites. To recapitulate, the nerve conduction velocity equals

$$\frac{\text{Dmm}}{L_p - L_d \text{ms}} = \frac{D}{L_p - L_d} \text{m/s}$$

where D represents the distance between the two stimulus points in millimeters, and Lp and Ld, the proximal and distal latencies in milliseconds. Stimulation at multiple points along the length of the nerve allows calculation of segmental conduction velocities. Separation of the two stimulation points by at least several, and preferably more than 10 centimeters, improves the accuracy of surface measurement and, consequently, determination of conduction velocity. In the case of restricted lesions, as in a compressive neuropathy, however, the inclusion of longer unaffected segments dilutes the effect of slowing and lowers the sensitivity of the test. Here, incremental stimulation across the shorter segment helps isolate the localized abnormality that may otherwise escape detection (see Chapters 6-3 and 11-7).

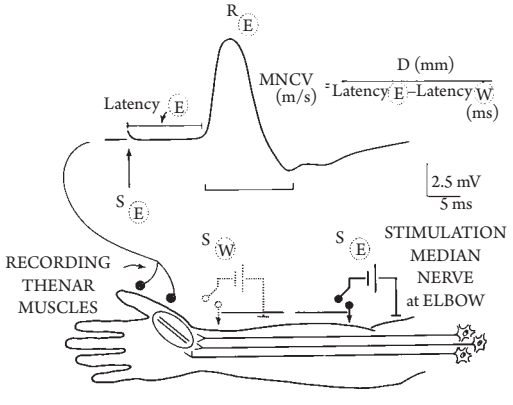

FIGURE 5-2 Compound muscle action potential recorded from the thenar eminence following the stimulation of the median nerve at the elbow. The nerve conduction time from the elbow to the wrist equals the latency difference between the two responses elicited by the distal and proximal stimulations. The motor nerve conduction velocity (MNCV) calculated by dividing the surface distance between the stimulus points by the subtracted times concerns the fastest conducting fibers.

The latency from the most distal stimulus point to the muscle includes not only the nerve activation and conduction time but also time for neuromuscular transmission and muscle action potential. Because of these additional factors, one cannot calculate a conduction velocity over the most distal segment. Here, meaningful comparison requires the use of either premeasured fixed distance or anatomic landmarks for electrode placement, which should improve the accuracy of latency determination. The actual conduction time in the terminal segment (L_d) slightly exceeds the calculated value ($L_d' = D/CV$) for the same distance (D) based on the conduction velocity (CV) of more proximal segments. The difference ($L_d - L_d'$), known as the residual latency, provides a measure of the conduction delay at the nerve terminal and at the neuromuscular junction.[73] The ratio between the calculated and measured latency (L_d'/L_d') referred to as the terminal latency index, also relates to distal conduction delay (see Chapter 6-3).[119] For example, a patient with a measured distal latency (L_d) of 4.0 ms for the terminal distance (D) of 8 cm and forearm conduction velocity (CV) of 50 m/s would have a calculated latency (L_d') of 1.6 ms (8 cm devided by 50 m/s), residual latency of 2.4 ms (4.0–1.6 ms), and terminal index ratio of 0.4 (1.6 ms/4.0 ms).

Waveform Analysis

In normal subjects, shocks of supramaximal intensity delivered at different sites along the course of the nerve elicit a nearly, but not exactly, identical CMAP, which varies depending on the nerve length between the stimulating and recording electrodes.

The impulses of the slow-conducting fibers lag progressively behind those of the fast-conducting fibers over a longer conducting path. Hence, a proximal stimulus gives rise to an evoked potential of slightly longer duration and lower amplitude than a distal shock (see Chapter 11-5). This physiologic temporal dispersion does not drastically alter the waveform of the muscle action potentials, as predicted by analysis of duration-dependent phase cancellation (see Fig. 11-11 in Chapter 11). The CMAP amplitude also changes with mild contraction, repositioning the target muscle and altering the length of muscle fibers that it dictates (see Chapter 18-2, Fig. 18-1).[41] Sustained isometric exercise may also induce temperature-sensitive pseudofacilitation.[115]

A low-intensity stimulation activates only part of the nerve fibers, distorting the waveform, whereas excessive stimulus intensity depolarizes the nerve a few millimeters away from the cathode, erroneously shortening the measured latency. With the use of some stimulators, an action potential may originate under the anode depending on the shape of the stimulus output.[150,152] The surface length measured between the two cathodal points under these conditions does not precisely correspond to the conduction distance of the nerve segment under study. If the CMAP elicited by the distal and proximal stimuli appear dissimilar in waveform, their onset latencies may not represent the same motor fibers, precluding accurate calculation of conduction velocity.

Traces recorded with high amplification sometimes reveala small negative peak preceding the main negative component of the muscle action potential. This potential, not considered part of the CMAP in latency determination, may represent a mixed nerve potential recorded from small nerve fibers near the motor point.[128] When recording a CMAP from E1 placed on the lumbricalis and E2 on the index finger, the premotor potential, at least in part, reflects a far-field potential generated by the sensory impulse as it crosses the metacarpophalangeal junction, making E2 positive compared to E1 (see Chapter 19-3).[29,67] A premotor potential, if misinterpreted as part of a CMAP, will cause errouneous identification of a short onset latency. The use of different amplifier sensitivities for distal and proximal stimulation would affect waveform analysis, leading to a measurement error.[133]

Types of Abnormalities

Assessment of a nerve as a whole, as opposed to individual nerve fibers, usually reveals more complicated features because different types of abnormalities tend to coexist. Nonetheless, axonal and demyelinative lesions give rise to characteristic abnormalities in motor NCS when stimulating the nerve distally and proximally flanking the presumed site of involvement. The amplitude of the muscle response varies considerably from one normal subject to another. Thus, a side-to-side comparison helps elucidate minor diminution in the recorded potential, which may otherwise escape detection. The CMAP amplitude elicited by proximal stimulation usually reflects the number of functional axons (Fig. 5-3). For example, two-thirds of the normal size imply axonal degeneration or conduction block involving one-third (Fig. 5-4) and an absent response, all the nerve fibers (Fig. 5-5). If segmental demyelination affects the majority of the nerve fibers more or less equally without a conduction block, stimulation above the lesion evokes a relatively normal CMAP amplitude with delayed latency (Fig. 5-6). This type of abnormality may

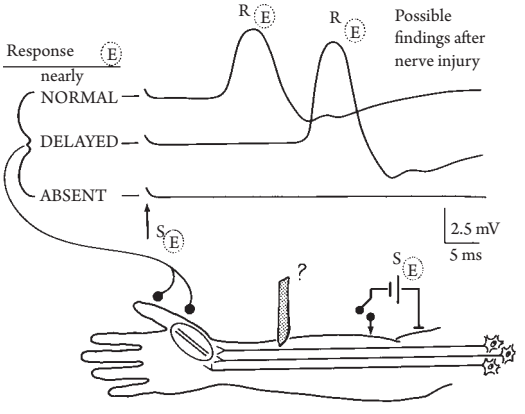

FIGURE 5-3 Three basic types of alteration in the compound muscle action potential occur after a presumed nerve injury distal to the site of stimulation: mildly reduced amplitude with nearly normal latency (*top*), normal amplitude with substantially increased latency (*middle*), or absent response even with a shock of supramaximal intensity (*bottom*).

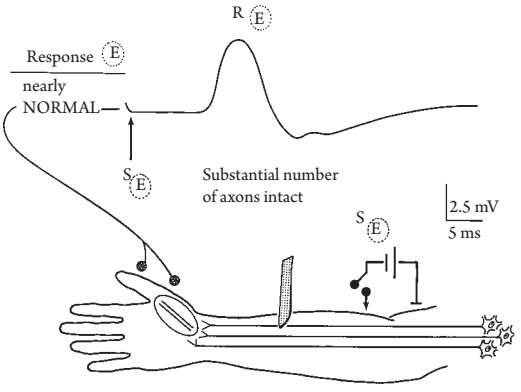

FIGURE 5-4 Mild reduction in amplitude of the compound muscle action potential with a nearly normal latency. This type of abnormality indicates that a substantial number of axons remain functional. The affected axons constituting only a small portion of the total population have either neurapraxia or axonotmesis. The normal latency reflects the surviving axons that conduct normally. Because of inherent individual variability, minor changes in amplitude may escape detection as a sign of abnormality.

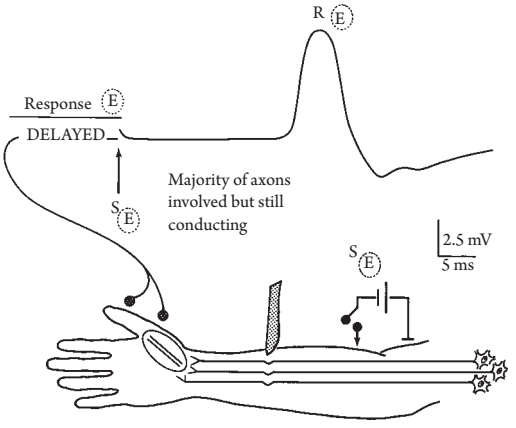

FIGURE 5-6 Increased latency of the compound muscle action potential with normal amplitude. This type of abnormality indicates demyelination affecting the majority of nerve fibers more or less equally, as in a compression neuropathy. Conduction block, if present during acute stages, will diminish the amplitude of the recorded response.

affect the nerve diffusely along the course as in demyelinated polyneuropathy or segmentally as in an entrapment neuropathy (Fig. 5-7).

During the first week of injury, a distally elicited CMAP remains normal regardless of the type of pathology (Fig. 5-8), which therefore initially cannot differentiate neurapraxia from axonotmesis. Repeating distal stimulation during the second week, however, can distinguish these two possibilities. With a total axonal degeneration, stimulation below the point of the lesion produces no CMAP (Fig. 5-8), initially reflecting the failure at the neuromuscular junction followed by the loss of nerve excitability. In cases of partial axonal loss, distally elicited response matches proximally elicited response, both showing amplitude reduction in proportion to the number of lost axons. In neuropraxia, a distal stimulation evokes a normal CMAP indicating preservation of the axons, whereas a proximal stimulation continues to show a reduced amplitude because of conduction block (Figs. 5-9). A reduction in size of the evoked response, however, may also result, in the absence of a conduction block, from phase cancellation between peaks of opposite polarity associated with pathological temporal dispersion.[66] In acquired demyelinative neuropathies (Fig. 5-10) showing conduction block or phase cancellation, CMAPs elicited by distal and proximal stimulation may not represent the same groups of motor fibers, a prerequisite for calculation of conduction velocity.

A mild slowing of conduction also results from axonal neuropathy with loss of the fast-conducting fibers.[36] This type of slowing has its limits defined by the characteristics of the remaining physiologically slow-conducting fibers. With a CMAP amplitude above 80% of the lower limits, the conduction velocity should

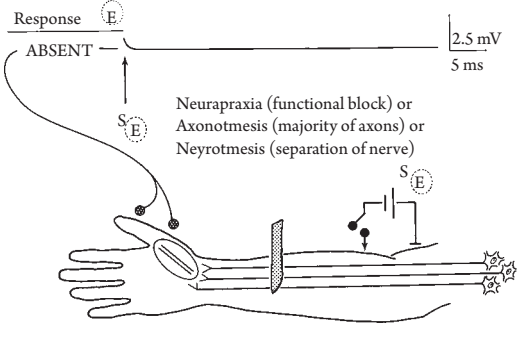

FIGURE 5-5 No evoked potential with supramaximal stimulation of the nerve proximally. This type of abnormality indicates the loss of conduction in the majority of axons but fails to distinguish neurapraxia from axonotmesis or neurotmesis.

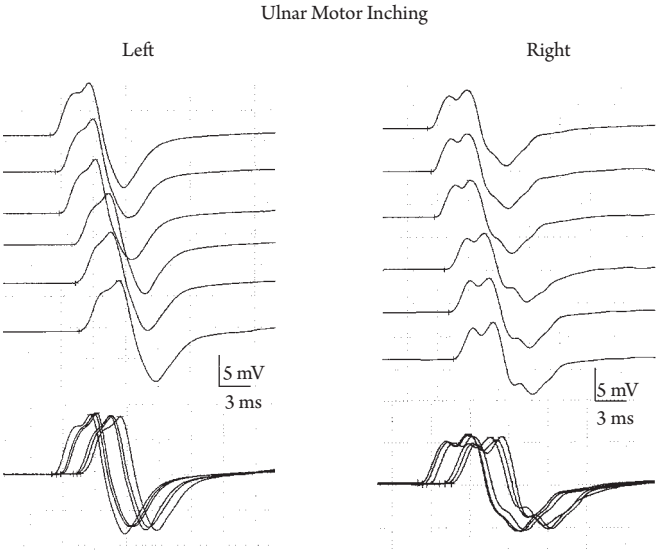

FIGURE 5-7 A 40-year-old woman with complaints of hand pain and paresthesia involving the little finger and ulnar half of the ring finger on both sides. Short incremental stimulation of the ulnar nerve revealed a nonlinear shift of the motor response from abductor digiti minimi, indicating a localized delay at the elbow on both sides.

not fall below 80% of the lower limits. A value below this limit, therefore, suggests the presence of demyelination. With further diminution of amplitude to less than 80% of the lower limits, the conduction velocity may fall to 70% of the lower limit solely on the basis of axonal loss. For the same reason slowed motor conduction seen in myelopathies also results from a loss of the large anterior horn cells with fast-conducting motor axons. Serial electrophysiologic studies help establish the time course of conduction block and wallerian degeneration (Fig. 5-11) during the acute phase of nerve damage. During the

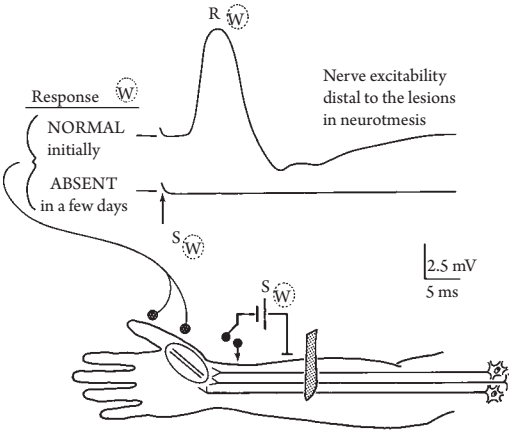

FIGURE 5-8 Motor nerve excitability distal to the lesion in neurotmesis or substantial axonotmesis. Distal stimulation elicits a normal compound muscle action potential during the first few days after injury, even with a complete separation of the nerve. Unlike neurapraxia, wallerian degeneration subsequent to transection will render the distal nerve segment inexcitable in 5–10 days.

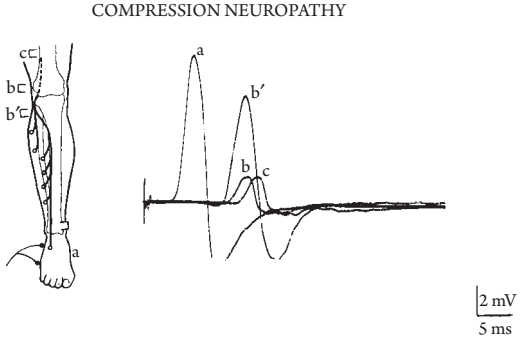

FIGURE 5-9 A 34-year-old man with selective weakness of foot dorsiflexors and low back pain radiating to the opposite leg. The nerve conduction studies revealed a major conduction block between the two stimulation sites, b and b′, at the knee. The weakness abated promptly when the patient refrained from habitual leg crossing. (From Kimura,[63] with permission.)

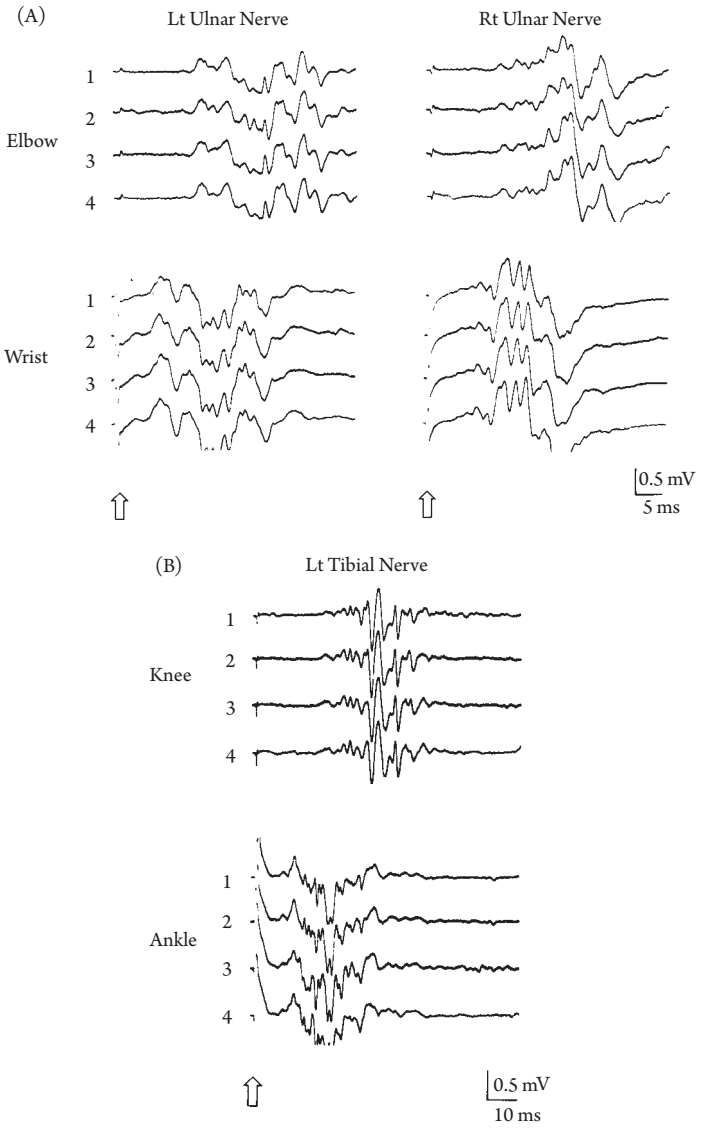

FIGURE 5-10 (***A***) A 31-year-old man with the Guillain-Barré syndrome. Stimulation of the ulnar nerves at the elbow or wrist elicited delayed temporally dispersed compound muscle action potentials of the abductor digiti minimi bilaterally. Four consecutive trials at each stimulus site confirm the consistency of the evoked potentials. (***B***) In the same patient as shown in (***A***), stimulation of the tibial nerve at the knee or ankle elicited delayed and temporally dispersed compound muscle action potentials of the abductor hallucis.

chronic phase, a repeat NCS can delineate nerve regeneration, which accompanies a progressive recovery of CMAP amplitude (Figs. 5-12 and 5-13).

Single stimulation may evoke various types of repetitive responses usually representing focal reexcitation of hyperexcitable axons, which also characterize myokymia and neuromyotonia (see Chapter 28-5 and 28-6). Stimulation applied at different levels combined with collision method helps clarify the origin of stimulus-induced high-frequency discharges.[92,108] Other causes of repetitive muscle action potentials[133] include intramuscular nerve reexcitation,[107] abnormalities of neuromuscular junction such as excess acetylcholine or acetylcholinesterase

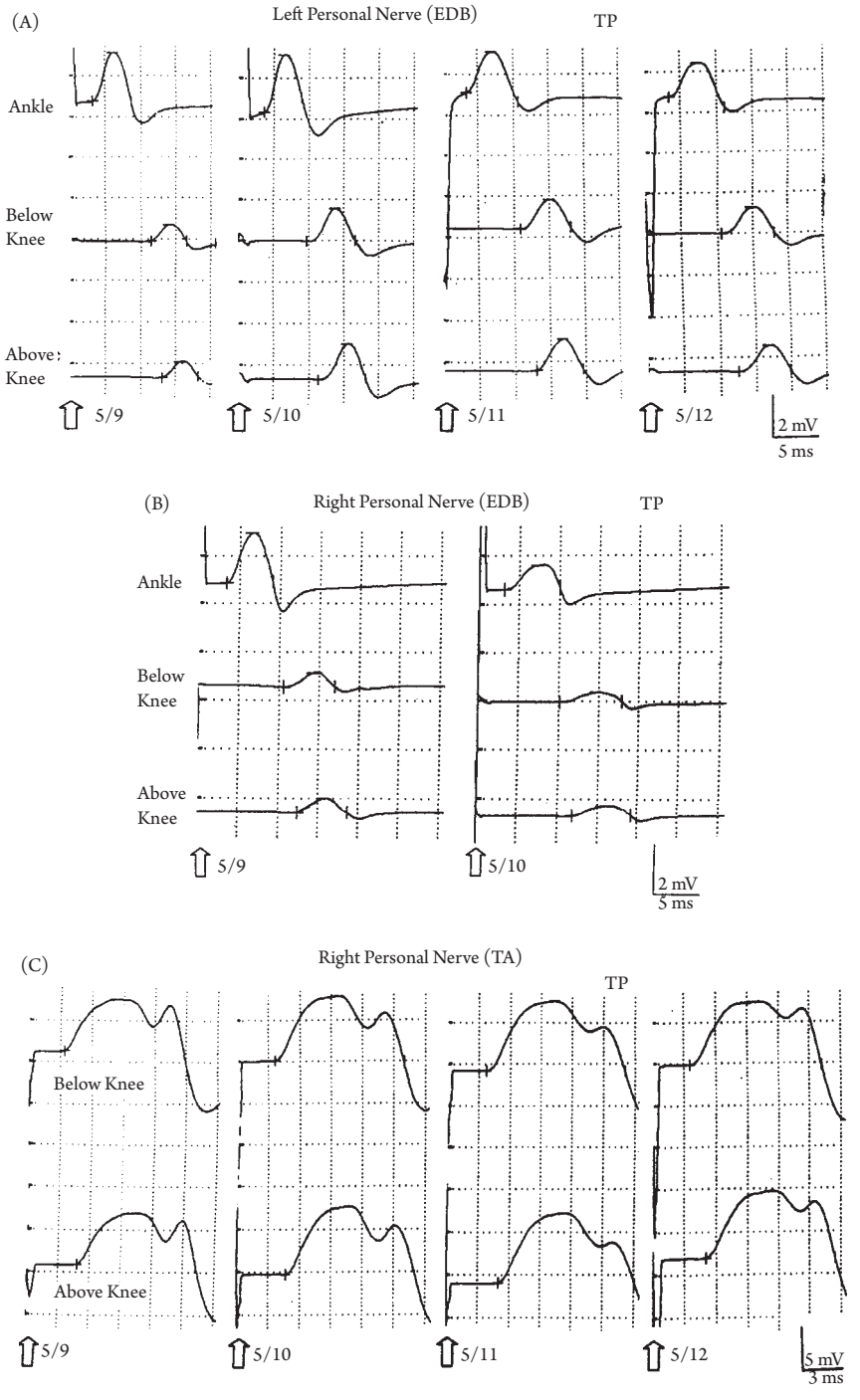

FIGURE 5-11 A 21-year-old man, known asthmatic, developed purpura on palms and soles 4 days before admission followed 2 days later by weakness of plantar flexion and loss of balance. (***A***) A series of recordings from left extensor digitorum brevis (EDB) showed reduced amplitude with proximal stimulation of the peroneal nerve below and above knee (May 9), its partial recovery indicating resolving conduction block (May 10), and reduction of amplitude with distal stimulation at the ankle indicating the onset of wallerian degeneration (May 11 and 12). (***B***) Recording from right EDB showed reduced amplitude with proximal stimulation (May 9) and later also with distal stimulation (May 10). (***C***) Recording from tibialis anterior showed no abnormality, indicating a focal lesion of the distal nerve branch innervating the EDB. Muscle biopsy confirmed the diagnosis of Churg Straus vasculitis.

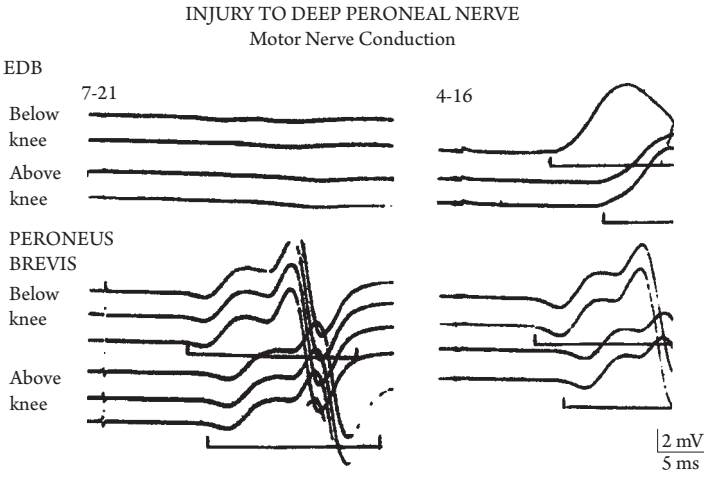

FIGURE 5-12 Isolated injury of the deep peroneal nerve at the knee. Stimulation of the common peroneal nerve below and above the popliteal fossa elicited no response from the extensor digitorum brevis (EDB), but normal response from the peroneus brevis and longus (July 21). A follow-up study showed recovery of EDB response with nerve regeneration (April 16).

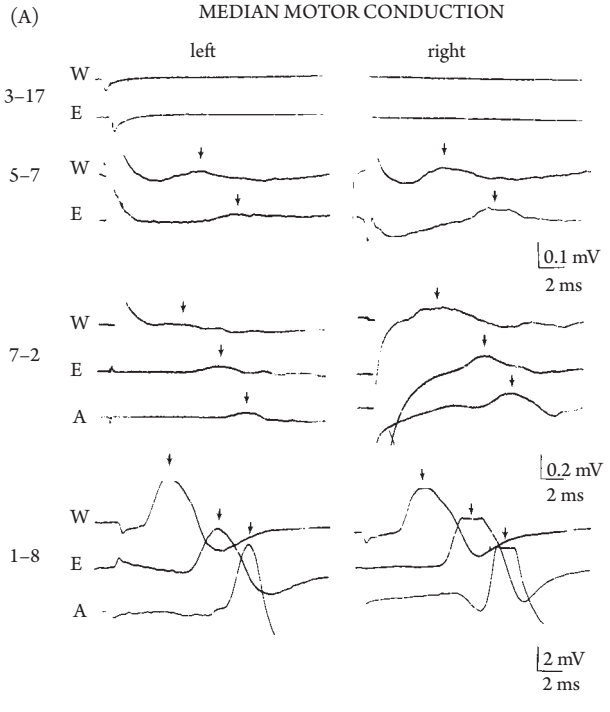

FIGURE 5-13 A 2 ½-year-old boy developed severe axonal polyneuropathy following prolonged exposure to freezing weather on a frigid winter night in Iowa. (***A***) Compound muscle action potentials recorded over the thenar eminence after stimulation of the median nerve at the wrist (W), elbow (E), and axilla (A). The initial study on March 17 revealed no response on either side followed by progressive return in amplitude and latency, with full recovery by January 8.

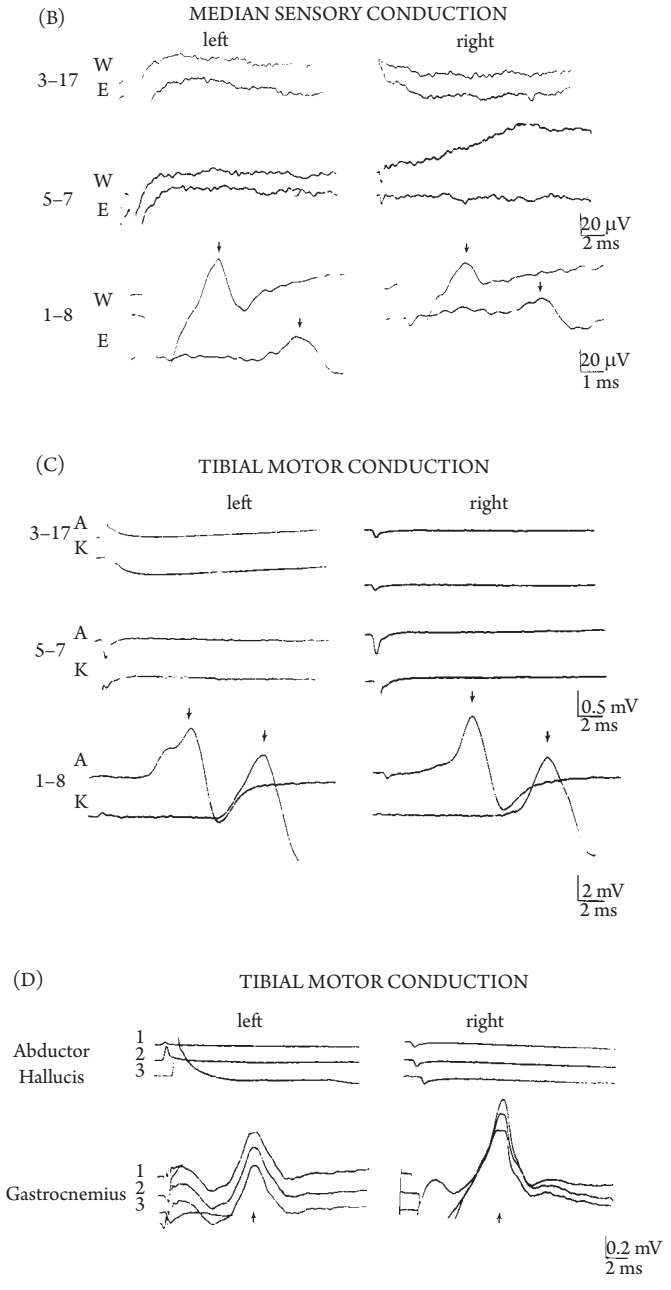

FIGURE 5-13 (Continued) (***B***) Antidromic sensory nerve action potential recorded from the index finger after stimulation of the median nerve at the wrist (W) and elbow (E). The studies on March 17 and May 7 showed no response on either side, with full recovery by January 8. (***C***) Compound muscle action potential recorded from the abductor hallucis after stimulation of the tibial nerve at the ankle (A) or knee (K). The studies on March 17 and May 7 revealed no response on either side, with full recovery by January 8. (***D***) Motor conduction studies of the tibial nerve on May 17. Stimulation at the knee elicited no response in the intrinsic foot muscle on either side (top three tracings) but a small compound action potential in the gastrocnemius bilaterally (bottom) as the result of early reinnervation. (From Afifi, Kimura, and Bell,[1] with permission.)

deficiency[34] (see Chapter 26-4), and hyperexcitability of muscle fibers as seen in myotonia (see Chapter 28-2).

5. SENSORY NERVE CONDUCTION

Stimulation and Recording

For clinical study of the upper limb, we prefer recording an antidromic digital potential after stimulation of the nerve trunk segmentally. Simultaneous activation of muscle potential may obscure the intended signal, but usually not to the extent of interfering with the measurements. Surface electrodes placed on either side of the digit register sensory potentials from both digital nerves through volume conduction, thus invalidating a study of individual branch.[70] Alternatively, stimulation of the digital nerves elicits an orthodromic sensory potential over the nerve trunk selectively without contamination from motor potentials. This approach, however, does not allow segmental comparison of amplitude, which varies primarily based on the depth of the nerve. Thus, apparent reduction in orthodromic sensory potentials may not necessarily imply the loss of axons when recording at the point where the nerve lies some distance from the recording surface.

Stimulation of the nerve trunk also evokes a mixed nerve potential proximally. For example, shocks applied to the ulnar or median nerve at the wrist give rise to an antidromic potential on the appropriate digits and mixed nerve potential at the elbow. The large-diameter sensory fibers have lower thresholds and faster conduction by about 5%–10% compared to the motor fibers. Thus, the onset latency of mixed nerve potentials relates to the fastest sensory nerve conduction in healthy subjects. In patients with neuropathies predominantly affecting sensory fibers,[81] however, relationship may not always hold. Such circumstances would make assessment of sensory fibers difficult in the presence of motor nerve potentials.

For routine clinical studies, surface electrodes suffice for stimulation and recording.[3,37] The size of the electrode and the pressure applied during recording influences the amplitude of sensory nerve potential.[135] Some electromyographers prefer the use of a subcutaneous needle placed near the nerve to improve the signal-to-noise ratio, especially in assessing small late components. [55,76,90] Here, a signal averaging helps elucidate a sensitive measure of early nerve damage by defining temporally dispersed components that originate from demyelinated, remyelinated, or regenerated fibers.[45] Minimum conduction velocity calculated from these late components normally averages 15 m/s corresponding to the fibers of about 4 μm in diameter.[121] Although it may prove useful as the only abnormalities in some neuropathies, this method suffers from difficulties in identifying the normal range of the late components.

The technique of near nerve recording also provides a unique opportunity to assess various skin and muscle afferents in humans.[122] These include Meissner's corpuscles excited by mechanical stimulus[20] and Pacinian corpuscles driven by vibration.[50] In contrast, the conventionally recorded orthodromic and antidromic compound SNAPs result from activation of all the large-diameter fibers activated by supramaximal electric shocks, which bypass the receptors and axon terminals.[84]

Latency and Conduction Velocity

Unlike motor latency, which includes neuromuscular transmission (NMT), sensory latency consists only of the nerve activation and conduction time. The latency of activation, or a fixed delay of about 0.15 ms at the cathodal point,[75] makes the measured latency slightly greater than the calculated latency difference between two recording sites flanking the same nerve segment. Disregarding this minimal discrepancy, stimulation at a single site and recording from another site suffices for calculation of conduction velocity.

With the biphasic digital potential recorded antidromically, the onset latency measured to the takeoff of the negative peak corresponds to the conduction time of the fastest fibers from the cathode to E1. The use of modern amplifiers with high resolution now makes it feasible in most cases to measure the onset latency for sensory

conduction. The use of the peak latency has some justification as a quick estimate of abnormal temporal dispersion, which increases the onset-to-peak duration of the evoked potential. Measuring both the onset latency as well as the total duration, however, provides more complete data. The onset to peak interval increases in proportion to the nerve length tested, reflecting the increasing time interval between fast- and slow-conducting fibers. Therefore, the peak-to-peak latency difference between two stimulus sites slightly exceeds the onset-to-onset latency difference for a given nerve segment. The same holds true in measuring a triphasic orthodromic SNAP with the use of the initial positive peak or subsequent negative peak as the point of reference.

In one study, antidromic conduction times, despite identical mean values, showed slightly higher standard deviations than orthodromic measurements.[14] For the same segment of the sensory nerve, however, the orthodromic and antidromic potentials recorded using the same interelectrode distance have identical latencies.[21]

Waveform Analysis

Bipolar recording registers a signal as the potential difference between E1 and E2 when the impulse propagates under the electrodes. Assuming a conduction velocity of 50 m/s and signal duration of 0.8 ms, a 4-cm interelectrode distance allows the impulse to pass the E1 site before arriving at the E2 location,[46] which causes a least waveform distortion. Theoretical consideration not withstanding, some favor the use of a 2–3 cm over a 4-cm separation for two practical reasons: less noise and easier application, for example, when recording antidromic potentials from a short digit.[137] Like many others, we used a 2-cm separation to establish our normative values by using a commercially available recording bar with a pair of electrodes mounted at this fixed distance.

The antidromic digital potential has, as expected, an initially negative biphasic waveform when recording with a pair of ring electrodes directly placed on the nerve lying superficially. In monopolar derivation, both E1 and E2 electrodes register a stationary far-field potential (FFP) generated as the impulse crosses the base of the digit (see Chapters 2-4 and 19-3). This positivity, which affects E1 and E2 equally, however, does not appear in a bipolar derivation, which registers only the potential difference between the two. Coactivation of motor axons evokes a muscle action potential, which, though delayed by 1.0 ms for NMT, obscure antidromic SNAP with an overlap. The commonly used assessments include the amplitude from the baseline to the negative peak and the duration from the initial deflection to the intersection between the descending phase and the baseline. Some prefer to measure the amplitude from the negative to positive peak, and the duration, from the onset to the much less definable point where the tracing finally returns to the baseline.

In an orthodromic study, the position of the recording electrodes alters the waveform of a SNAP.[97] Recording with E1 on the nerve and E2 at a remote site generally gives rise to an initially positive triphasic potential. A separate late phase may appear in the response recorded at a more distant site, reflecting greater desynchronization between fast- and slow-conducting fibers. Placing E2 near the nerve at a distance of more than 3 cm from E1 makes the recorded potential tetraphasic, with addition of the final negativity because the two electrodes register the potential sequentially.[14] Submaximal stimulation in anode proximal arrangement may induce double peak sensory potential indicating additional activation of the nerve under the anode (see Chapter 11-2) with the use of some stimulators.[5] The orthodromic response recorded through surface electrodes from the nerve trunk lying a few centimeters under the skin has less amplitude than the antidromic sensory potentials recorded from digital nerves near the surface. The relationship reverses with the use of needle electrodes inserted near the nerve.

The amplitude of the sensory potential varies substantially among subjects and to a lesser extent between the two sides in the same individual whether recorded with surface or needle electrodes. In addition to the density of sensory innervation, body mass index determines the amplitude of an orthodromic SNAP, mainly reflecting the depth of the nerve from the skin surface [16] and skin thickness.[52] Left-handers often

have a greater median nerve SNAP at the wrist on the right side and vice versa, perhaps for the same reason.[82] Women tend to have greater SNAPs than men,[56,78] possibly because the nerves lie more superficially.

Types of Abnormalities

The types of abnormalities described for motor conduction apply in principle to sensory conduction as well.[74,75] Demyelination causes substantial slowing in conduction velocity with or without conduction block, whereas axonotmesis results in reduced amplitude with distal stimulation. Sural nerve potential serves as an early and sensitive measure for length-dependent distal axonal polyneuropathy.[2] Reflecting this preferential involvement, sural to radial nerve SNAP ratio often falls below 0.40 compared to the normal mean of 0.71 in patients with neuropathy.[111] The sensory fibers degenerate only with a lesion involving the sensory ganglion or postganglionic axon (Fig. 5-13). Thus, the normal study of distal sensory potential from anesthetic digits implies a preganglionic root lesion rather than plexopathy or neuropathy.

Radicular lesions, if located inside the spinal canal, can also involve the ganglion or postganglionic portion of the root affecting the digital nerve potential.[58,79] In this case, the distribution of SNAP abnormalities helps differentiate plexopathy, which tends to affect multiple digits, and radiculopathy, which usually shows selective changes of one or two digits: thumb by C6, index and long fingers by C7, and ring and little fingers by C8 root lesions.[38]

6. NERVE CONDUCTION IN THE CLINICAL DOMAIN

The validity of the calculated nerve conduction velocity depends primarily on the accuracy in determining the latencies and the conduction distances. Sources of error in measuring latencies include unstable or incorrect triggering of the sweep, poorly defined takeoff of the evoked response, inappropriate stimulus strength, and inaccurate calibration. Errors in estimating the conduction distance by surface measurement result from uncertainty as to the exact site of stimulation and the nonlinear course of the nerve segments. Surface determination yields particularly imprecise results when the nerve takes an angulated path, as in the brachial plexus or across the elbow or knee.

Because of these uncontrollable variables, the calculated values only approximate the true nerve conduction velocities. On repeated testing, the results may vary as much as 5 to 10 m/s, because of the limitations inherent in the technique (see Chapter 11-7).[71] Changes in limb temperature in part account for this variability. Strict adherence to the standard procedures minimizes the error, improves the reproducibility, and helps establish a small range of normal values, which justify the use of conduction studies as a diagnostic measure. Unlike conduction velocity, latency comparison calls for a constant distance between the stimulating and recording electrodes.

A combined index improves diagnostic classification over use of single test results.[32,102] Analyzing multiple measurements, however, poses statistical problems, necessitating a technique for data reduction (see Chapter 30-2).[103] The common assumption that conduction values follow a normal, bell-shaped Gaussian distribution appears unwarranted.[17] If so, calculation of reference values as the mean ±2 (or 2.5) standard deviations must use the optionally transformed data to remove the effect of skew and unacceptable rate of misclassification.

Variation among Different Nerve Segments

Both motor and sensory fibers conduct substantially more slowly in the legs than in the arms. A small reduction in temperature cannot account for the recorded differences, ranging from 7 to 10 m/s.[68] Longer nerves generally conduct slower than shorter nerves.[143,145] Available data further indicate a good correlation between conduction velocity and estimated axonal length in peroneal and sural nerves but not in motor or sensory fibers of the median nerve.[124] These findings might suggest, without histologic proof, an abrupt distal axonal tapering in the lower limbs. Other factors possibly responsible for the velocity gradient include progressive reduction in axonal diameter, shorter internodal distances,

and lower temperatures over the distal segment. Statistical analyses of conduction velocities show no difference between median and ulnar nerves or between tibial and peroneal nerves. These measures also reveal a high degree of symmetry with only small side-to-side differences (see Chapters 6-3 and 6-5).[13]

The nerve impulse propagates faster in the proximal than in the distal nerve segments. For example, the cord-to-axilla F-wave conduction velocity (FWCV) clearly exceeds the elbow-to-wrist motor nerve conduction velocity (MNCV).[22,33,59,65] Statistical analyses, however, show no significant difference between cord-to-axilla and axilla-to-elbow segments.[59] The F ratio (see Chapter 7-3), comparing the proximal and distal motor nerve conduction time,[60] helps establish the pattern of conduction abnormality characteristic of a neuropathy as a group. For example, an increase in this ratio indicates a proximal slowing considered typical of the acute and chronic inflammatory demyelinating neuropathies (AIDP and CIDP) (see Chapter 24-3), whereas a decrease implies a distal involvement seen in dying-back axonal neuropathy (see Chapter 24-2).

Effects of Temperature

Lower temperatures tend to retard the propagation of the impulse while augmenting the amplitude of the nerve and muscle potential.[24,94,98,110,116] For example, cooling the hand increases distal latencies by 0.3 ms per degree for both median and ulnar nerves.[18] A localized temperature change, like cold elbow, may induce a focal slowing.[77,79] These principles apply for both normal and demyelinated fibers as a straightforward consequence of the temperature coefficients governing voltage-sensitive sodium and potassium conductance. In particular, the cold-induced delay of sodium channel opening accounts for slowing of conduction, and the subsequent delay of its closing, for an increase in amplitude. In contrast, a higher body temperature tends to increase the speed of nerve impulses and reduce the amplitude. A parallel temperature-dependent change also affects the refractory period.

The conduction velocity shows an almost linear change averaging 2.4 m/s, or approximately 4%–5%, per degree, for the temperature from 29°C to 38 °C,[54,57] although changes becomes more pronounced in the lower range.[130] Very high temperatures also induce a marked effect, decreasing motor and sensory potentials by 27% and 50% in amplitude, and 19% and 26% in duration with warming of the limb from 32°C to 42°C.[112] In demyelinated nerve fibers, conduction velocity increases as temperature rises until propagation ceases at a vulnerable site. Here, faster conduction reflects quick activation of sodium channels over a length of a fiber, whereas conduction failure results from reduction of the action potential below the critical level by quick inactivation of sodium channels at the demyelination site with a low safety factor.[40,140] Thus, latency shortening and conduction block result from two completely separate effects of temperature rise.

Studies conducted in a warm room with ambient temperature maintained between 21°C and 23°C minimize this type of variability. In practice, the skin temperature measured with a plate thermistor correlates linearly with the subcutaneous and intramuscular temperatures.[49] A skin temperature of 34°C or above indicates a muscle temperature close to 37°C.[25] A measured value falling below 32°C calls for warming of the limb with an infrared heat lamp or other readily available devices such as a hair dryer or hot water blankets.[27] Some advocate immersion of the limb in warm water for a sufficient time in the order of 30 minutes,[39] and others use a bicycle ergometer to raise skin temperature.[114] Warming the skin, however, may provide misleading interpretation if it fails to raise the core temperature equally. Alternatively, one may add 4% of the calculated conduction velocity for each degree below 32°C to normalize the result. Although conversion factors, based upon an average of healthy subjects, may not necessarily apply in diseases of the peripheral nerve,[26,89] the practice minimizes the incidence of false-positive results based on misinterpretation of the temperature-induced slowing.

Height and Other Factors

In addition to temperature and age (see Chapter 29-4), other factors that influence nerve conduction measures include anthropometric

characteristics.[42,113] For example, the height shows a negative association with the sensory amplitude and a positive association with the distal latencies. Sural, peroneal, and tibial nerve conduction velocities all have an inverse correlation with height in normals[99] as well as in patients with diabetic neuropathy.[44] In one series, dealing with sural NCS, [131] however, velocity changes attributable to height fell within the experimental error of 2.3% expected from the method. In another study,[100] nerve conduction velocities showed a stronger correlation with height compared to age. Women have faster conduction velocity and greater amplitude for both motor and sensory studies than men.[104] Most gender differences resolve when adjusted by height, whereas amplitude differences persist despite such correction and may, at least in part, relate to volume conductor characteristics of the body.

Ischemia, induced by a pneumatic tourniquet, alters nerve excitability substantially, with progressive slowing in conduction velocity, decrease in amplitude, and increase in duration of the action potential.[118] These changes affect the median nerve more rapidly in patients with the carpal tunnel syndrome (CTS) than in normal controls.[43] Conversely, patients with diabetes or uremia or elderly subjects have a greater resistance to ischemia with regard to peripheral nerve function.[19] Threshold tracking provides confirmatory evidence for this characteristic of the motor axons in diabetic subjects (see Chapter 10-4).[141] In chronic hypoxemia and diabetes, reduction in amplitude of nerve potential during ischemia shows a time course correlated with the blood oxygen saturation. Thus, prior hypoxic exposures may induce resistance to ischemic conduction failure.[51]

Clinical Values and Limitations

Over the years, NCSs have made major contributions to the understanding of peripheral nerve function in health and disease states. Such evaluations can precisely delineate the extent and distribution of the lesion, showing an overall distinction between axonal and demyelinating involvement. This dichotomy provides a simple and practical means of correlating conduction abnormalities with major pathologic changes in the nerve fibers. In support of this concept, in vitro recordings from the sural nerve have clearly established close relationships between histologic and physiologic findings.[10,31]

In addition to such a broad classification, the pattern of nerve conduction abnormalities can often characterize the general nature of the clinical disorder.[86] For example, hereditary demyelinating neuropathies commonly, though not always, show diffuse abnormalities, with little difference from one nerve to another in the same patient and among different members in the same family.[80] Measurement of the high-frequency attenuation may help quantify waveform changes in distinguishing uniform and nonuniform motor nerve conduction slowing (see Chapter 11-6).[15] Approximately equal involvement of different nerve fibers limits the degree of pathological temporal dispersion despite a considerably increased latency. In contrast, acquired demyelination tends to affect certain segments of the nerve disproportionately, giving rise to more asymmetric abnormalities and substantial increases in temporal dispersion. Electrophysiologic studies also help separate sensorimotor neuropathies from pure sensory neuropathies.[105] Pattern of distribution in sensory nerve conduction abnormalities helps differentiate demyelinating and axonal polyneuropathies. For example, a reduced SNAP amplitude of the median nerve compared with that of the sural nerve supports the diagnosis of a primary demyelination.[12] In contrast, a reduced sural nerve amplitude compared with the radial nerve implies an axonal polyneuropathy. [96,111] Other reported results include a reduced median/radial and an increased sural/radial ratio in acquired demyelination and decreased median/radial and sural/radial ratios in dying-back degeneration.[129]

Optimal application of NCSs depends on understanding the principles and recognizing the pitfalls of the technique. The conventional methods deal primarily with distal nerve segments in the four limbs. Special techniques[64] enable assessment of nerve segments in less accessible anatomic regions, provide better evaluation of a focal lesion, and improve the detection of subclinical abnormalities (see Chapter 11-7). Despite certain limitations, these methods can uncover diagnostically pertinent information

if used judiciously in appropriate clinical contexts.[98] The automated device, which may accurately record raw data, falls short of providing specificity necessary for a screening or diagnostic examination.[115]

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6

Assessment of Individual Nerves

Abbreviations: BMI—body mass index, CMAP—compound muscle action potential, CTS—carpal tunnel syndrome, D—distance, E1—active electrode, E2—reference electrode, EMG—electromyography, FSH—fascioscapulohumeral, NCS—nerve conduction study, SD—standard deviation, SEP—somatosensory evoked potential, SNAP—sensory nerve action potential

1. INTRODUCTION

Nerve conduction studies consist of stimulating a nerve and recording the evoked potential either from the nerve itself or from a muscle innervated by the nerve. The basic principles outlined in the previous section apply to any studies, although the anatomic peculiarities dictate specific approaches to each of the commonly tested individual nerves. The ordinary nerve conduction studies provide limited information regarding the most proximal nerve segment such as the brachial or lumbosacral plexus. Supplemental methods help evaluate the motor and sensory conduction in this region by measuring the F wave (see Chapter 7-4), H reflex (see Chapter 9-2), and somatosensory evoked potentials (SEPs) (see Chapter 19-6).

In addition to the spinal accessory nerve, studies of the facial nerve and blink reflex constitute an integral part of the cranial nerve investigation. Those commonly tested in the limb comprise the motor and sensory fibers of the median, ulnar, and radial nerves and the motor and sensory fibers of the peroneal and tibial nerves, including the sural and superficial peroneal nerves. The less readily accessible include the nerves of the shoulder girdle such as the phrenic nerve, brachial plexus, and musculocutaneous nerve and forearm nerves such as lateral, medial, posterior antebrachial cutaneous nerves and the dorsal sensory branch of the ulnar nerve. The nerves of the lumbosacral plexus in this category comprise femoral, sciatic, lateral femoral cutaneous, saphenous, and lateral and medial plantar nerves.

To minimize the bias induced by different techniques, each laboratory should develop its own normal ranges or use an established criterion following the same standardized method (see Chapter 30-2). For the latency and conduction velocity, 95% of the measures from a healthy population fall within the mean plus or minus two standard deviations (SDs) defined in control subjects. The same does not apply to amplitude, which distributes in a non-Gaussian manner. Most of individual measures of amplitude exceed one-half the mean of the control value in healthy subjects, which thus serves as a lower limit of normal. An alternative approach uses a log transformation of the amplitude data to accomplish an equal distribution, and then expresses the normal range as plus or minus two SD confidence intervals (see Chapter 30-2). This section will describe the usual points of stimulation and recording sites together with the normal values established in our institution or as reported in the literature.

2. CRANIAL NERVES

The most commonly tested cranial nerves in the electromyographic (EMG) laboratory include the facial, trigeminal, and spinal accessory nerves. Chapters 8-2 and 8-3 will deal with studies of the facial nerve and the ophthalmic branch of the trigeminal nerves as they relate to the blink reflex, and Chapter 9-3, the mandibular branch of the trigeminal nerve in conjunction with the masseter reflex.

Spinal Accessory Nerve

The accessory nerve runs superficially along the posterior border of the sternocleidomastoid muscle. Surface stimulation at this point elicits a compound muscle action potential (CMAP) of the trapezius, usually recorded from the upper portion by an active electrode (E1) placed at the angle of the neck and shoulder and a reference electrode (E2) over the tendon near the acromion process. Changes in amplitude provide reliable information, with reduction to one-half that of the response on the healthy side, suggesting distal degeneration. Some electromyographers prefer needle electrodes to stimulate the nerve. In one series of 25 subjects, 10–60 years of age, normal latencies to the upper trapezius ranged from 1.8 ms to 3.0 ms.[22] In another study of 21 nerves, the onset latency (mean $\pm$ SD) averaged 3.0 ± 0.2 ms to the middle trapezius and 4.6 ± 0.3 ms to the lower trapezius.[47]

Mylohyoid and Lingual Nerves

Intraoral surface stimulation of the mylohyoid nerve evokes the mylohyoid muscle potential under the chin in the anterior submandibular area. The cathode, taped to a tongue depressor, faces anteriorly in the pterygomandibular space at the level of the rear molars. The subject opens

the mouth and pushes the tongue up against the front teeth to activate the muscle for placement of E1. In one study of 42 healthy subjects,[31] who all had a response bilaterally, the reported values (mean ± SD) included latency of 1.9 ± 0.2 ms and amplitude of 4.9 ± 1.8 mV.

Stimulation of the mandibular nerve by a needle electrode inserted in the infratemporal fossa at the level of the foramen ovale elicits muscle action potentials of the masseter and mylohyoideus.[102] The same needle registers sensory nerve action potentials elicited by stimulation of the lingual nerve along the inferolateral edge of the tongue and of the inferior alveolar nerve at the mental foramen. This method may prove useful in measuring the lingual and inferior alveolar nerve lesion subsequent to dental or orthognathic surgery.[63,151]

Hypoglossal Nerve

Submandibular surface stimulation of this nerve evokes glossal muscle action potential detectable over the anterior surface of the tongue. In one series of 30 normal subjects studied on both sides, reported values (mean ± SD) included latency of 2.2 ± 0.4 ms and amplitude of 3.8 ± 1.6 mV, taking the best of five responses measured baseline to peak.[143] In one series, hypoglossal CMAP showed a reduction in patients with obstructive sleep apnea.[140]

3. COMMONLY TESTED NERVES IN THE UPPER LIMB

Median Nerve

Tables 6-1, 6-2, and 6-3 (see also Appendix Tables 1-4 and 1-5) summarize normal values.

MOTOR STUDIES

The median nerve runs relatively superficially in its entire course from the axilla to the palm (Fig. 6-1). The usual sites of stimulation for motor nerve conduction study (NCS) include palm, wrist, elbow, axilla, and Erb's point. For each of these stimulation sites, we place the cathode near the line dividing middle and proximal third of the palm (see Chapter 11-3), 3 cm proximal to the most distal crease at the wrist, over the brachial pulse near the volar crease at the elbow, and in the mid clavicular region.[75] The other electrodes comprise the anode, located 2 cm from the cathode, and the ground electrode placed on the forearm between the stimulating and recording electrodes or the dorsum of the hand (Fig. 6-2A). Stimulation at the axilla or Erb's point tends to coactivate other nerves in close proximity. In the presence of an anomalous crossover from the median to ulnar nerve in the forearm, stimulation of the median nerve at the elbow also activates an ulnar component. Then, the onset latencies of distally and proximally evoked responses may represent two different nerves, invalidating the use of the usual formula for calculation of nerve conduction velocities (see Chapter 11-4). The use of the collision technique circumvents these problems (see Chapter 11-3).

With stimulation at the wrist, elbow, and axilla, the convention calls for placing the cathode distally to the anode (see Chapter 5-2). The reversal of the electrode position works better when stimulating the thenar nerve in the palm at the branching point from the main trunk of the median nerve (see Chapter 11-3). With this arrangement, the cathode placed in the mid palm with the anode 2 cm more distally elicits no muscle response because neither electrode lies on the nerve. Stimulation given slightly more proximally first activates the palmar branch of the ulnar nerve, adducting the thumb. The cathode placed 1 cm further proximally lies over the branching point of the thenar nerve. Stimulation here should cause abduction of the thumb, which verifies selective activation of the target nerve (Fig. 6-3). Palmar stimulation may inadvertently activate the deep palmar branch of the ulnar nerve.[133] Inability to clearly identify the contracting muscle by observing the twitches invalidates the procedure[19,133] in about 10% of the general population based on our own experience. To further compound the problem, the recurrent branch may take an anomalous course in rare instances.[191]

The recording leads consist of E1 over the belly of the abductor pollicis brevis and E2 just distal to the metacarpophalangeal joint (Fig. 6-2A). Depending on the electrode positioning, the potentials from other intrinsic hand muscles innervated by the

Table 6-1 Median Nerve*

SITE OF STIMULATION	AMPLITUDE†: MOTOR (mV) SENSORY (μV)	LATENCY‡ TO RECORDING SITE (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CONDUCTION TIME BETWEEN TWO POINTS (ms)	CONDUCTION VELOCITY (m/s)
Motor fibers					
Palm	6.9 ± 3.2(3.5)§	1.86 ± 0.28 (2.4)¶	0.19 ± 0.17 (0.5)¶		
Wrist	7.0 ± 3.0 (3.5)	3.49 ± 0.34 (4.2)	0.24 ± 0.22 (0.7)	1.65 ± 0.25 (2.2)¶	48.8 ± 5.3 (38)**
Elbow	7.0 ± 2.7 (3.5)	7.39 ± 0.69 (8.8)	0.31 ± 0.24 (0.8)	3.92 ± 0.49 (4.9)	57.7 ± 4.9 (48)
Axilla	7.2 ± 2.9 (3.5)	9.81 ± 0.89 (11.6)	0.42 ± 0.33 (1.1)	2.42 ± 0.39 (3.2)	63.5 ± 6.2 (51)
Sensory fibers					
Digit				1.37 ± 0.24 (1.9)	58.8 ± 5.8 (47)
Palm	39.0 ± 16.8 (20)	1.37 ± 0.24 (1.9)	0.15 ± 0.11 (0.4)	1.48 ± 0.18 (1.8)	56.2 ± 5.8 (44)
Wrist	38.5 ± 15.6 (19)	2.84 ± 0.34 (3.5)	0.18 ± 0.14 (0.5)	3.61 ± 0.48 (4.6)	61.9 ± 4.2 (53)
Elbow	32.0 ± 15.5 (16)	6.46 ± 0.71 (7.9)	0.29 ± 0.21 (0.7)		

*Mean ± standard deviation (SD) in 122 nerves from 61 healthy subjects, 11 to 74 years of age (average. 40), with no apparent disease of the peripheral nerves.

†Amplitude of the evoked response, measured from the baseline to the negative peak.

‡Latency, measured to the onset of the evoked response.

§Lower limits of normal, based on the distribution of the normative data.

¶Upper limits of normal, calculated as the mean + 2 SD.

**Lower limits of normal, calculated as the mean − 2 SD.

Table 6-2 Motor and Sensory Latencies Comparing Median and Ulnar Nerve Studies Conducted Using Conventional Technique*

SITE OF STIMULATION	MEDIAN NERVE (ms)	ULNAR NERVE (ms)	DIFFERENCE (ms)
Motor fibers			
Wrist	3.34 ± 0.32 (4.0)†	2.56 ± 0.37 (3.3)†	0.79 ± 0.31 (1.4)†
Elbow	7.39 ± 0.72 (8.8)	7.06 ± 0.79 (8.6)	0.59 ± 0.60 (1.8)
Sensory fibers			
Palm	1.33 ± 0.21 (1.8)	1.19 ± 0.22 (1.6)	0.22 ± 0.17 (0.6)
Wrist	2.80 ± 0.32 (3.4)	2.55 ± 0.30 (3.2)	0.29 ± 0.21 (0.7)

*Mean ± standard deviation (SD) In 70 nerves from 35 healthy subjects, 14 to 74 years of age (average, 37), with no apparent disease of the peripheral nerve.

†Upper limits of normal, calculated as mean + 2 SD.

median nerve contribute to the evoked response. The same pair of recording electrodes also registers a CMAP from the adductor pollicis after stimulation of the ulnar nerve,[80] allowing latency comparison between the two nerves.[192]

An alternative recording utilizes E1 over just medial to the first metacarpophalangeal joint and E2 on the second digit. This arrangement allows comparison between the muscle action potentials from the second lumbrical innervated by the median nerve and the first volar interosseus innervated by the ulnar nerve,[1, 139,160,172,174,176] In either comparison, a difference greater than 0.5 ms suggests a delay of whichever nerve showing a longer latency across the distal segment (see Chapter 25-5 and 25-6). A small premotor potential known to precede this CMAP after median nerve stimulation probably comprises antidromic SNAP, orthodromic motor nerve potential, and far-field potential generated at the base of the index finger (see Chapter 2-4 and 19-3). A prominent premotor potential may interfere with determination of CMAP onset latency by overlap.

The terminal latency index serves as a measure of the terminal latency (L_d) adjusted to the terminal distance (D) and expressed as a percentage of the conduction velocity between wrist and elbow (CV). It equals $D/(L_d \times CV)$ or terminal distance divided by the product of terminal latency and conduction velocity.[9,158] A value of 0.34 or less suggests a disproportionate distal slowing as in the CTS and distally prominent polyneuropathy (see Chapter 5-4).

Stimulation of the median nerve in the antecubital fossa also elicits a CMAP in the muscles innervated by the anterior interosseous nerve. In one study,[188] recording with E1 over the belly of the flexor pollicis longus and E2, 6-8 cm distally on the radial styloid, normal values (mean ± 2SD) obtained from 50 healthy subjects included 5.7 ± 2.0 mV with side-to-side difference of 0.7 ± 0.8 mV for amplitude and 3.9 ± 1.2 ms for onset latency. Surface recording from the pronator quadratus gave rise to a slightly smaller response with an average amplitude of 3.1 mV.[117 145]

SENSORY STUDIES

Stimulation delivered at sites listed for the motor fibers also activates antidromic sensory nerve action potentials (SNAPs), recordable with ring electrodes placed 2–4 cm apart around the proximal (E1) and distal (E2) interphalangeal joints of the index finger (Fig. 6-2A). For wrist and palm stimulation, we place the cathode 3 cm proximal and 5 cm distal to the most distal crease of the wrist (Fig. 6-4). Alternative techniques use a fixed distance from the recording electrode, most commonly 12–14 cm. Unlike a CMAP that maintains nearly the same amplitude irrespective of stimulus sites, the antidromically activated digital

Table 6-3 Distal Sensory Conduction Study Comparing Median and Ulnar Nerves*

RECORDING NERVE FINGER	SITE OF STIMULATION	MEASUREMENT OF ANTIDROMIC SENSORY POTENTIAL		CALCULATED VALUES FOR WRIST TO PALM SEGMENT	
		AMPLITUDE† (μV)	LATENCY‡ (ms)	CONDUCTION TIME (ms)	CONDUCTION VELOCITY (m/s)
Median nerve	Palm	49.8 ± 21.5(25)§	1.43 ± 0.16 (1.7)¶	1.44 ± 0.20 (1.9)¶	57.1 ± 8.3 (40)**
Index finger	Wrist	38.4 ± 15.6 (19)	2.87 ± 0.31 (3.5)		
Median nerve	Palm	37.6 ± 17.2 (19)	1.45 ± 0.20 (1.9)	1.43 ± 0.22 (1.9)	57.4 ± 8.9 (40)
Ring finger	Wrist	22.3 + 8.2 (11)	2.88 ± 0.35 (3.6)		
Ulnar nerve	Palm	46.1 + 24.3 (23)	1.48 ± 0.26 (2.0)	1.38 ± 0.30 (1.8)	59.1 ± 8.3 (43)
Ring finger	Wrist	29.0 ± 14.8 (25)	2.86 ± 0.37 (3.6)		
Median and	Palm	8.5 ± 20.7	0.02 ± 0.17 (0.3)	0.04 ± 0.20 (0.4)	
ulnar difference	Wrist	5.9 ± 10.1	0.01 ± 0.17 (0.4)		

*Mean ± standard deviation (SD) in 31 healthy subjects, 16 to 64 years of age (average 38), with no apparent disease of the peripheral nerve.

†Amplitude of the evoked response, measured from the baseline to the negative peak.

‡Latency, measured to the onset of the evoked response, with a standard distance of 8 cm between the stimulus sites at the wrist and palm.

§Lower limits of normal, based on the distribution of the normative data.

¶Upper limits of normal, calculated as the mean + 2 SD.

**Lower limits of normal, calculated as the mean − 2 SD.

potentials normally diminish substantially with increasing nerve length. The drop in amplitude and area results from physiologic temporal dispersion between fast- and slow-conducting fibers, causing the duration-dependent phase cancellation (see Chapter 11-5).[79]

Recording from the thumb provides assessment of C6, upper trunk and lateral cord, whereas the index and long fingers serve to evaluate C7, middle trunk and lateral cord, and the ring and little fingers, C8, lower trunk and medial cord.[42] Recording from the thumb or long finger

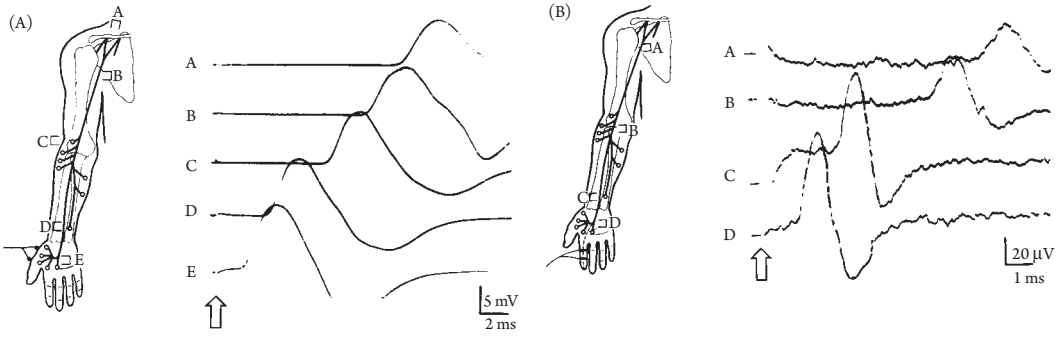
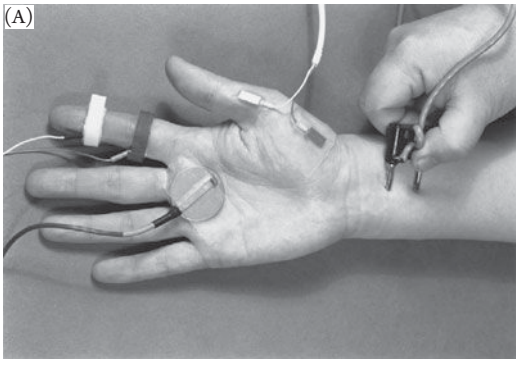


FIGURE 6-1 (***A***) Motor nerve conduction study of the median nerve. The sites of stimulation include Erb's point (A), axilla (B), elbow (C), wrist (D), and palm (E). The tracings show compound muscle action potentials recorded with surface electrodes placed on the thenar eminence. (***B***) Sensory nerve conduction study of the median nerve. The sites of stimulation include axilla (A), elbow (B), wrist (C), and palm (D). The tracings show antidromic sensory potentials recorded with a pair of ring electrodes placed around the index finger.



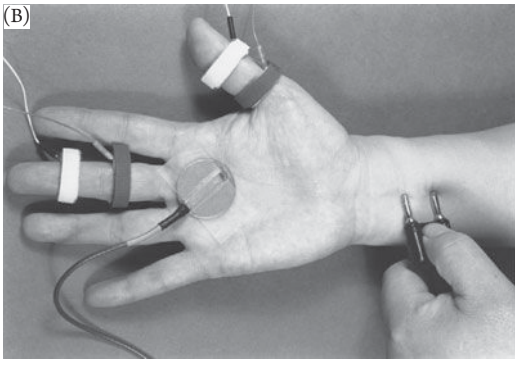


FIGURE 6-2 (***A***) Motor and sensory conduction studies of the median nerve. The photo shows stimulation at the wrist, 3 cm proximal to the distal crease, and recording with a pair of electrodes placed over the belly (E1) and tendon (E2) of the abductor pollicis brevis for motor conduction, and with a pair of ring electrodes placed 2 cm apart around the proximal (E1) and distal (E2) interphalangeal joints of the index finger for antidromic sensory conduction with the ground electrode located in the palm. (***B***) Alternative recording sites for sensory conduction study of the median nerve with the ring electrodes placed around the proximal (E1) and distal (E2) interphalangeal joints of the long finger or the base (E1) and the interphalangeal joint (E2) of the thumb.

(Fig. 6-2B) or the lateral half of the ring finger (Fig. 6-4) often reveals abnormalities not detectable from the index finger.[183] In contrast to postganglionic lesions, which cause degeneration of the sensory axons, preganglionic root avulsion results in no abnormalities of the sensory potential recorded from the anesthestic digits.

The thumb and index finger receive a mixed sensory supply of median and radial nerves, whereas the ring finger[93] has a split innervation from median and ulnar nerves. Thus, inadvertent spread of stimulating current to the radial or ulnar

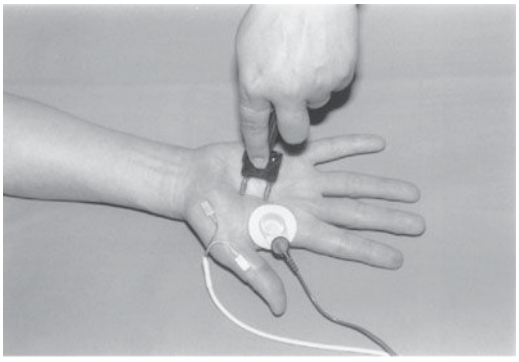


FIGURE 6-3 Stimulation of the median nerve with the cathode placed at the origin of the recurrent thenar nerve and anode, 2 cm distally, and recording of the muscle response over the belly (E1) and tendon (E2) of the abductor pollicis brevis. Another lead placed between the stimulating and recording electrodes or on the dorsum of the hand serves as the ground electrode (cf. Fig. 6–12).

nerve may confuse the issue when recording from these digits.[164] Some investigators take advantage of this spread to gain an instantaneous comparison of the median nerve to the ulnar nerve[183] or to the radial nerve.[135] Alternatively, separate stimulation of the median and ulnar nerves at the wrist evokes a corresponding SNAP from the ring finger at nearly the identical latency for the same conduction distance (Fig. 6-5). Additional palmar stimulation at a fixed distance from the wrist, usually 6 to 8 cm, allows latency comparison between

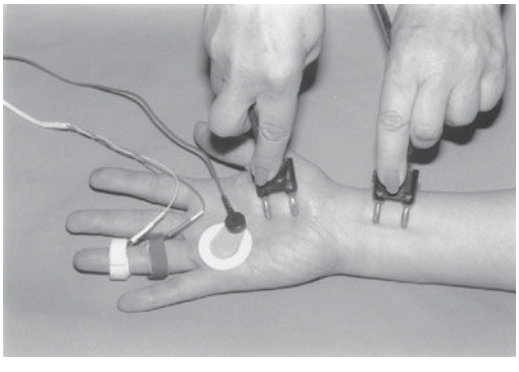


FIGURE 6-4 Stimulation of the median nerve at the wrist and palm with the cathode placed 3 cm proximal and 5 cm distal to the wrist crease, and anode, 2 cm proximally, and recording of the antidromic digital potential with the ring electrodes placed 2 cm apart around the proximal (E1) and distal (E2) interphalangeal joints of the ring finger (cf. Fig. 6-13).

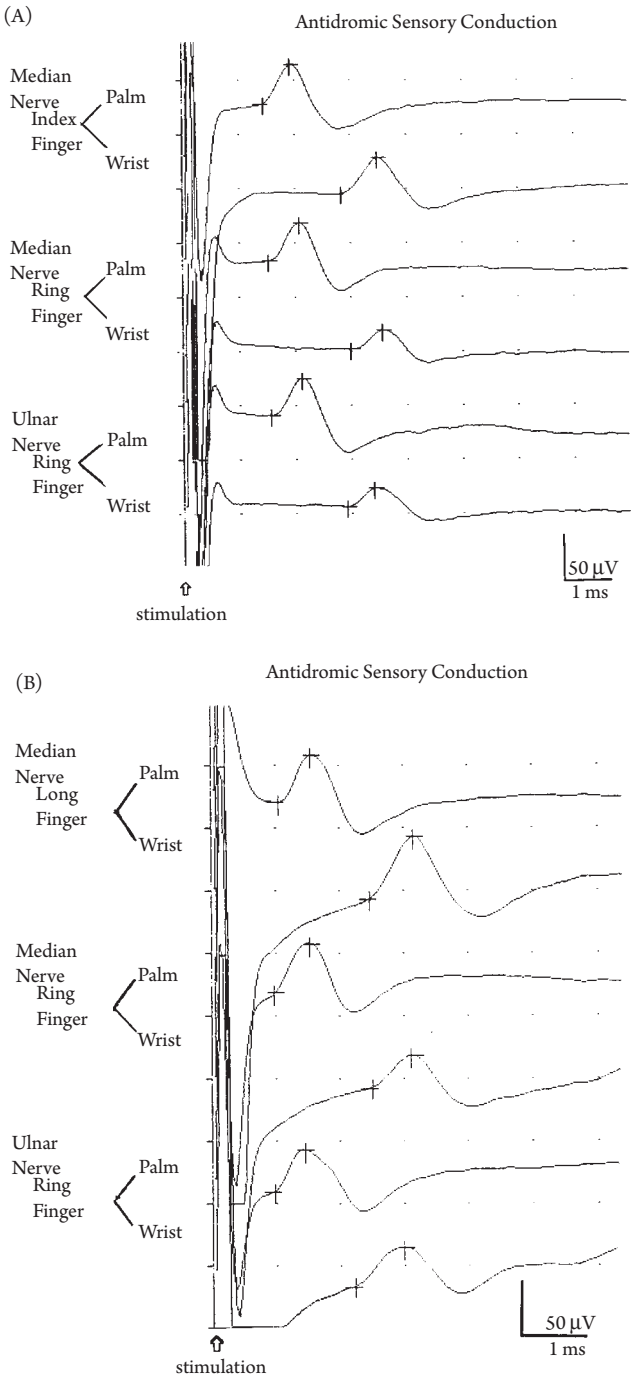


FIGURE 6-5 (***A***) Comparison between median and ulnar nerve antidromic sensory potentials in a healthy subject. Tracings show recordings from the index (*top*) and ring finger (*center*) after stimulation of the median nerve at the palm and wrist, and from the ring finger (*bottom*) after stimulation of the ulnar nerve at the comparable sites (cf. Figs. 6-4 and 6-11B). Median and ulnar nerve responses showed nearly identical latencies with stimulation at the palm and at the wrist regardless of the recording fingers. (***B***) The same arrangement as in (***A***) except for the use of the long finger (*top*) instead of the index finger in another healthy subject.

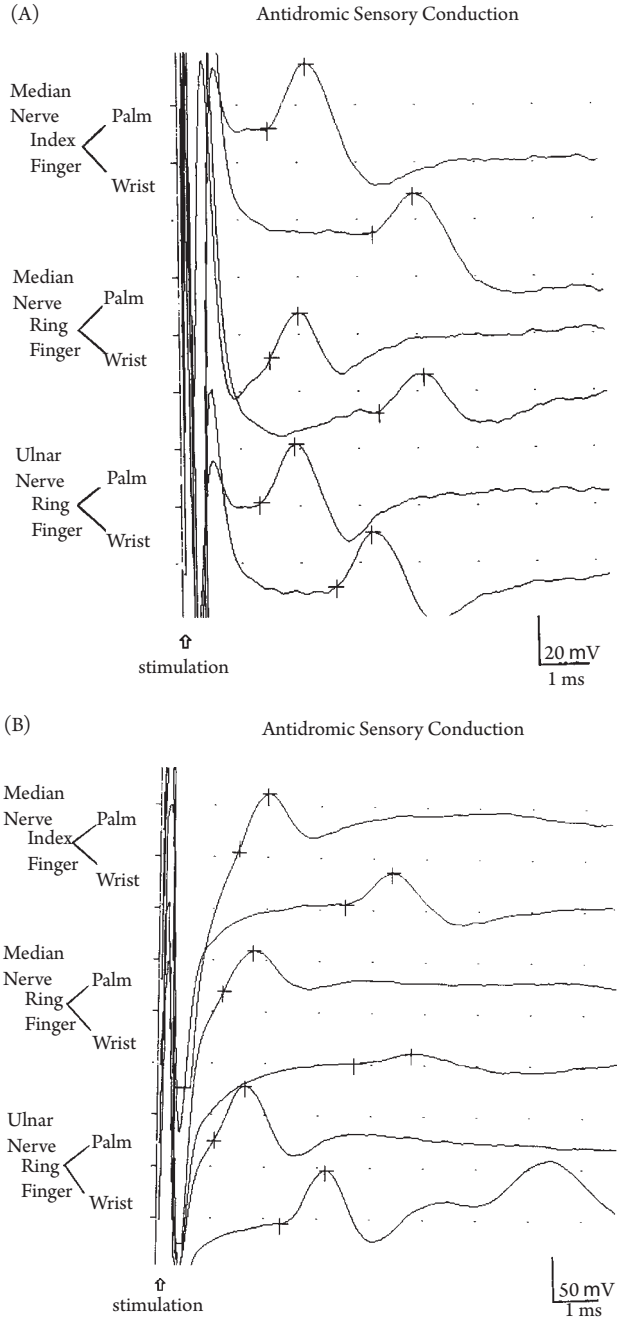


FIGURE 6-6 (***A***) The same arrangement as in Figure 6-5 in a patient with mild carpal tunnel syndrome. Despite normal latency from the wrist to the index finger (3.2 ms) and to the ring finger (3.2 ms), the latency difference between median and ulnar nerve (0.7 ms) clearly exceeded the upper limit of normal value (0.4 ms). In contrast, median and ulnar responses showed nearly identical latencies with stimulation at the palm regardless of the recording finger, confirming a delay of median conduction between the wrist and palm. (***B***) Another patient with carpal tunnel syndrome showing a more pronounced latency difference (0.9 ms) between median and ulnar nerves and a reduced and temporally dispersed median nerve response recorded from the ring finger. A normal median response elicited by palm stimulation suggests a focal demyelination across the carpal ligament with no evidence of distal axonal degeneration.

the two nerves for the wrist to palm segment (Fig. 6-6). Normal values in our laboratory (Table 6-3) include the onset latency of 2.88 ± 0.35 ms (mean ± SD) after wrist stimulation and distal amplitude of 37.6 ± 17.2 μV after palm stimulation for the median nerve, and 2.86 ± 0.37 ms and 46.1 ± 24.3 μV for the ulnar nerve. The latency difference between the two nerves, averaging 0.01 ± 0.17 ms, should not exceed 0.4 ms (mean + 2.5D).

Motor axons have a threshold similar to that of the large myelinated sensory axons. Thus, superimposition of action potentials from distal muscles may obscure the antidromically recorded SNAP. Palmar stimulation distal to the origin of the motor fibers, however, selectively activates the sensory fibers of the median nerve. This helps identify muscle action potentials, if elicited with more proximal stimulation, by a change in waveform of the evoked response.[76] Unnecessarily strong shocks applied to the palm tend to co-activate the median and ulnar sensory fibers innervating the ring finger. Careful placement of electrodes along the line extended from the medial or lateral aspect of this finger enables selective stimulation of one or the other branch.[165] A light twitch of ulnar or median innervated muscle usually signals proper stimulation placement.

Digital[12] or palmar stimulation[26] elicits an orthodromic sensory nerve or mixed sensory and antidromic motor nerve potentials, recordable at a more proximal site with either surface or needle electrodes. A smaller size of the orthodromic SNAP reflects the depth of the nerve trunk from the skin surface. The averaging technique helps detect low-amplitude potentials seen in a diseased nerve. Women tend to have greater amplitude at the wrist than men, possibly because of smaller wrist size.[103]

The palmar cutaneous branch of the median nerve usually arises about 5.5 cm proximal to the radial styloid and innervates skin of the thenar eminence. Stimulation of the median nerve above the branching point elicits an antidromic SNAP over the mid thenar eminence. In one series, normal values over 10 cm segments included the onset latency of 2.6 ± 0.2 ms (mean ± SD) and amplitude of 12 ± 4.6 μV.[107] Alternatively, stimulation at the lateral thenar eminence gives rise to an orthodromic SNAP at the wrist showing the onset latency of 2.0 ± 0.2 ms and amplitude of 4.1 ± 1.7 μV over a 10-cm segment.[56,189] Despite the common belief that the CTS results from an entrapment distal to this cutaneous branch, its abnormalities may not necessarily speak against the diagnosis.[141]

INCHING TECHNIQUE

The use of palmar stimulation (Fig. 6-7)[75] provides a simple means of identifying conduction abnormalities of sensory or motor fibers along its most affected segment under the transverse carpal ligament.[98,101,127] This technique differentiates the CTS from a more distal involvement seen, for example, in patients with diabetic polyneuropathy.[48,81]

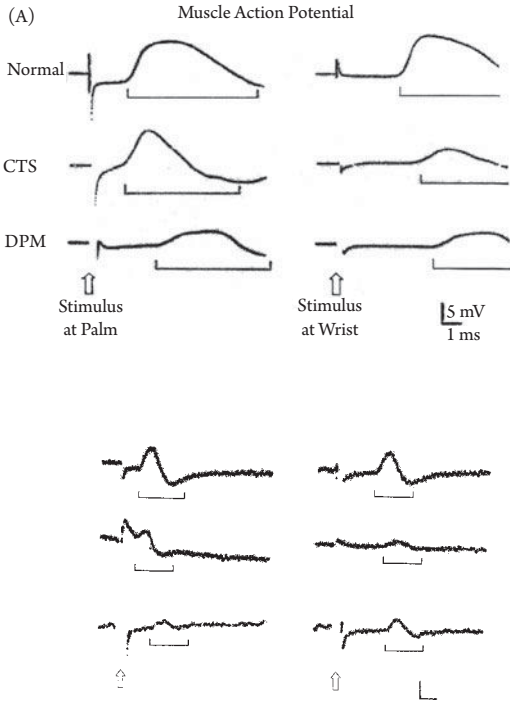


FIGURE 6-7 (***A***) stimulation of the median nerve at the wrist elicited a delayed thenar muscle response in both carpal tunnel syndrome (CTS) and diabetic polyneuropathy (DPN), whereas palmar stimulation revealed a delay only in DPN, and not in CTS. (***B***) The same distinction of antidromic sensory potentials recorded from the index finger from the same patients with CTS and DPN (From Kimura, Yamada, Rodnitzky, et al.[81])

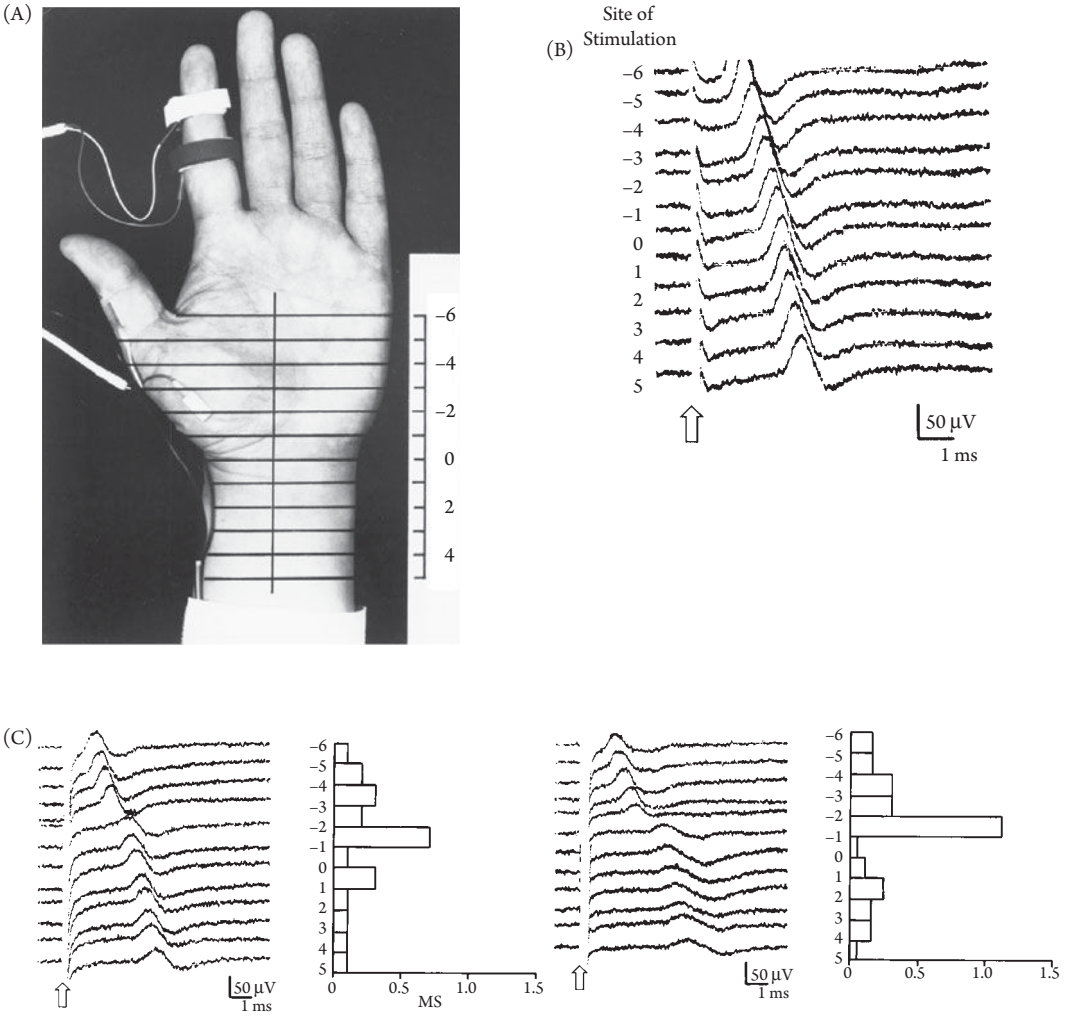


FIGURE 6-8 (***A***) Twelve sites of stimulation in 1-cm increments along the length of the median nerve. The "0" level at the distal crease of the wrist corresponds to the origin of the transverse carpal ligament. The photo shows a recording arrangement for sensory nerve potentials from the index finger and muscle action potentials from the abductor pollicis brevis. (From Kimura,[76] with permission.) (***B***) Sensory nerve potentials in a normal subject recorded after stimulation of the median nerve at multiple points across the wrist. The numbers on the left indicate the site of each stimulus (cf. ***A***). The latency increased linearly with stepwise shifts of stimulus site proximally in 1-cm increments. (From Kimura,[76] with permission.) (***C***) Sensory nerve potentials in a patient with the carpal tunnel syndrome. Both hands showed a sharply localized slowing from –2 to –1 with the calculated segmental conduction velocity of 14 m/s on the left (*left*) and 9 m/s on the right (*right*). Note a distinct change in waveform of the sensory potential at the point of localized conduction delay. (From Kimura,[76] with permission.)

(*Continues*)

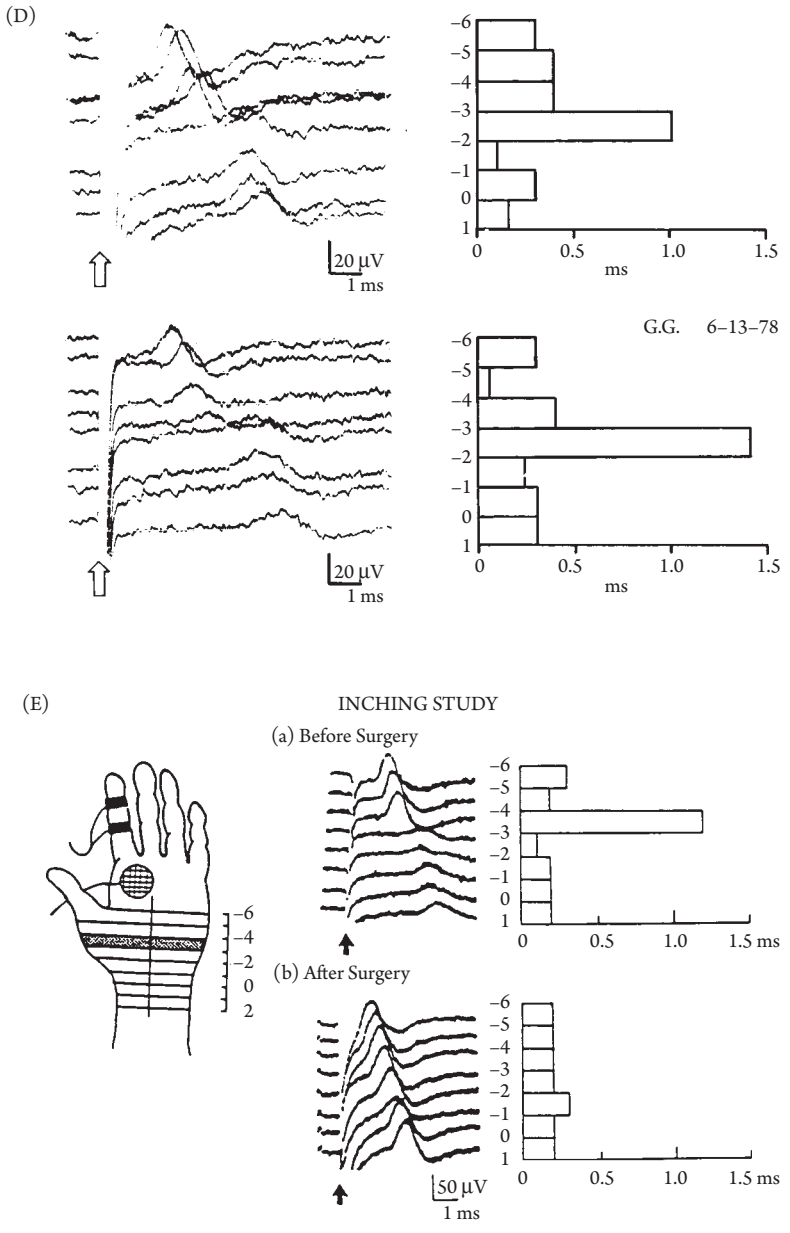


FIGURE 6-8 (*Continued*) (***D***) Sensory nerve potential in a patient with carpal tunnel syndrome. Both hands show a sharply localized slowing from –3 to –2 with a segmental conduction velocity of 10 m/s on the left (*top*) and 7 m/s on the right (*bottom*). An abrupt change in waveform of the sensory potential also indicates the point of localized conduction delay. Temporally dispersed proximal responses on the right had a greater negative-to-positive peak amplitude as well as area compared to more distal, normal responses, presumably indicating the loss of physiologic phase cancellation (see Chapter 11–5). (From Kimura,[76] with permission.) (***E***) Sensory nerve potential in a patient with carpal tunnel syndrome before (a) and after surgery (b). Preoperative study showed a localized slowing from –4 to –3 with the calculated segmental conduction velocity of 8 m/s, which normalized in a repeat study 6 months postoperatively. (From Ross and Kimura.[146])

Stimulation of the median nerve at multiple sites across the wrist (Fig. 6-8A) further localizes the point of maximal conduction delay within the distal segment of the median nerve (see Chapter 25-5).[75,76,118;146] Short segmental stimulation of the motor fibers poses a more technical challenge when recording from abductor pollicis brevis because the thenar nerve takes a recurrent course. The use of the second lumbricals circumvents this difficulty (Fig. 6-9) (see Chapter 11-3).

The inching studies normally show a predictable latency change of 0.16 to 0.20 ms/cm with a series of stimulation from mid palm to distal forearm in 1-cm increments for both motor and sensory axons (Fig. 6-8B). A sharply localized latency increase across a 1-cm segment indicates focal abnormalities of the median nerve (Fig. 6-8C, D, and E). A nonlinear shift in latency usually accompanies an abrupt change in waveform showing pathological temporal dispersion. Sensory responses elicited by proximal stimulation may show a paradoxical increase in size if excessive desynchronization prevents physiologic phase cancellation between fast and slow signals (see Chapter 11-5). Stimulation of the median nerve at the digit[78] or at the elbow[58] evokes orthodromic and mixed nerve potentials recordable simultaneously at several sites across the carpal tunnel with multi channel-recording electrodes. This technique offers instantaneous comparison of latencies but not amplitudes, which vary substantially depending on the depth of the nerve at each recording site. [78,153]

Ulnar Nerve

Tables 6-2, 6-3, and 6-4 (see also Appendix Tables 1-4 and 1-5) summarize normal values.

MOTOR STUDIES

Like the median nerve, the ulnar nerve takes a relatively superficial course along its entire length. Common sites of stimulation include palm, wrist, axilla, and Erb's point (Fig. 6-10). Routine motor NCS consist of stimulating the nerve segmentally and recording the CMAP from the hypothenar muscles with surface electrodes placed over the belly of the abductor digiti minimi (E1) and its tendon (E2), 3 cm distally (Fig. 6-11).[3] The bi-lobed appearance of CMAP indicates contribution not only from superficial but also from deep motor branch innervated muscles.[52] Alterative recording sites include first palmar interosseus and forearm muscles such as flexor carpi ulnaris[181] and flexor digitorum profundus. The use of a fixed distance from the distal crease of the wrist or from the recording electrode improves the accuracy of latency comparison between the two sides and among different subjects. In our laboratory, we place the cathode 3 cm proximal to the distal crease of the wrist and the anode, 2 cm further proximally. Spread of stimulus current at Erb's point or in the axilla causes less obvious distortion of waveform in studying the ulnar nerve as compared with the median nerve, which gives rise to volume-conducted potentials from the thenar eminence unless eliminated by the collision technique.[74]

Stimulation of the motor fibers above and below the elbow helps document a tardy ulnar palsy and a cubital tunnel syndrome usually by detecting an absolute slowing of conduction across the elbow but also, to a lesser extent, by comparison to an adjacent segment.[92,159] The longer the distance between the proximal and distal sites of stimulation across the elbow, the less the measurement error, and consequently more accurate the determination of conduction velocity.[91,92,184] Studies of longer segment, however, often fail to uncover a mild abnormality because a focal slowing induces an insignificant delay unless assessed by short segmental study, which also helps localize the lesion precisely (see Chapter 11-7). The ulnar nerve slides back and forth in the cubital tunnel with flexion and extension of the elbow joint. Thus, normal values vary depending on the position of the elbow, and to a lesser degree, of the wrist.[149] Holding the arm either at slight (l35 degrees) or moderate (90 degrees) flexion during stimulation and measurement minimizes the error.[82,85]

The study of the deep palmar motor branch depends on recording the muscle potential from the abductor digiti minimi (Fig. 6-11A) and first dorsal interosseus (Fig. 6-11B) after stimulation of the ulnar nerve at the wrist. The latency difference between these two muscles or between the hypothenar and thenar responses yields an approximate measure of conduction along the

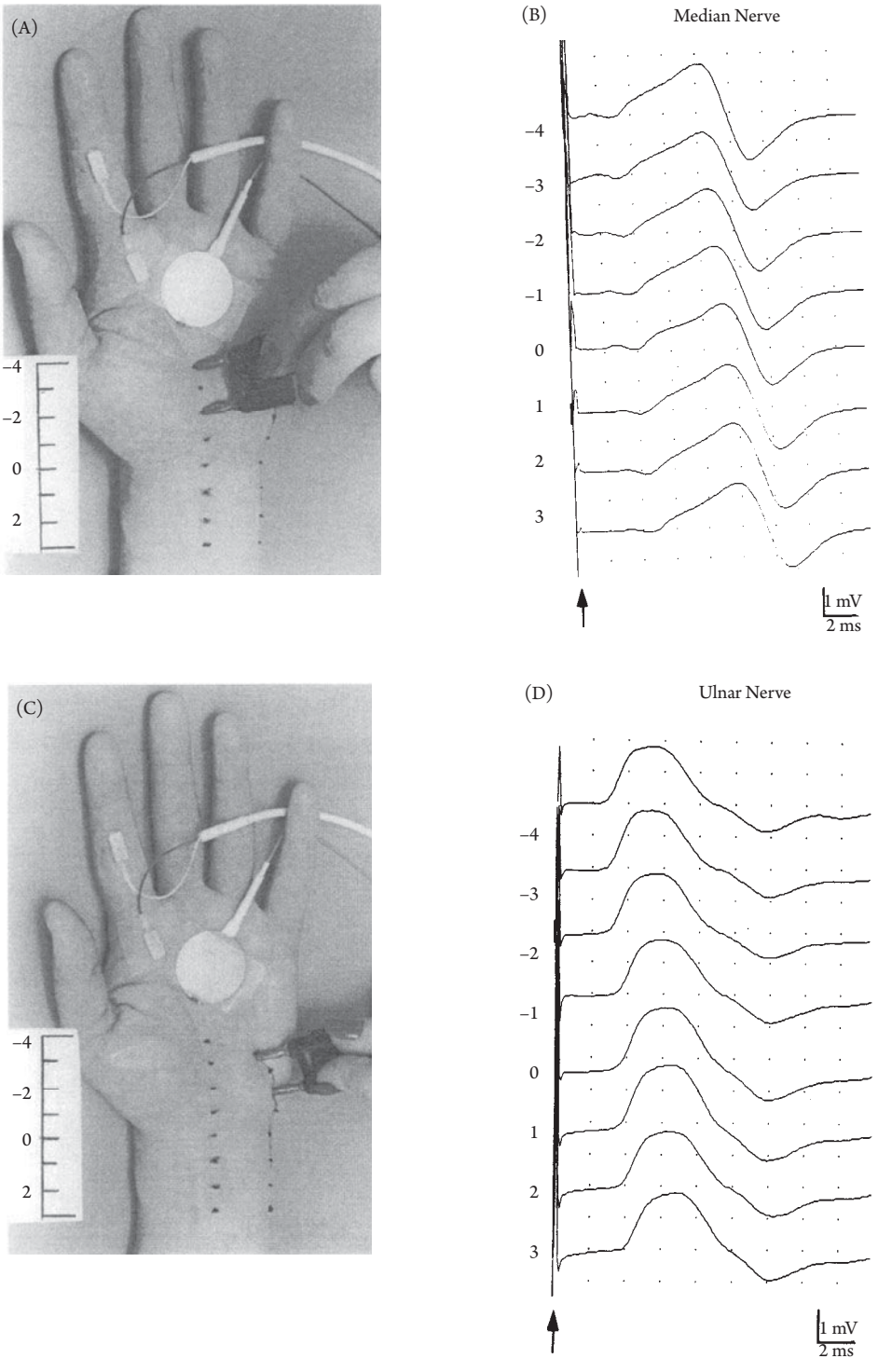


FIGURE 6-9 The inching study of median (***A*** and ***B***) and ulnar nerve (***C*** and ***D***) across the wrist in 1-cm increments at eight sites of stimulation along the course of the nerve. The zero level at the distal crease of the wrist corresponds to the origin of the transverse carpal ligament and Guyon's canal. The photograph shows a recording arrangement for muscle action potentials from the second lumbricalis after stimulation of the median nerve (***A***) and the first volar interosseous after stimulation of the ulnar nerve (***C***). The latency increases linearly with stepwise shifts of stimulus site proximally in 1-cm increments for both median (***B***) and ulnar study (***D***).

Table 6-4 Ulnar Nerve*

SITE OF STIMULATION	AMPLITUDE†: MOTOR (mV) SENSORY (μV)	LATENCY‡ TO RECORDING SITE (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CONDUCTION TIME BETWEEN TWO POINTS (ms)	CONDUCTION VELOCITY (m/s)
Motor fibers					
Wrist	5.7 ± 2.0 (2.8)§	2.59 ± 0.39 (3.4)¶	0.28 ± 0.27 (0.8)¶		
Below elbow	5.5 ± 2.0 (2.7)	6.10 ± 0.69 (7.5)	0.29 ± 0.27 (0.8)	3.51 ± 0.51 (4.5)¶	58.7 ± 5.1 (49)**
Above elbow	5.5 ± 1.9 (2.7)	8.04 ± 0.76 (9.6)	0.34 ± 0.28 (0.9)	1.94 ± 0.37 (2.7)	61.0 ± 5.5 (50)
Axilla	5.6 ± 2.1 (2.7)	9.90 ± 0.91 (11.7)	0.45 ± 0.39 (1.2)	1.88 ± 0.35 (2.6)	66.5 ± 6.3 (54)
Sensory fibers					
Digit				2.54 ± 0.29 (3.1)	54.8 ± 5.3 (44)
Wrist	35.0 ± 14.7 (18)	2.54 ± 0.29 (3.1)	0.18 ± 0.13 (0.4)	3.22 ± 0.42 (4.1)	64.7 ± 5.4 (53)
Below elbow	28.8 ± 12.2 (15)	5.67 ± 0.59 (6.9)	0.26 ± 0.21 (0.5)	1.79 ± 0.30 (2.4)	66.7 ± 6.4 (54)
Above elbow	28.3 ± 11.8 (14)	7.46 ± 0.64 (8.7)	0.28 ± 0.27 (0.8)		

*Mean ± standard deviation (SD) in 130 nerves from 65 healthy subjects, 13 to 74 years of age (average, 39), with no apparent disease of the peripheral nerves.

†Amplitude of the evoked response, measured from the baseline to the negative peak.

‡Latency, measured to the onset of the evoked response, with the cathode 3 cm above the distal crease in the wrist.

§Lower limits of normal, based on the distribution of the normative data.

¶Upper limits of normal, calculated as the mean + 2 SD.

**Lower limits of normal, calculated as the mean – 2 SD.

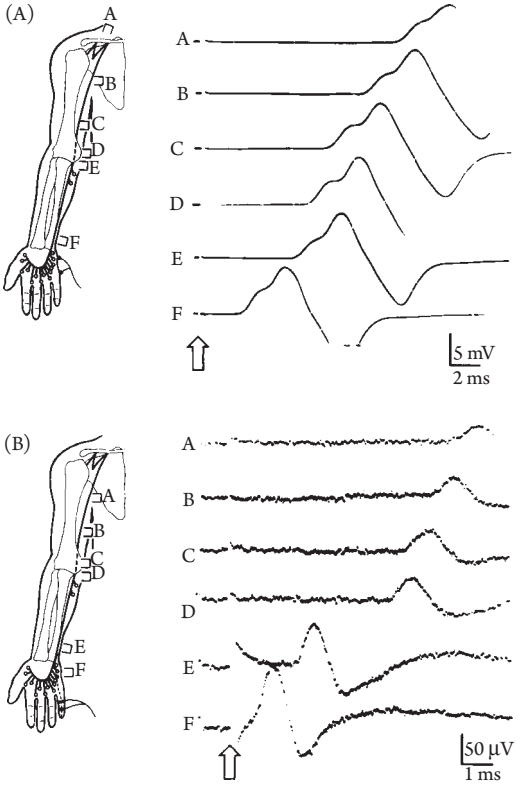


FIGURE 6-10 (***A***) Motor nerve conduction study of the ulnar nerve. The sites of stimulation include Erb's point (A), axilla (B), above elbow (C), elbow (D), below elbow (E), and wrist (F). The tracings show compound muscle action potentials recorded with a pair of surface electrodes placed on the hypothenar eminence. (***B***) Sensory nerve conduction study of the ulnar nerve. The sites of stimulation include axilla (A), above elbow (B), elbow (C), below elbow (D), wrist (E), and palm (F). The tracings show antidromic sensory potentials recorded with a pair of ring electrodes placed 2 cm apart around the little finger.

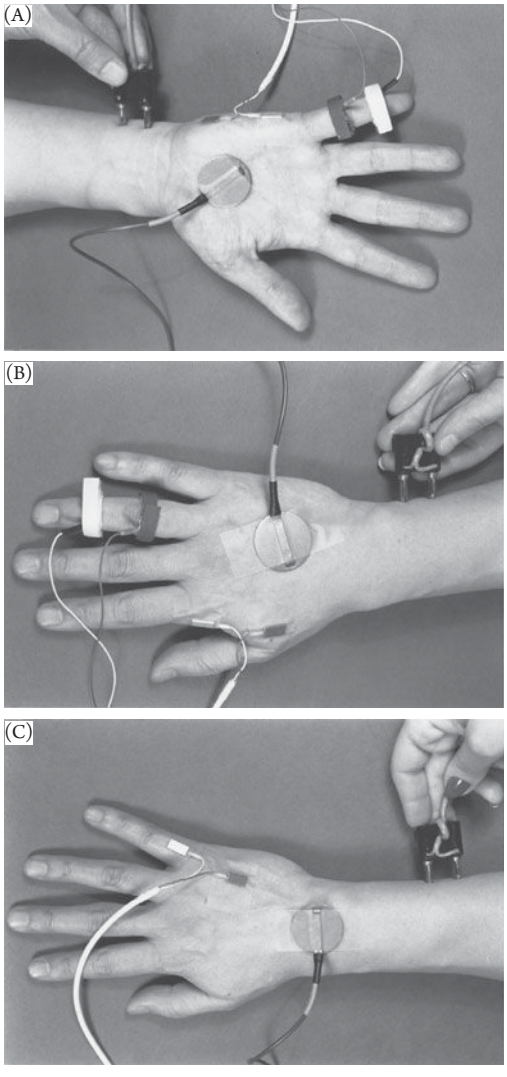


FIGURE 6-11 (***A***) Motor and sensory conduction study of the ulnar nerve. The photo shows stimulation at the wrist, 3 cm proximal to the distal crease, and recording with a pair of electrodes placed over the belly (E1) and tendon (E2) of the abductor digiti minimi for motor conduction, and with a pair of ring electrodes placed 2 cm apart around the proximal (E1) and distal (E2) interphalangeal joints of the little finger for antidromic sensory conduction. (***B***) Alternative recording sites for ulnar nerve conduction studies with the surface electrodes over the belly (E1) and tendon (E2) of the first dorsal interosseus muscle for motor conduction and around the proximal (E1) and distal (E2) interphalangeal joints of the ring finger for antidromic sensory conduction. (***C***) Sensory conduction study of the dorsal cutaneous branch of the ulnar nerve. The photo shows stimulation along the medial aspect of the forearm between the tendon of the flexor carpi ulnaris and the ulna, 14–18 cm from the active electrode, and recording over the dorsum of the hand between the fourth and fifth metacarpals (E1) and the base of the little finger (E2).

deep branch. In one series of 373 studies, the upper limit latency range included 4.5 ms for the first dorsal interosseous, 1.3 ms for the side-to-side difference, and 2.0 ms for the difference compared to the abductor digiti minimi.[125] In the assessment of the deep palmar branch, the size of CMAP elicited by stimulation in the palm distal to the site of lesion provides a good measure of the number of remaining motor axons (Fig. 6-12). The lumbrical-interosseus comparison described for median nerve motor studies also serves in assessing a distal ulnar nerve lesion, which typically causes a latency difference greater

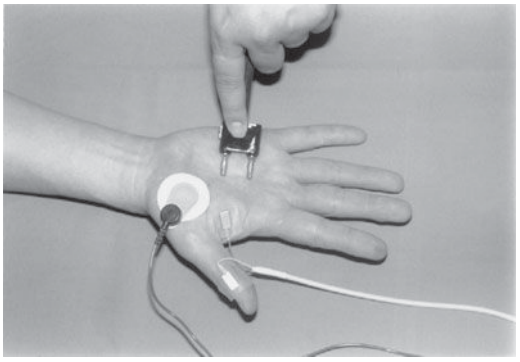


FIGURE 6-12 Stimulation of the ulnar nerve in the palm with the cathode placed over the palmar branch and the anode 2 cm distally, and recording of the muscle response over the belly of the adductor pollicis brevis (E1) referenced to the thumb (E2). Appropriate thumb twitch confirms activation of the deep palmar branch of the ulnar nerve as opposed to the recurrent thenar nerve, which usually lies 1 cm more proximally (cf. Fig. 6-3).

than 0.4 ms compared to the unaffected median nerve.[86,161] Short segmental stimulation (Fig. 6-9) helps localize a lesion within the wrist segment.[70]

SENSORY STUDIES

Stimulation of the ulnar nerve trunk elicits an antidromic sensory potential of the ring and small fingers, which receive sensory nerve fibers

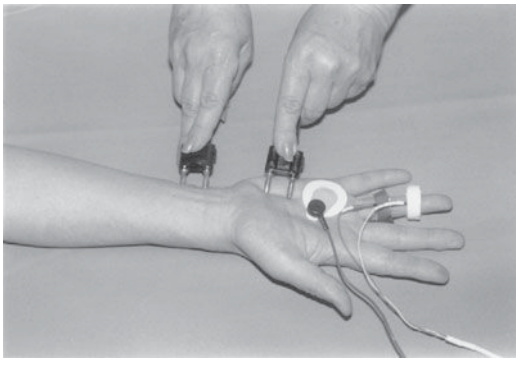


FIGURE 6-13 Stimulation of the ulnar nerve at the wrist and palm with cathode placed 3 cm proximal and 5 cm distal to the wrist crease and the anode placed 2 cm proximally, and recording of the antidromic digital potential with the ring electrodes placed 2 cm apart around the proximal (E1) and distal (E2) interphalangeal joints of the ring finger. This arrangement yields results directly comparable to the analogous study of the median nerve (cf. Figs. 6-4).

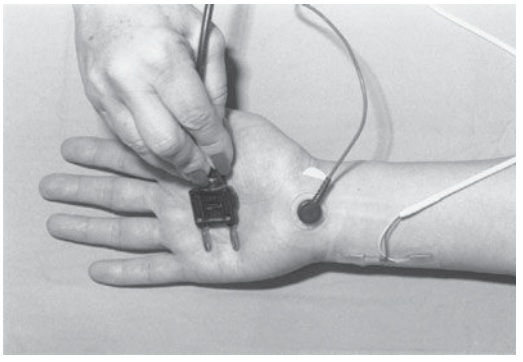


FIGURE 6-14 Stimulation of the ulnar nerve in the palm with the cathode placed 2 cm proximal to the anode, and recording of mixed nerve potential with the active electrode (E1) over the ulnar nerve trunk 8 cm proximal to the cathode and the reference electrode (E2) 2 cm further proximally.

from C8 root, lower trunk and medial cord (Figs. 6-10B and 11A, B). The common sites of cathodal points include above and below the elbow, 3 cm proximal to the distal crease at the wrist, and 5 cm distal to the crease in the palm, with the anode located 2 cm further, proximally (Fig. 6-13). These stimulus sites make the studies comparable to those of the median nerve (Fig. 6-4). Stimulation of the digital nerve with ring electrodes placed around the interphalangeal joints of the little finger, cathode proximally, elicits orthodromic SNAP at various sites along the course of the nerve. Stimulation of the nerve at the palm or wrist gives rise to a mixed nerve potential of the ulnar nerve proximally at the wrist or elbow (Fig. 6-14). Preganglionic C8 avulsion spares sensory potentials despite the clinical sensory loss. Thus, these studies help differentiate lesions of C8 and T1 from those of the lower trunk, medial cord of the brachial plexus, or ulnar nerve.

The dorsal sensory branch, called the dorsal ulnar cutaneous nerve, leaves the common trunk of the ulnar nerve 5–8 cm proximal to the ulnar styloid.[64] It becomes superficial between the tendon of the flexor carpi ulnaris and the ulna.[10] Surface stimulation here selectively evokes antidromic SNAP over the dorsum of the hand, although anatomic variations may alter cutaneous innervation.[136] Placing the active electrode (El) between the fourth and fifth metacarpals with the reference electrode (E2) at the base of the

little finger optimizes the recording (Fig. 6-11C). Stimulation of the ulnar nerve trunk more proximally elicits a mixed nerve potential that slightly precedes a large muscle action potential from the intrinsic hand muscles. The dorsal ulnar cutaneous nerve, like the ulnar nerve proper, derives from C8 roots, the lower trunk, and the medial cord but usually escapes compression at Guyon's canal.

The normal values (mean ± SD) of the dorsal cutaneous nerve SNAP recorded 8 cm from the point of distal stimulation[64] include amplitude of 20 ± 6 μV, distal latency of 2.0 ± 0.3 ms, and conduction velocity of 60 ± 4.0 m/s between elbow and forearm. This technique complements the conventional study, especially if a lesion at the wrist abolished the digital sensory potentials. Its abnormality localizes the lesion proximal to the origin of this branch, on the average, 6.4 cm above the wrist.[10] Conversely, a normal dorsal cutaneous response combined with abnormal digital ulnar sensory potential usually, though not always,[185] suggests a lesion at the wrist. An absent dorsal ulnar cutaneous nerve response may result from anomalous innervation by superficial radial nerve found in 9% of the population at large.[100]

INCHING TECHNIQUE

Segmental stimulation across the elbow in 1–2 cm increments detects, at the site of localized compression, an abrupt change in latency and waveform of the CMAP recorded from abductor digit minimi[5,15, 77] or flexor carpi ulnaris.[105] A greater percentage change over the affected short segment more than compensates for possible errors caused by unintended spread of the stimulus current (see Chapter 11-7). Ulnar dislocation of the nerve, sometimes associated with elbow flexion, may make stimulation insufficient to activate the nerve segment at the glove, erroneously suggesting a conduction block.[72] In questionable cases, showing a linear latency change above and below the lesion site further confirms a focal abnormality localized by nonlinear shift in the middle (see Fig. 5-7). Similarly, incremental stimulation across the wrist reveals an abrupt change of CMAP waveforms recorded from the first palmar interosseus, disclosing a compression site within Guyon's canal (Fig. 6-9C, D).

Radial Nerve

Table 6-5 (see also Appendix Tables 1-4 and 1-5) summarizes normal values.[178]

MOTOR STUDIES

The radial nerve becomes relatively superficial in the forearm, above the elbow, near the spinal groove, in the axilla, and at the supraclavicular fossa (Fig. 6-15A). The optimal sites of electrical

Table 6-5 Radial Nerve*

CONDUCTION	*n*	CONDUCTION VELOCITY (m/s) OR CONDUCTION TIME (ms)	AMPLITUDE: MOTOR (mV) SENSORY (μV)	DISTANCE (cm)
Motor				
Axilla–elbow	8	69 ± 5.6	11 ± 7.0	15.7 ± 3.3
Elbow–forearm	10	62 ± 5.1	13 ± 8.2	18.1 ± 1.5
Forearm–muscle	10	2.4 ± 0.5	14 ± 8.8	6.2 ± 0.9
Sensory				
Axilla–elbow	16	71 ± 5.2	4 ± 1.4	18.0 ± 0.7
Elbow–wrist	20	69 ± 5.7	5 ± 2.6	20.0 ± 0.5
Wrist–thumb	23	58 ± 6.0	13 ± 7.5	13.8 ± 0.4

*Mean ± standard deviation (SD) in healthy subjects.

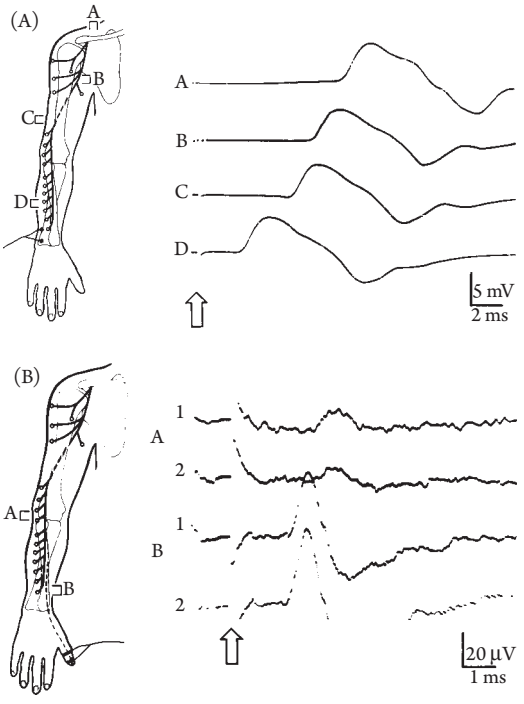


FIGURE 6-15 (***A***) Motor nerve conduction study of the radial nerve. The sites of stimulation include Erb's point (A), axilla (B), above elbow (C), and mid forearm (D). The tracings show compound muscle action potentials recorded with a pair of surface electrodes placed on the extensor indicis. (***B***) Sensory nerve conduction study of the radial nerve. The sites of stimulation include elbow (A) and distal forearm (B). The tracings show antidromic sensory potentials recorded with a pair of ring electrodes placed around the thumb.

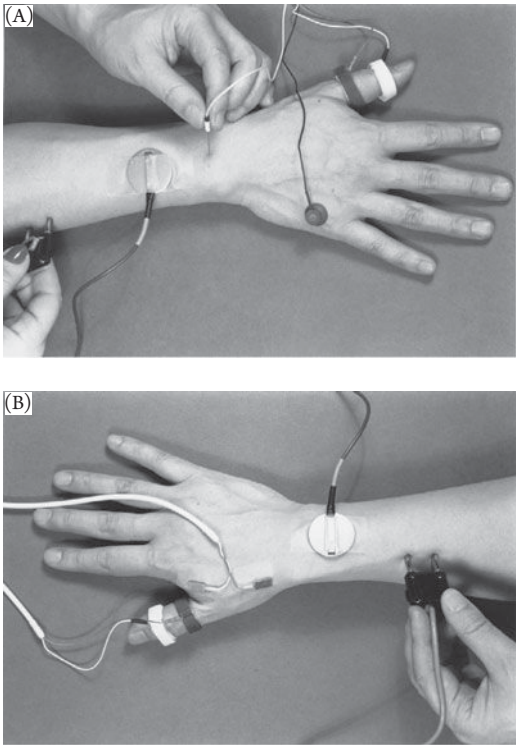


FIGURE 6-16 (***A***) Motor and sensory conduction studies of the radial nerve. The photo shows surface stimulation in the forearm with the cathode at the lateral edge of the extensor carpi ulnaris muscle, 8–10 cm proximal to the styloid process. Recording electrodes comprise a monopolar needle (E1) inserted in the extensor indicis with a reference electrode (E2) over the dorsum of the hand laterally for motor conduction studies and ring electrodes placed around the base (E1) and interphalangeal joint (E2) of the thumb for antidromic sensory conduction. (***B***) Alternative stimulation and recording sites for antidromic sensory nerve conduction study of the radial nerve. The photo shows the cathode placed at the lateral edge of the radius in the distal forearm, with the anode 2 cm proximally with the recording electrodes placed either around the base (E1) and interphalangeal joint (E2) of the thumb, or over the palpable nerve between the first and second metacarpals (E1) and 2–3 cm distally (E2).

stimulation of the motor fibers, therefore, include (1) between the extensor carpi ulnaris and extensor digiti minimi on the dorsolateral aspect of the ulna, 8 to 10 cm proximal to the styloid process, (2) between the brachioradialis and the tendon of the biceps 6 cm proximal to the lateral epicondyle, (3) between the coracobrachialis and medial edge of the triceps about 18 cm proximal to the medial epicondyle, and (4) Erb's point. Either needle or surface electrodes suffice (Fig. 6-16A) when recording a CMAP from the extensor indicis or the extensor digitorum communis.

In the motor NCS, commonly encountered errors include such technical problems as submaximal stimulation in an obese or muscular limb and coactivation of a number of extensors and distortion of the waveform by volume conducted potentials from neighboring muscles. Furthermore, distal stimulation activates fewer muscles than does proximal stimulation, making a valid comparison between the two responses difficult. The use of needle electrodes for stimulation and recording helps circumvent some of these limitations. Needle studies also enable relatively selective recording from more proximal muscles such as the anconeus, brachioradialis,

and triceps. In assessing the distance between the axilla to elbow segment, anterior surface measurement by a tape compares most favorably with the actual nerve length.[66]

SENSORY STUDIES

The sensory branches run deep at the level of the elbow where the posterior antebrachial cutaneous nerve emerges to innervate the dorsolateral aspect of the forearm. It then becomes more superficial about 8–10 cm above the lateral styloid process, crossing the extensor pollicis longus at this point, and divides into medial and lateral branches. The sensory fibers, palpable at the base of the thumb, originate primarily from C6, traverse the upper and middle trunk, and enter the posterior cord. Preganglionic avulsion of the C6 results in a clinical sensory loss without abnormalities of the sensory potentials. The usual NCS consists of surface stimulation at the lateral edge of the radius in the distal forearm 10–14 cm proximal to the base of the thumb and recording an antidromic sensory potential by a pair of ring electrodes placed around the thumb (Fig. 6-16B). Alternative arrangements for medial and lateral branches combine a disc electrode (E1) over the snuffbox and lateral to abductor pollicis longus and a reference electrode (E2) near the first dorsal interosseus.[108,129] An additional stimulation at the elbow under the brachioradialis muscle lateral to the biceps tendon (Fig. 6-15A) allows determination of conduction velocities in the segments between the elbow and wrist and the wrist and thumb.[17]

Stimulation of the radial nerve at the thumb or the wrist elicits an orthodromic SNAP in the elbow and axilla. Spread of the current to the median nerve, which partially supplies the thumb, accounts for 25% of the sensory potential recorded over the radial nerve at the wrist or elbow and 50% of that recorded at the axilla[178] Stimulation at the wrist, especially with needle electrodes placed along the nerve, accomplishes more selective activation of the radial nerve. Stimulation of the long finger may occasionally elicit an orthodromic potential over snuffbox indicating its anomalous innervation by the radial nerve.[67] Anomalous superficial radial nerve may also innervate most of the dorsum of the hand, including the area usually supplied by the dorsal branch of the ulnar nerve.[88]

INCHING TECHNIQUE

Stimulation of the radial nerve 10 cm proximal to the styloid process of the radius allows serial recording of antidromic sensory potential along the length of the radial nerve distally. In addition to theoretical interest in elucidating the mechanisms of a far-field potential (see Fig. 19-2), a nonlinear latency change can localize a focal lesion seen, for example, in a hand cuff neuropathy.

4. NERVES IN THE CERVICAL AND THORACIC REGION

Phrenic Nerve

Table 6-6 (see also Appendix Table 1-4) summarizes normal ranges established in 66 healthy subjects divided into two subgroups: middle and old age.[57]

Conduction studies of the phrenic nerve, though described early,[119] have gained popularity only recently. Surface stimulation in the cervical area along the posterior edge of the sternocleidomastoid requires shocks of a relatively high intensity. Supramaximal stimulation may coactivate the brachial plexus located posteriorly behind the anterior scalene muscle. In one study,[144] stimulation just above the clavicle between the sternal and clavicular heads of the sternocleidomastoid muscles elicited responses at the lowest stimulation strength. In our experience, pressing the stimulator placed in this location posteriorly tends to achieve selective phrenic activation (Fig. 6-17A). As an alternative method, some investigators[111] use a standard monopolar needle electrode inserted medially from the lateral aspect of the neck at the level of the cricoid cartilage (Fig. 6-17B). After traversing the posterior margin of the sternocleidomastoid muscle, the needle tip comes to within a few millimeters of the phrenic nerve and adequately distant from the carotid artery anteriorly and the apex of the lung inferiorly. A metal plate placed on the manubrium serves as the anode. Selective stimulation of the phrenic nerve

Table 6-6 Phrenic Nerve

MEASUREMENT	MIDDLE AGE (n = 25)		OLD AGE (n = 41)	
	MEAN ± SD	RANGE	MEAN ± SD	RANGE
Latency (ms)				
Right	6.80 ± 0.72	5.2–8.0	7.46 ± 1.08	5.9–10.6
Left	6.82 ± 0.80	5.0–8.0	7.43 ± 1.08	5.7–10.6
Right–Left	0.30 ± 0.25	0.0–1.1	0.27 ± 0.27	0.0–1.0
% Difference	3.5 ± 3.2	0.0–14.2	3.6 ± 3.5	0.0–14.5
Amplitude (μV)				
Right	439 ± 182	140–780	263 ± 122	100–546
Left	368 ± 170	100–680	225 ± 102	96–440
Right–Left	121 ± 74	25–300	96 ± 72	20–393
% Difference	35.1 ± 26.5	5.3–100.0	41.4 ± 26.1	6.5–112.4

Middle age: 35–55 (mean 45) years, old age: 60–101 years. % Difference calculated as [absolute value of (R – L)/(mean of R and L)]. (From Imai, Yuasa, Kato, et al.[57] with permission), not From Imai, Yuasa, Kato, et al.[57] (with permission).)

induces diaphragmatic contraction as evidenced by hiccup or interruption of voluntarily sustained vocalization. Simultaneous fluoroscopic observation can confirm diaphragm excursion associated with the muscle contraction.[2]

The diaphragmatic action potential gives rise to a strong positivity at the 7th or 8th intercostal space near the costochondral junction and a mild negativity at the xiphoid process.[112] Therefore, placing the active lead (E1) over the lower end of sternum and the reference lead (E2) a few centimeters below the nipple registers the largest amplitude with summation of out-of-phase activities. These measures show good intraindividual side-to-side agreement for latency but not for amplitude.[170] Nonetheless, the amplitude value serves better in predicting respiratory dysfunction.[20,16] In one study of 50 phrenic nerves from 25 healthy subjects,[20] normal values (mean ± SD) included the latency of 6.54 ± 0.77 ms and the amplitude of 660 ± 201 μV, with the right—left difference of 0.34 ± 0.27 ms and 66.3 ± 65.3 μV. Phrenic nerve conduction studies complement needle electromyography of the diaphragm by identifying the nature and site of disorder of the respiratory system.[9]

Greater Auricular Nerve

The greater auricular nerve, derived mainly from the C2 and C3 roots, ascends cephalad from the neck to the ear winding around the posterior border of the sternocleidomastoid. Stimulation with a pair of surface electrodes firmly placed here elicits an orthodromic sensory potential detectable on the back of the ear lobe. Reported values include latency of 1.7 ± 0.2 ms (mean ± SD) for the distance of 8 cm and conduction velocity of 46.8 ± 6.6 m/s in 20 healthy subjects,[128] and latency of 1.9 ± 0.2 ms and amplitude of 22.4 ± 8.9 μV in 32 normal control subjects.[73]

Cervical Spinal Nerve

A localized stimulus applied through a needle electrode can directly activate the spinal nerve at the junction of the respective ventral and dorsal roots.[111,114] The uninsulated tip comes to an optimal position when a standard 50–75 mm monopolar needle, inserted perpendicular to the skin surface, rests directly on the vertebral transverse process. Despite theoretical interest, technical difficulties abound in accomplishing selective,

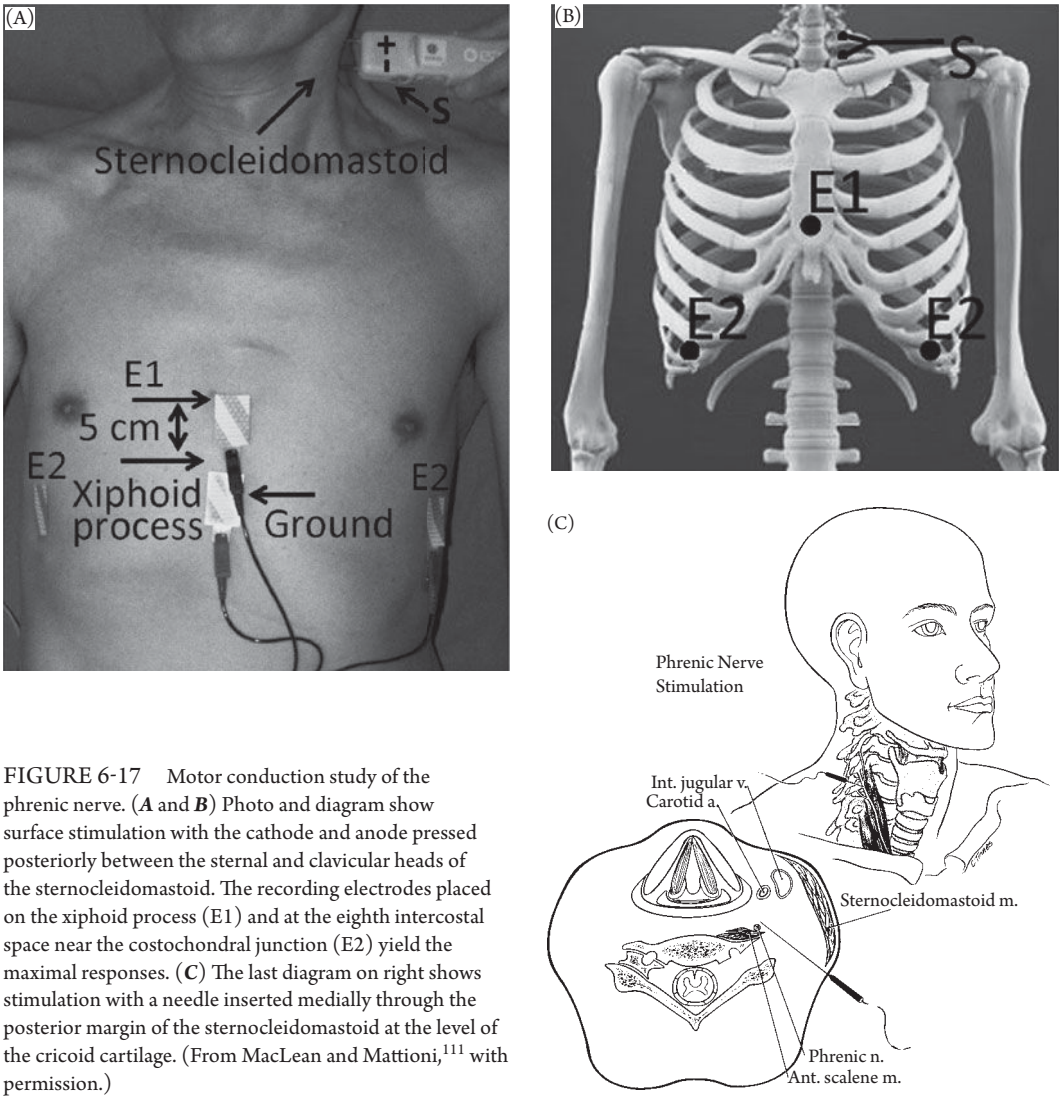


FIGURE 6-17 Motor conduction study of the phrenic nerve. (***A*** and ***B***) Photo and diagram show surface stimulation with the cathode and anode pressed posteriorly between the sternal and clavicular heads of the sternocleidomastoid. The recording electrodes placed on the xiphoid process (E1) and at the eighth intercostal space near the costochondral junction (E2) yield the maximal responses. (***C***) The last diagram on right shows stimulation with a needle inserted medially through the posterior margin of the sternocleidomastoid at the level of the cricoid cartilage. (From MacLean and Mattioni,[111] with permission.)

supramaximal activation of the intended roots, which greatly limits its practical value in clinical evaluation.

Joint stimulation of the C5 and C6 spinal nerves by placing the needle 1–2 cm lateral to the C5 spinous process tests the upper trunk and lateral cord (Fig. 6-18A). Similarly, positioning the needle slightly caudal to the C7 spinous process stimulates the C8 and T1 spinal nerves simultaneously for conduction across the lower trunk and medial cord (Fig. 6-18B). The needle inserted between these two points activates the C6, C7, and C8 spinal nerves simultaneously for evaluation of the posterior cord. A metal plate or disk electrode on the skin surface or a second needle electrode placed lateral to the cathode serves as the anode.

Brachial Plexus

Table 6-7 summarizes nerve conduction times to various shoulder girdle muscles across the brachial plexus from stimulation at Erb's point, and Table 6-8 shows corresponding values obtained with nerve root stimulation after subtracting the distal latency of the ulnar nerve.[110]

The brachial plexus comprises the anterior rami of the spinal nerves derived from the C5

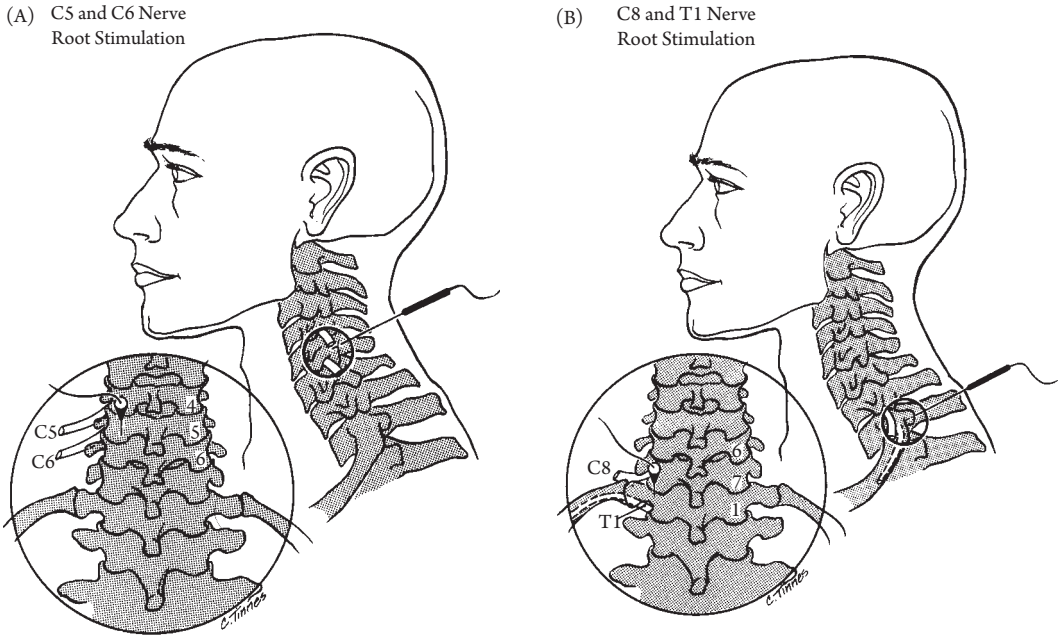


FIGURE 6-18 Motor conduction study with spinal nerve stimulation. The diagram shows the following: (***A***) C5 and C6 stimulation with the needle inserted perpendicular to the skin, 1–2 cm lateral to the C5 spinous process and (***B***) C8 and T11 stimulation with the needle inserted slightly caudal to the C7 spinous process. (From MacLean,[110] with permission.)

through C8, and T1 roots. Surface stimulation at Erb's point (see Fig. 1-8) activates the proximal muscles of the shoulder girdle. It also evokes action potentials in the distal muscles such as those of the thenar and hypothenar eminence. The volume-conducted potentials from a number of coactivated muscles interfere with the accurate recording of the intended signal even with the electrode placed over a specific intrinsic hand muscle. The collision technique circumvents this

Table 6-7 Nerve Conduction Times from Erb's Point to Muscle

MUSCLE	*n*	DISTANCE (cm)	LATENCY (ms)*
Biceps	19	20	4.6 ± 0.6
	15	24	4.7 ± 0.6
	14	28	5.0 ± 0.5
Deltoid	20	15.5	4.3 ± 0.5
	17	18.5	4.4 ± 0.4
Triceps	16	21.5	4.5 ± 0.4
	23	26.5	4.9 ± 0.5
	16	31.5	5.3 ± 0.5
Supraspinatus	19	8.5	2.6 ± 0.3
	16	10.5	2.7 ± 0.3
Infraspinatus	20	14	3.4 ± 0.4
	15	17	3.4 ± 0.5

*Mean ± standard deviation (SD) in healthy subjects. (Modified from Gassel, 1964.[45])

Table 6-8 Brachial Plexus Latency with Nerve Root Stimulation

PLEXUS (TUNK AND CORD)	SITE OF STIMULATION	RECORDING SITE	LATENCY ACROSS PLEXUS (ms)		
			RANGE	MEAN	SD
Brachial (upper trunk and lateral cord)	C5 and C6	Biceps brachii	4.8–6.2	5.3	0.4
Brachial (posterior cord)	C6, C7, C8	Triceps brachii	4.4–6.1	5.4	0.4
Brachial (lower trunk and medial cord)	C8 and Tl	Abductor digiti quinti	3.7–5.5	4.7	0.5

(Modified from MacLean.[110])

difficulty by blocking the unwanted impulse with a second stimulus applied distally to the nerve not under consideration (see Chapter 11-3). Stimulation with needle electrodes accomplishes more selective activation but carries the risk of inducing pneumothorax.[187] Selective recording with needle electrodes makes the latency measurement more reliable even with simultaneous activation of many nerves. Unlike surface electrodes, however, an intramuscular needle with restricted recording radius does not register the overall size of the CMAP.

The triceps has the endplate zone vertically oriented with the distal portion of the muscle innervated by longer nerve branches. Thus, the latency of a recorded response increases with the distance from the stimulus point. The latency changes nonlinearly, reflecting irregularly spaced points of innervation. The biceps and deltoid muscles have one or more horizontally directed endplates mostly in the middle of the fibers. The point of recording does not affect the latency of the response in these muscles as much as in the triceps. The same probably applies to the infraspinatus and supraspinatus. When testing a unilateral involvement of the brachial plexus, comparison between the affected and normal sides offers the most sensitive indicator (Table 6-7).[173] The standard protocol calls for equalizing the distance between the stimulating and recording electrodes on both sides. This principle holds in the study of any muscle of the shoulder girdle in general and that of the triceps in particular for the reasons stated previously.

Recording from several muscles helps evaluate different portions of the brachial plexus, for example, biceps for the upper trunk and lateral cord, triceps for the posterior cord, and ulnar-innervated intrinsic hand muscles for the lower trunk and medial cord. The side-to-side difference of brachial plexus latency exceeding 0.6 ms indicates unilateral lesions, making a more sensitive index than the absolute latency. The latency criteria, however, rarely provides useful information in axonal degeneration because remaining axons tend to show a relatively normal value. In contrast, the amplitude of the recorded response determines the degree of axonal loss despite its considerable variability among different subjects and between the two sides in the same individual. An amplitude preservation above one-half compared to the normal side suggests limited distal degeneration and good prognosis.

Musculocutaneous Nerve

Table 6-9 summarizes normal values for motor and sensory conduction studies.[175]

Optimal sites of stimulation for motor conduction include the axilla between the axillary artery medially and the coracobrachialis muscle laterally and the posterior cervical triangle 3 to 6 cm above the clavicle just behind the sternocleidomastoid muscle (see Fig. 1-9). Either surface electrodes or needle electrodes suffice to stimulate the nerve and to record the muscle action potentials from the biceps brachii.

Table 6-9 Musculocutaneous Nerve

AGE	MOTOR NERVE CONDUCTION BETWEEN ERB'S POINT AND.AXILLA				ORTHODROMIC SENSORY NERVE CONDUCTION BETWEEN ERB'S POINT AND AXILLA			ORTHODROMIC SENSORY NERVE CONDUCTION BETWEEN AXILLA AND ELBOW		
	n	RANGE OF CONDUCTION VELOCITY (m/s)	RANGE OF AMPLITUDE (μV)		*n*	RANGE OF CONDUCTION VELOCITY (m/s)	RANGE OF AMPLITUDE (μV)	*n*	RANGE OF CONDUCTION VELOCITY (m/s)	RANGE OF AMPLITUDE (μV)
			AXILLA	ERB'S POINT						
15–24	14	63–78	9–32	7–27	14	59–76	3.5–30	15	61–75	17–75
25–34	6	60–75	8–30	6–26	6	57–74	3–25	8	59–73	16–72
35–44	8	58–73	8–28	6–24	7	54–71	2.5–21	8	57–71	16–69
45–54	10	55–71	7–26	6–22	10	52–69	2–18	13	55–69	15–65
55–64	9	53–68	7–24	5–21	9	49–66	2–15	10	53–67	14–62
65–74	4	50–66	6–22	5–19	4	47–64	1.5–12	6	51–65	13–59

(Modified from Trojaborg.[175])

Long Thoracic Nerve

This motor nerve arises from C5, C6, and C7 and descends through the neck and the thoracic wall. Stimulation at Erb's point or axilla allows recording of muscle action potentials from the serratus anterior with surface or needle electrodes located on the 7th or 8th rib along the anterior axillary line.[28] Normative data (mean ± SD) in one study[155] included latency of 2.2 ± 0.3 ms and amplitude of 5.3 ± 2.4 mV with surface recording.

Lateral Antebrachial Cutaneous Nerve

Table 6-10 (see also Appendix Table 1-5) summarizes normal values reported in two series.[61,167]

The sensory branch of the musculocutaneous nerve runs superficially at the level of the elbow just lateral to the biceps tendon. Stimulation of the nerve at this point elicits orthodromic sensory potentials usually recorded by the same electrodes positioned to stimulate motor fibers at the posterior cervical triangle and axilla. The same stimulus also elicits antidromic SNAP over the lateral antebrachial cutaneous nerve, usually recorded with surface electrodes placed 12 cm from the stimulus point along the straight line to the radial artery at the wrist (Fig. 6-19). Study of this sensory potential provides evaluation of C6, upper trunk and lateral cord better than the median nerve sensory potentials recorded from the index finger, which, more often than not, represent C7 and middle trunk.[42]

Medial Antebrachial Cutaneous Nerve

Table 6-10 (see also Appendix Table 1-5) shows the results of three studies.[61,142,154]

The medial antebrachial cutaneous nerve originates primarily from T1 via the lower trunk and medial cord.[84] It subserves the sensation over the medial aspect of the forearm, the area not affected by lesions of the ulnar nerve. The nerve pierces the deep fascia 4 cm above the elbow on a line bisecting the distance between the biceps tendon and the medial epicondyle. Surface stimulation at this point elicits antidromic SNAP best recorded over the course of its volar branch on the same line extended distally 8 cm from the elbow (Fig. 6-20). Careful adjustment of the recording

Table 6-10 Lateral and Medial Antebrachial Cutaneous Nerves (Mean ± SD)

Antidromic Study of Lateral Antebrachial Cutaneous Nerve

	SUBJECTS	AGE (mean)	DISTANCE (cm)	ONSET LATENCY (ms)	PEAK LATENCY (ms)	VELOCITY (m/s)	AMPLITUDE (μV)
Spindler and Felsenthal[167]	30	20–84	12	1.8 ± 0.1	2.3 ± 0.1	65 ± 4	24.0 ± 7.2
Izzo et al.[61]	154	17–80	14		2.8 ± 0.2	62 ± 4	18.9 ± 9.9

Antidromic Study of Medial Antebrachial Cutaneous Nerve

	SUBJECTS/ NERVES	SENSORY CONDUCTION VELOCITY	SNAP AMPLITUDE
Reddy[142]	30/60	65.9 ± 4.3	15.4 ± 4.2 (2–29)
Izzo et al.[61]	157/157	62.7 ± 4.9	11.4 ± 5.2 (8–32)
Seror[154]	70/140	60.0 ± 5.1	17.7 ± 5.8 (7–41)

SNAP, peak-to-peak sensory nerve action potential.

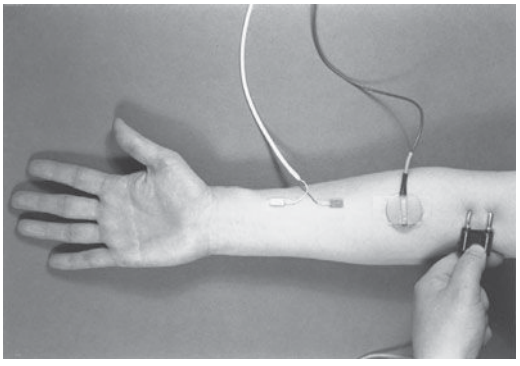


FIGURE 6-19 Antidromic sensory conduction study of the lateral antebrachial cutaneous nerve of the forearm. The photo shows stimulation just lateral to the tendon of the biceps and recording from the nerve with the electrodes placed 12 cm distal to the cathode along the straight line to the radial artery (E1) and 3–4 cm further distally (E2).

position helps maximize the response amplitude and minimize interside differences.[53] Its preservation, in conjunction with absent sensory potential of the ulnar nerve, implies a lesion at the elbow rather than medial cord of the plexus. Testing this nerve also facilitates identification of distal symmetrical polyneuropathy.[171]

Posterior Antebrachial Cutaneous Nerve

The posterior antebrachial cutaneous nerve, derived from C5 through C8 and the posterior cord, separates from the radial nerve in the spiral groove and innervates the skin of the lateral arm and the dorsal forearm. At its origin, it pierces the lateral head of the triceps, dividing into proximal and distal branches. Surface stimulation above the lateral epicondyle, between the biceps and triceps brachii, elicits antidromic SNAP best recorded with surface electrodes placed 12 cm distally along the line extended from the stimulus point to the wrist, midway between the ulnar and radial styloid processes (Fig. 6-21). In one study of 63 healthy adults,[138] normal values (mean ± SD) comprised 2.1 ± 0.2 ms and 2.4 ± 0.2 ms for onset and peak latencies, 58.2 ± 4.3 m/s for velocity, and 6.1 ± 2.1 μV for amplitude.

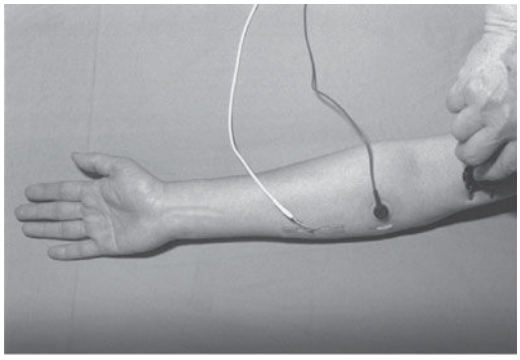


FIGURE 6-20 Antidromic sensory conduction study of the medial antebrachial cutaneous nerve of the forearm. The photo shows stimulation with the cathode placed medial to the brachial artery 4 cm above the elbow crease on a line drawn from the ulnar styloid process to a point halfway between the medial epicondyle and biceps brachi tendon, and recording from the nerve with electrodes placed 8 cm distal to the elbow crease (E1) and 3–4 cm further distally along the same line (E2). This arrangement yields results directly comparable to the analogous study of the lateral antebrachial cutaneous nerve (cf. Fig. 6-19).

Intercostal Nerves

Surface stimulation of this nerve elicits intercostal muscle action potentials with inconsistent latency. Recording from the rectus abdominis muscle may improve reproducibility of the waveform for

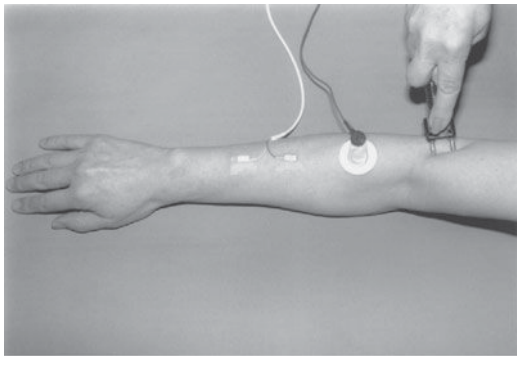


FIGURE 6-21 Antidromic sensory conduction study of the posterior antebrachial cutaneous nerve of the forearm. The photo shows stimulation with the cathode placed just above the lateral epicondyle between the biceps brachi and triceps brachi, and recording from the nerve with the electrodes placed 12 cm distally (E1) and 3–4 cm further distally (E2), along a line extended from the stimulus point to the mid dorsum of the wrist, midway between the ulnar and radial styloid processes.

calculation of conduction velocity after stimulating the nerve at two points.[137]

5. COMMONLY TESTED NERVES IN THE LOWER LIMB

Tibial Nerve

Tables 6-11 and 6-12 (see also Appendix Tables 1-4 and 1-5) summarize the normal values in our laboratory.

MOTOR STUDIES

Motor conduction studies record the muscle response from one of the intrinsic foot muscles after stimulation of the tibial nerve at the ankle posterior to the medial malleolus and at the popliteal fossa.[132] The nerve, after sending medial calcaneal nerve, a sensory branch to medial heel, bifurcates into two branches, medial and lateral plantar nerves within 1 cm of the malleolar-calcaneal axis in 90% of feet.[27] The usual choices for recording sites include the abductor hallucis and flexor pollicis brevis, innervated by the medial plantar nerve with E1 immediately inferior and posterior to the navicular prominence. Other options include abductor digiti quinti supplied by Baxter's nerve, the first branch of the lateral plantar nerve, with E1 midway between the tip of the lateral malleolus and sole, and flexor digiti minimi innervated by the terminal branch of the lateral plantar nerve with E1 on the lateral aspect of the foot at the midpoint of the 5th metatarsal (Figs. 6-22 and 6-23). Recording a normal response from the gastrocnemius or soleus helps localize a distal lesion associated with absent responses from the intrinsic foot muscles. Proximal recording also permits a quantitative estimate of nerve length during the progress of regeneration (see Figs. 5-12 and 5-13C).

One study reports normal distal latencies (mean ± SD) of 4.9 ± 0.6 ms for medial and 6.0 ± 0.7 ms for lateral plantar nerves over a 12 cm segment.[60] Stimulation of the tibial nerve above and below the medial malleolus determines the conduction characteristics of the motor fibers across the tarsal tunnel.[41] Reported normal values across a 10 cm length (mean ± SD) include 3.8 ± 0.5 ms for the medial and 3.9 ± 0.5 ms for the lateral plantar nerves.[43] A lower tibial than peroneal CMAP may suggest neuromuscular disorders such as a polyneuropathy or S1 radiculopathy.[147] Some authors advocate needle recording for latency analysis of the distal segment.[180]

SENSORY STUDIES

Sensory conduction studies consist of stimulating the medial or lateral plantar nerves on the sole 11–13 cm distal to the ankle[50,120,124] and recording an orthodromic SNAP with surface or needle

Table 6-11 Tibial Nerves*

SITE OF STIMULATION	AMPLITUDE† (mV)	LATENCY‡ TO RECORDING SITE (ms)	DIFFERENCE BETWEEN TWO SIDES (ms)	CONDUCTION TIME BETWEEN TWO POINTS (ms)	CONDUCTION VELOCITY (m/s)
Ankle	5.8 ± 1.9 (2.9)§	3.96 ± 1.00 (6.0)¶	0.66 ± 0.57 (1.8)¶	8.09 ± 1.09 (10.3)¶	48.5 ± 3.6 (41)**
Knee	5.1 ± 2.2 (2.5)	12.05 ± 1.53 (15.1)	0.79 ± 0.61 (2.0)		

*Mean ± standard deviation (SD) in 118 nerves from 59 healthy subjects, 11 to 78 years of age (average, 39), with no apparent disease of the peripheral nerves.

†Amplitude of the evoked response, measured from the baseline to the negative peak.

‡Latency, measured to the onset of the evoked response, with a standard distance of 10 cm between the cathode and the recording electrode.

§Lower limits of normal, based on the distribution of the normative data.

¶Upper limits of normal, calculated as the mean +2 SD.

**Lower limits of normal, calculated as the mean –2 SD.

Table 6-12 Latency Comparison between Two Nerves in the Same Limb*

SITE OF STIMULATION	PERONEAL NERVE (ms)	TIBIAL NERVE (ms)	DIFFERENCE (ms)
Ankle	3.89 ± 0.87 (5.6)†	4.12 ± 1.06 (6.2)†	0.77 ± 0.65 (2.1)†
Knee	12.46 ± 1.38 (15.2)	12.13 ± 1.48 (15.1)	0.88 ± 0.71 (2.3)

*Mean ± standard deviation (SD) in 104 nerves from 52 healthy subjects, 17 to 86 years of age (average, 41), with no apparent disease of the peripheral nerve.

†Upper limits of normal, calculated as the mean +2 SD.

electrodes placed just below the medial malleolus (Figs. 6-24 and 6-25).[106] Alternative sites of stimulation include the first and fifth toes with a pair of ring electrodes.[49] The medial plantar nerve has latencies (mean ± SD) of 2.4 ± 0.2 ms, 3.2 ± 0.3 ms, and 4.0 ± 0.2 ms for 10, 14, and 18 cm segments and the lateral plantar nerve, 3.2 ± 0.3 ms and 4.0 ± 0.3 ms for 14 and 18 cm segments. With the use of averaging technique, stimulation of the interdigital nerve also gives rise to an orthodromic SNAP for assessment of interdigital neuropathy or Joplin's neuroma.[40,121] Some authors advocate the comparison between branches of the common plantar interdigital nerves as a sensitive measure, using 0.17 ms as the upper limit of interlatency difference.[182] Stimulation on the medial aspect of the hallux activates the terminal sensory branch of the medial plantar nerve or medial plantar proper digital nerve, another uncommon site of Joplin's neuroma.[23]

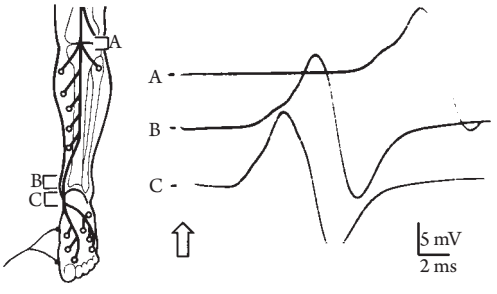


FIGURE 6-22 Motor nerve conduction study of the tibial nerve. The sites of stimulation include knee (A) and above (B) and below the medial malleolus (C) with compound muscle action potentials recorded by surface electrodes placed over the abductor hallucis.

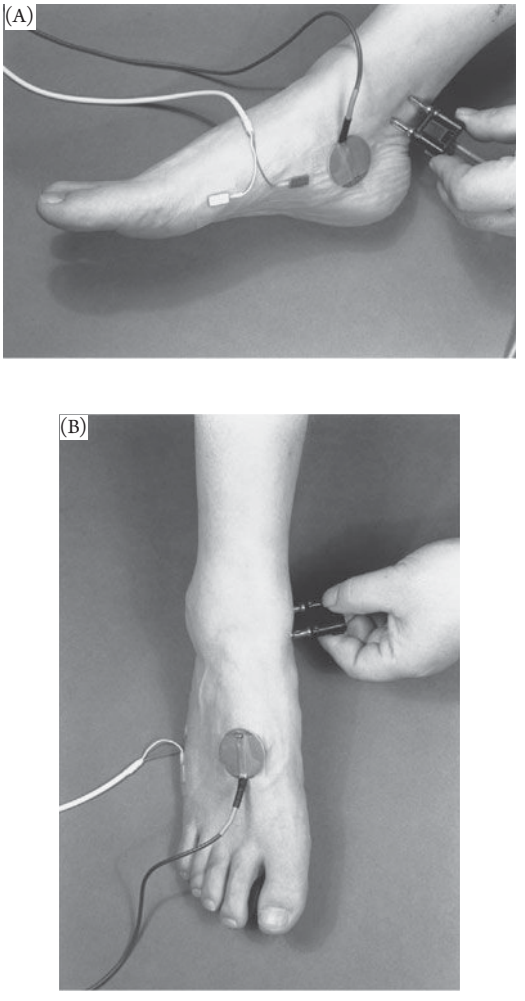


FIGURE 6-23 Motor conduction study of the medial (***A***) and lateral (***B***) plantar nerves. The photo shows stimulation of the tibial nerve posterior to the medial malleolus, 10 cm from the recording electrodes placed over the belly (E1) and tendon (E2) of the abductor hallucis, and those placed on the belly (E1) and tendon (E2) of the flexor digit minimi.

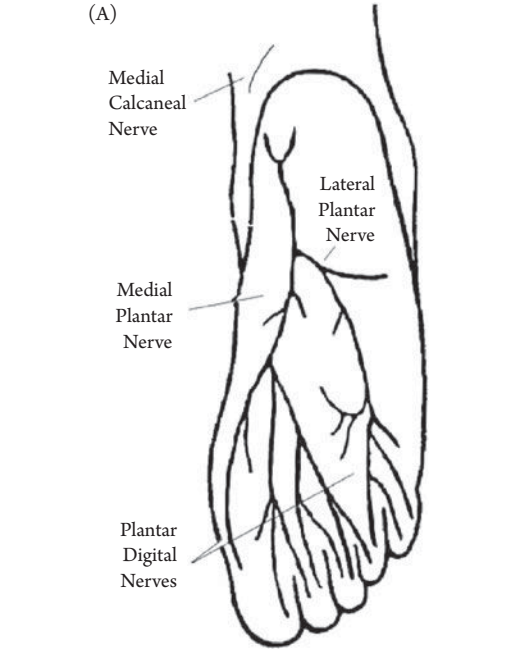


FIGURE 6-24 (***A***) Four branches of the tibial nerve used for orthodromic or antidromic sensory conduction studies. (***B***) The photo shows stimulation with the cathode placed over the medial and lateral aspects in the mid portion of the sole and the anode placed 2 cm further distally, and recording from the nerve with the electrodes placed immediately posterior to the medial malleolus 11–13 cm from the cathode (E1) and reference electrode 3–4 cm further proximal (E2).

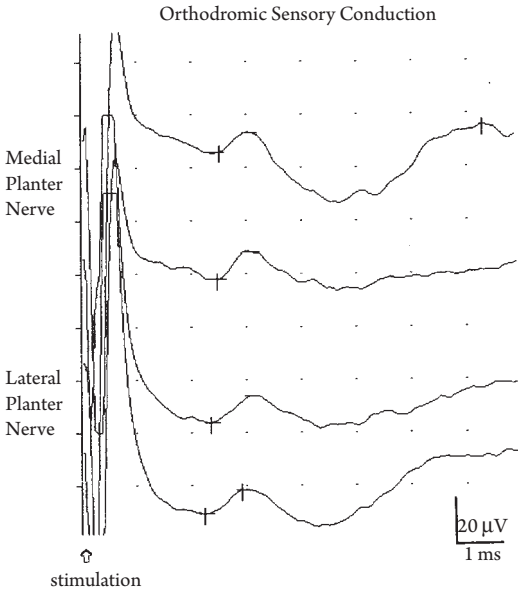


FIGURE 6-25 Orthodromic sensory nerve potentials of the medial (two top tracings) and lateral plantar nerves (two bottom tracings) recorded from the tibial nerve at the ankle following stimulation of each nerve on the sole in a 48-year-old healthy man (cf. Fig. 6-24).

The responses recorded from the popliteal fossa after stimulation of the tibial nerve at the ankle comprise orthodromic sensory and antidromic motor nerve potentials.[113] Stimulation of the tibial nerve below the medial malleolus elicits the antidromic sensory nerve potentials of the medial and lateral plantar nerves at the first and fifth toes[55,71] and of the medial calcaneal nerve at the heel.[18,131] In these cases, the use of an averaging technique improves the resolution of small signals that would otherwise escape detection. The study of the plantar nerves helps evaluate the integrity of the postganglionic sensory fibers derived from L4 and L5, for example, in patients with footdrop.

Deep and Superficial Peroneal Nerve

Tables 6-12, 6-13, and 6-14 (see also Appendix Tables 1-4 and 1-5) summarize the normal values in our laboratory.

MOTOR STUDIES

Stimulation of the common peroneal nerve above the ankle and above and below the head of the fibula elicits muscle action potentials in the extensor digitorum brevis (Figs. 6-26 and 6-27). This muscle, primarily supplied by the deep peroneal nerve, may also receive an anomalous innervation from the superficial peroneal nerve, sometimes entirely.[116] The communicating branch, called the accessory deep peroneal nerve, passes behind the

Table 6-13 Common and Deep Peroneal Nerves*

SITE OF STIMULATION	AMPLITUDE† (mV)	LATENCY‡ TO RECORDING SITE (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CONDUCTION TIME BETWEEN TWO POINTS (ms)	CONDUCTION VELOCITY (m/s)
Ankle	5.1 ± 2.3(2.5)§	3.77 ± 0.86 (5.5)¶	0.62 ± 0.61 (1.8)¶	7.01 ± 0.89 (8.8)¶	48.3 ± 3.9 (40)**
Below knee	5.1 ± 2.0 (2.5)	10.79 ± 1.06 (12.9)	0.65 ± 0.65 (2.0)	1.72 ± 0.40 (2.5)	52.0 ± 6.2 (40)
Above knee	5.1 ± 1.9 (2.5)	12.51 ± 1.17 (14.9)	0.65 ± 0.60 (1.9)		

*Mean ± standard deviation (SD) in 120 nerves from 60 healthy subjects, 16 to 86 years of age (average, 41), with no apparent disease of the peripheral nerves.

†Amplitude of the evoked response, measured from the baseline to the negative peak.

‡Latency, measured to the onset of the evoked response, with a standard distance of 7 cm between the cathode and the recording electrode.

§Lower limits of normal, based on the distribution of the normative data.

¶ Upper limits of normal, calculated as the mean +2 SD.

**Lower limits of normal, calculated as the mean –2 SD.

lateral malleolus to reach the lateral portion of the muscle. In these cases, stimulation of the deep peroneal nerve at the ankle and the common peroneal nerve at the knee shows a mismatch with the difference corresponding to the response derived from the anomalous innervation (see Chapter 11-4).

The longer the distance between the proximal and distal sites of stimulation, the more accurate the determination of conduction velocity across the knee. Series of shocks applied in short increments (see Chapter 11-7), however, delineates a focal conduction abnormality better.[68,77] In an advanced neuropathy, recording from the tibialis anterior[29] or extensor digitorum longus,[25] instead of the atrophic foot muscle, may facilitate the assessment. Recording from the proximal muscles also helps delineate isolated lesions of the deep or superficial peroneal nerve. For example, a cyst selectively compressing the deep peroneal nerve would involve the tibialis anterior and extensor digitorum brevis. Stimulation of the common peroneal nerve at the knee then activates only the superficial peroneal nerve, eliciting a normal CMAP of the peroneus longus and brevis associated with eversion and plantar flexion of the foot (see Fig. 5-12 in Chapter 5). Conduction abnormalities detected only from extensor digitorum brevis, sparing tibialis anterior, indicate a lesion affecting the distal branch of the nerve, sometimes seen in vasculitis (see Fig. 5-11 in Chapter 5). Conversely, a peripheral type of foot drop associated with normal conduction study recording from extensor digitorum brevis may indicate selective abnormality of tibialis anterior sometimes seen as a variant of facioscapular humeral (FSH) dystrophy (see Chapter 27-2).

SENSORY STUDIES

The superficial peroneal nerve, derived from L5, originates below the fibular head as a branch of the common peroneal nerve and gives rise to two sensory nerves in the lower third of the leg: the medial and intermediate dorsal cutaneous nerves. They innervate the skin of the dorsum of the foot and the anterior and lateral aspects of the leg. The medial dorsal cutaneous nerve pierces the superficial fascia at the anterolateral aspect of the leg about 5 cm above and 2 cm medial to the lateral malleolus. Stimulation at this point with the cathode adjusted to produce a sensation radiating into the toes elicits antidromic sensory potential over the dorsum of the foot medially.[89] The averaging technique helps identify the potential with amplitude approximately half that of the sural nerve, especially in recording from a diseased nerve. Stimulation or recording from toes allows sensory nerve conduction studies of the most distal segments.[122] The near nerve needle recording with signal averaging

Table 6-14 Superficial Peroneal Nerve*

STIMULATION POINT	RECORDING SITE	*n*	AGE	AMPLITUDE (μ*V*)	LATENCY (ms)	CONDUCTION VELOCITY (m/s)
5 cm above, 2 cm medial to lateral malleolus	Dorsum of foot	50	1–15	13.0 ± 4.6	1.22 ± 0.40 (peak)	53.1 ± 5.3 (distal segment)
		50	Over 15	13.9 ± 4.0	2.24 ± 0.49 (peak)	47.3 ± 3.4 (distal segment)
Anterior edge of fibula, 12 cm above the active electrode	Medial border of lateral malleolus	50	3–60	20.5 ± 6.1	2.9 ± 0.3 (peak)	65.7 ± 3.7 (proximal segment)
Anterolateral aspect of leg, 14 cm above the active electrode	Medial border of lateral malleolus	80		18.3	2.8 ± 0.3 (onset)	51.2 ± 5.7 (proximal segment)

*Mean ± standard deviation (SD) in healthy subjects. (Modified from DiBenedetto,[30] Jabre,[65] and Izzo, Sridhara, Lemont, et al.[62])

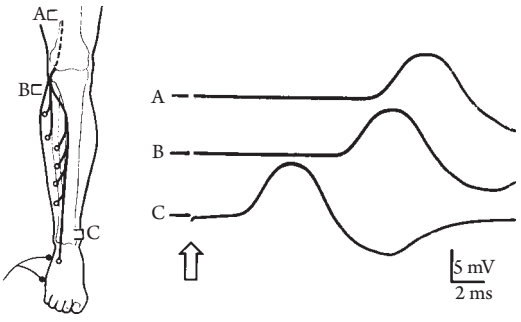


FIGURE 6-26 Motor nerve conduction study of the common peroneal nerve. The sites of stimulation include above the knee (A), below the knee (B), and ankle (C) for recording compound muscle action potentials with surface electrodes placed over the belly (E1) and the tendon of the extensor digitorum brevis.

makes it possible to assess small sensory action potential from interdigital nerves.[123]

The intermediate dorsal cutaneous branch becomes subcutaneous at 7–9 cm above the ankle.[130] Stimulation at this level or more proximally [62,65] with the cathode placed against the anterior edge of the fibula elicits the antidromic SNAP at the ankles just medial to the lateral malleolus (Fig. 6-28). Stimulation of the nerve at two points, 12–14 cm from the recording electrode and 8–9 cm further proximally, allows assessments of the distal and proximal segments. The study of this sensory nerve helps distinguish a distal lesion from a L5 radiculopathy, which usually spares the SNAP despite sensory deficits. Stimulation of the peroneal nerve at the ankle also elicits mixed nerve potentials at the fibula head.[46]

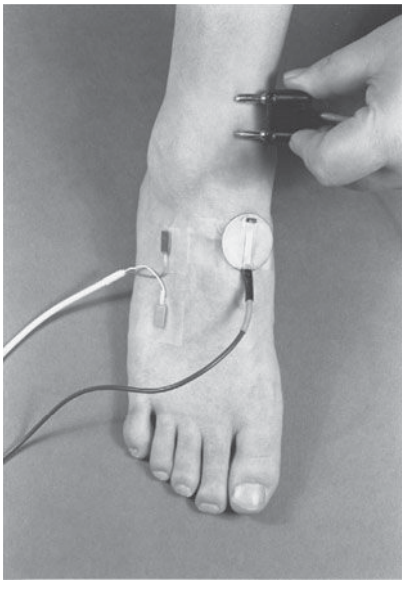


FIGURE 6-27 Motor conduction study of the common peroneal nerve. The photo shows stimulation over the dorsum of the foot near the ankle, 7 cm from the recording electrodes over the belly (E1) and tendon (E2) of the extensor digitorum brevis.

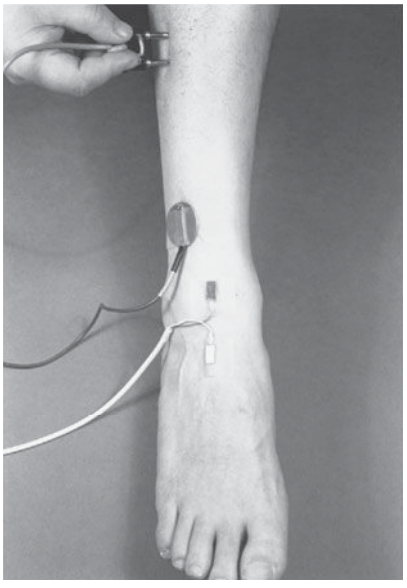


FIGURE 6-28 Antidromic sensory nerve conduction study of the superficial peroneal nerve. The photo shows stimulation against the anterior edge of the fibula, 12 cm from the recording electrodes located just medial to the lateral malleolus at the ankle (E1) and 2–3 cm distally (E2).

The deep peroneal sensory nerve innervates the web space between the first and second toes. The use of needle electrode or averaging technique improves resolution in recording small potentials.[95] In one study,[104] the mean amplitude ranged from 6.7 μV for age above 50 to 9.7 μV for age below 35 with absent responses seen in 21% of 38 normal subjects. The common peroneal nerve also gives off a short branch called lateral cutaneous nerve of the calf prior to the division into superficial and deep peroneal nerves. Studying this cutaneous branch, though technically challenging, may help precise localization of common peroneal nerve injury.[14]

Table 6-15 Sural Nerve*

AUTHORS	STIMULATION POINT	RECORDING SITE	*n*	AGE (yr)	AMPLITUDE (μV)	LATENCY (ms)	CONDUCTION VELOCITY (m/s)
Shinozaura and Mavor[163]	Foot	High ankle	40	13–41	6.3 (1.9–17)		44.0 ± 4.7
DiBenetto[30]	Lower third of leg	Lateral malleolus	38	1–15	23.1 ± 4.4	1.46 ± 0.43	52.1 ± 5.1
			62	Over 15	23.7 ± 3.8	2.27 ± 0.43 (peak)	46.2 ± 3.3
Behse and Buchthal[8]	15 cm above lateral malleolus	Dorsal aspect of foot	71	15–30			51.2 ± 4.5
				40–65			48.3 ± 5.3
Wainapel, Kim, Ebel, et al.[190]	Lower third of leg	Lateral malleolus	80	20–79	18.9 ± 6.7	3.7 ± 0.3 (peak)	41.0 ± 2.5
Truong, Russo, Vagi, et al.[179]	Distal 10 cm	Lateral malleolus	102				33.9 ± 3.25
	Middle 10 cm	Lateral malleolus	102				51.0 ± 3.8
	Proximal 10 cm		102				51.6 ± 3.8
Kimura (unpublished data)	14 cm above lateral malleolus	Lateral malleolus	52	10–40	20.9 ± 8.0	2.7 ± 0.3	52.5 ± 5.6
				41–84	17.2 ± 6.7	2.8 ± 0.3 (onset)	51.1 ± 5.9

*Mean ± standard deviation (SD) in healthy subjects.

Sural Nerve

Table 6-15 (see also Appendix Table 1-5) summarizes normal values.

This sensory nerve, primarily derived from S1, originates in the popliteal fossa as the medial sural branch of the tibial nerve. It becomes superficial at the junction of the mid and lower third of the leg, where it receives a communicating branch of the common peroneal nerve. In some cases, the peroneal branch contributes more than the main trunk from the tibial nerve (see Chapter 11-4). Descending toward the ankle, it turns anterolaterally along the inferior aspect of the lateral malleolus. Its terminal branch, the lateral dorsal cutaneous nerve, supplies the lateral aspect of the dorsum of the foot. The sural nerves may contain some motor fibers in about 6% of individuals.[4]

Stimulation of the nerve in the lower third of the leg over the posterior aspect slightly lateral to the midline elicits antidromic sensory potentials, usually recorded around the lateral malleolus (Figs. 6-29 and 6-30), but at times more distally for the study of the lateral dorsal cutaneous branch.[69,96] Sural potentials need no averaging for recording except perhaps in older populations or in patients with diseased nerve. Segmental studies dividing the nerve into three contiguous portions of 7 cm each revealed a smaller mean velocity in the most distal segment than in the middle or proximal segment.[179]

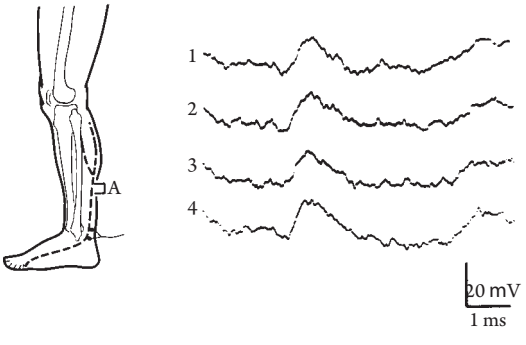


FIGURE 6-29 Antidromic sensory nerve potentials recorded four times from the sural nerve following stimulation of the nerve slightly lateral to the midline in the lower third of the leg.

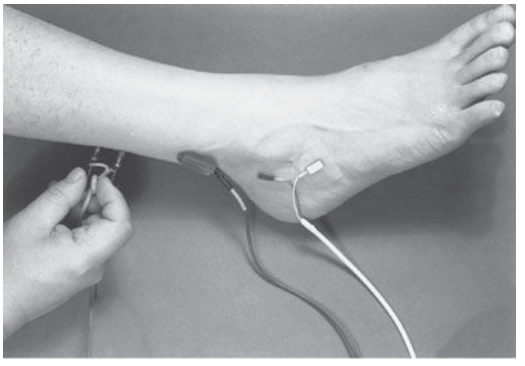


FIGURE 6-30 Antidromic sensory conduction study of the sural nerve. The photo shows stimulation along the posterior surface of the leg, slightly lateral to the midline and 7–10 cm from the ankle, and recording from the electrodes placed immediately postero-inferior to the lateral malleolus (E1) and 2–3 cm distally along the lateral dorsum of the foot (E2).

Averaging technique facilitates the study of orthodromic potentials after stimulation of the nerve over the lateral aspect of the foot.[54] Segmental studies depend on recording at the popliteal fossa and high at the ankle, 10–15 cm proximal to the lateral malleolus. The latency measured from the stimulus to the recording sites exceeds the latency difference over the same segment by activation or utilization time of about 0.15 ms, depending on the type of stimuli.[87] The SNAP amplitude shows a negative correlation with age and height.[83] The near-nerve potential recorded at mid calf showed a 32% higher amplitude in women than in men, probably reflecting different volume conductor properties.[54]

Sural nerve study offers one of the most sensitive means of detecting electrophysiologic abnormalities in various types of neuropathies.[177,186] In one study,[148] a sural to radial amplitude ratio less than 0.40, as compared to the normal mean of 0.71, predicted axonal neuropathy. Others reported a lower cutoff value such as 0.34[134] and 0.2.[126] Sural and radial SNAP, but not the ratio between the two, show an inverse correlation with age and body mass index (BMI).[38] Studies of the sural nerve help distinguish peripheral nerve lesions from S1 or S2 radiculopathy or cauda equina involvement, which spares the SNAP despite the clinical sensory symptoms. Sural

nerve study also provides a unique opportunity for direct comparison between physiologic and histologic findings of the biopsied specimen (see Chapter 4-4).[33,51,150]

6. OTHER NERVES IN THE LUMBOSACRAL REGION

Lumbosacral Plexus

Table 6-16 summarizes the normal value in one series.[110]

The lumbosacral plexus consists of the lumbar plexus with fibers derived from L2, L3, and L4 and the sacral plexus, which arises from L5, S1, and S2. The use of the F wave (see Chapter 7-4) and H reflex (see Chapters 9-2) permits an indirect measure of conduction across this region not accessible by conventional means. An alternative method uses needle[36,37,110,114] or high-voltage surface stimulation[59] of L4, L5, or S1 spinal nerve proximal to the plexus. Stimulation of the peripheral nerve just distal to the plexus allows calculation of conduction time through the plexus as the difference between the two latencies.

The study of the lumbar plexus involves the stimulation of the L4 spinal nerve by a 75 mm standard monopolar needle, placed so as to lie just below the level of the iliac crest. The needle inserted into the paraspinous muscle perpendicular to the skin surface must reach the periosteum of the articular process (Fig. 6-31A,B). With an optimal needle position, a shock of very low intensity elicits a maximal CMAP of the vastus medialis. For distal latency, stimulation with a surface or needle electrode, just distal to the inguinal ligament, activates the femoral nerve. The nerve lies immediately lateral to the readily palpable femoral artery (Fig. 6-31A). The study of the sacral plexus involves inserting a needle between the spinous process and posterior iliac spine for the S1 spinal nerve and halfway in between the L4 and S1 spinal nerves for the L5 spinal nerve. Needle stimulation of the sciatic nerve as it bisects a line drawn between the ischial tuberosity and the greater trochanter of the femur yields the distal latency (Fig. 6-31B). Careful adjustment of the needle position helps elicit a maximal CMAP of the tibialis anterior for the L5 and of the abductor hallucis for the S1 spinal nerve.

The commercially available magnetic coils fail to optimally stimulate lumbosacral roots as diagnostic aids. Specially constructed large-diameter coils, placed flat on the skin surface, however, adequately excite the cauda equina lying deep below the surface.[116,109] Cranially directed induced current via vertically oriented coil junction placed over the proximal cauda equina preferentially activates root entry zone of the conus medullaris. Horizontally oriented coil junction placed over the distal cauda equina excites the lumbar roots, and vertically oriented junction, sacral roots, at or near the intervertebral foramina. Comparing proximal and distal stimulation typically show a latency difference of 1.9 ms for vastus medialis, 2.3 ms for tibialis anterior, and 3.5 ms for abductor hallucis (see Chapter 20-4). High-voltage electrical stimulation applied to the skin surface can also activate the sciatic nerve for proximal and segmental nerve conduction measurements.[59] This

Table 6-16 Lumbosacral Plexus

PLEXUS	SITE OF STIMULATION	RECORDING SITE	LATENCY ACROSS PLEXUS (ms)		
			RANGE	MEAN	SD
Lumbar	L2, L3, L4 Femoral nerve	Vastus medialis	2.0–4.4	3.4	0.6
Sacral	L5 and Sl Sciatic nerve	Abductor hallucis	2.5–4.9	3.9	0.7

(Modified from MacLean.[110])

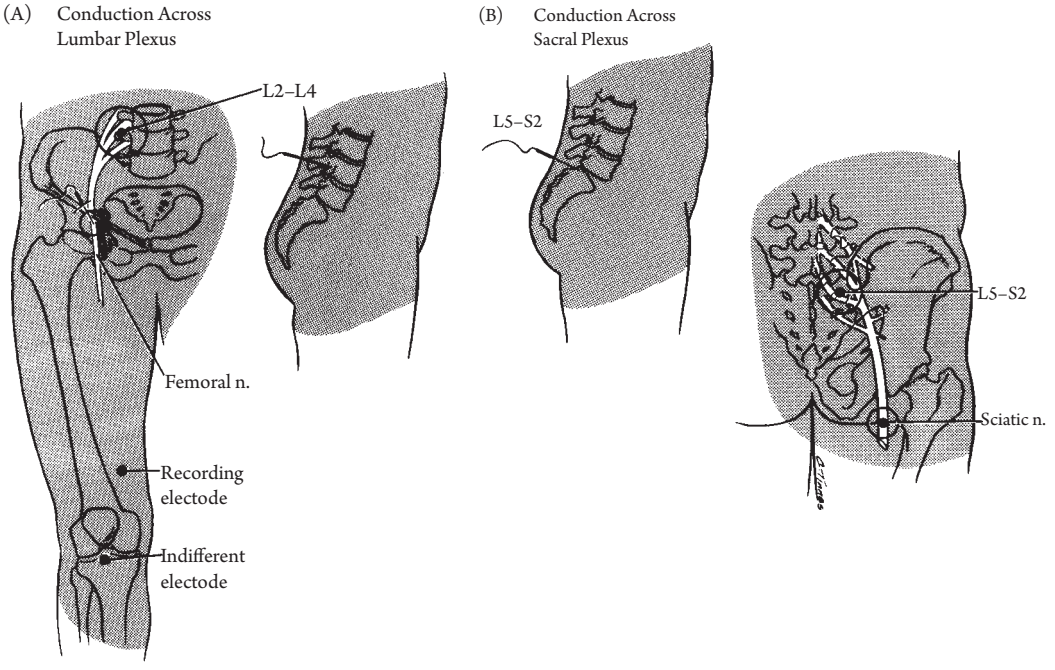


FIGURE 6-31 (***A***) Motor conduction study of the lumbar plexus. The diagram shows stimulation of L4 with the needle inserted perpendicular to the skin just below the level of the iliac crest, and of femoral nerve distal to the inguinal ligament immediately lateral to the femoral artery, and recording of muscle potentials with surface electrodes placed on the vastus medialis (E1) and patella (E2). (From MacLean,[110] with permission.) (***B***) Motor nerve conduction study of the sacral plexus. The diagram shows stimulation of S1 with the needle inserted at the level of the posterior iliac spine, of L5 halfway in between the L4 (shown in ***A***) and S1, and of the sciatic nerve at the level of gluteal skin fold midpoint between the ischial tuberosity and the greater trochanter of the femur, and recording of muscle potentials with electrodes (not shown) placed on the belly (E1) and tendon (E2) of the tibialis anterior for L5 and of the abductor hallucis for S1 studies. (From MacLean,[110] with permission.)

type of stimulation excites the peroneal and tibial division of the sciatic nerve simultaneously. The collision technique (see Chapter 11-3) eliminates the unintended impulse for selective study of the target nerve.[74]

Femoral Nerve

Table 6-17 summarizes normal values.

Shocks delivered to the femoral nerve above or below the inguinal ligament elicit the response recordable in the rectus femoris muscle at various

Table 6-17 Femoral Nerve*

STIMULATION POINT	RECORDING SITE	NO.	AGE	ONSET LATENCY (ms)	CONDUCTION VELOCITY (m/s)
Just below inguinal ligament	14 cm from stimulus point	42	8–79	3.7 ± 0.45	70 ± 5.5 between the two recording sites
	30 cm from stimulus point	42	8–79	6.0 ± 0.60	

*Mean ± standard deviation (SD) in healthy subjects. (Modified from Gassel.[44])

distances from the point of stimulation. Because of a large side-to-side variability, criteria for axonal degeneration calls for a reduction in amplitude to less than 50% compared to the unaffected side. The latency of the response increases progressively with the distance reflecting vertical orientation of the endplate region. The femoral nerve conducts at an average rate of 70 m/s, based on the latency difference between the two responses recorded at 14 and 30 cm from the point of stimulation. This calculation, however, does not hold unless all branches supplying proximal and distal parts of the muscle have similar and directly comparable electrophysiologic characteristics.

Saphenous Nerve

Table 6-18 summarizes normal values in four series.

This largest and longest sensory branch of the femoral nerve lies deep along the medial border of the tibialis anterior tendon (Fig. 6-32). The nerve stimulation uses the surface electrodes pressed firmly between the medial gastrocnemius muscle and tibia, usually 12 to 14 cm above the ankle. Signal averaging improves the resolution of small antidromic SNAPs recorded just anterior to the highest prominence of the medial malleolus. Orthodromic studies[152] consist of stimulating the nerve at two levels, anterior to the medial malleolus and medial to the knee, and recording the evoked potential with a needle electrode placed near the femoral nerve trunk at the inguinal ligament. Stimulation of the infrapatellar branch near the midline also elicits a recordable response at the same site.[6] The orthodromic potentials average one-half the size of the antidromic potentials in amplitude. The saphenous nerve may degenerate with postganglionic lesions such as lumbar plexopathy or femoral neuropathy. In contrast, preganglionic L3 or L4 radiculopathy spares the distal SNAP despite clinical sensory deficits.

Lateral Femoral Cutaneous Nerve

The nerve becomes superficial about 10–12 cm below the anterior superior iliac spine, where it divides into large anterior and small lateral branches. Surface stimulation at this point elicits an orthodromic SNAP recordable with a needle electrode inserted 1 cm medial to the lateral end of the inguinal ligament.[156] Alternative technique consists of stimulation at the inguinal ligament with a surface or needle electrode and recording antidromic SNAP from the thigh (Fig. 6-33). In one study[13] using a pair of specially constructed 1.2 × 1.9 cm lead strips fastened 4 cm apart, the normal values (mean ± SD) in 25 healthy adults consisted of a latency of 2.6 ± 0.2 ms, an amplitude of 10–25 μV, and a calculated conduction velocity of 47.9 ± 3.7 m/s. In another study[166] the antidromic potentials recorded 25 cm distal to the stimulating electrode along the line connecting the stimulus site and the lateral edge of the patella showed amplitude of 2.0 ± 1.0 μV (mean ± SD) and onset conduction velocity

Table 6-18 Saphenous Nerve*

AUTHORS	METHOD	AGE	INGUINAL LIGAMENT—KNEE			KNEE—MEDIAL MALLEOLUS		
			NO.	AMPLITUDE (μV)	CONDUCTION VELOCITY (m/s)	NO.	AMPLITUDE (μV)	CONDUCTION VELOCITY (m/s)
Ertekin[34]	Orthodromic	17–38	33	4.2 ± 2.3	59.6 ± 2.3	10	4.8 ± 2.4	52.3 ± 2.3
Stohr, Schumm, and Ballier[168]	Orthodromic	<40	28	5.5 ± 2.6	58.9 ± 3.2	22	2.1 ± 1.1	51.2 ± 4.7
		>40	41	5.1 ± 2.7	57.9 ± 4.0	32	1.7 ± 0.8	50.2 ± 5.0
Wainapel, Kira, and Ebel[190]	Antidromic	20–79			Peak latency of 3.6 ± 1.4 for 14 cm	80	9.0 ± 3.4	41.7 ± 3.4
Senden, Van Mulders, Ghys, et al.[152]	Orthodromic	18–56	71					54.8 ± 1.9

*Mean ± standard deviation (SD) in healthy subjects.

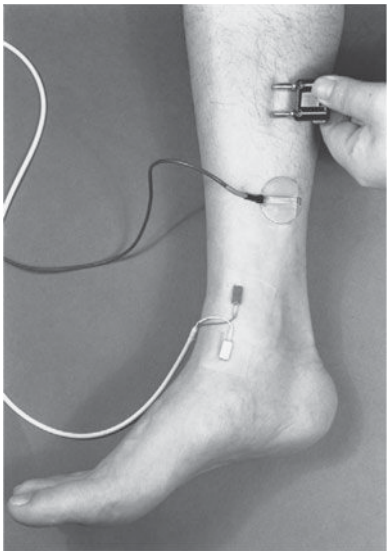


FIGURE 6-32 Antidromic sensory conduction study of the saphenous nerve. The photo shows stimulation 14 cm above the ankle along the medial surface of the leg between the tibia and gastrocnemius, and recording from the nerve 2–3 cm above (E1) and just anterior to the medial malleolus (E2).

of 62.3 ± 5.5 m/s. This technique allows assessment of a distal lesion involving this nerve.[90] The measurement of a higher amplitude recorded at two different sites may minimize interside variability.[162]

Posterior Femoral Cutaneous Nerve

This sensory nerve originates from the anterior and posterior divisions of S1, S2, and S3, exits the pelvis distal to the piriformis muscle, and proceeds distally between the medial and lateral hamstring muscles. Recording electrodes placed 6 cm above the mid popliteal fossa register an antidromic SNAP after stimulation of the nerve 12 cm further proximally on a line drawn to the ischial tuberosity. Normal values (mean ± SD) obtained in 40 subjects[32] with a mean age of 34 years included peak latency of 2.8 ± 0.2 ms (range, 2.3–3.4 ms) and amplitude of 6.5 ± 1.5 μV (range, 4.1–12.0 μv). This method may help evaluate the peripheral nerve in a patient with lower-limb amputations.

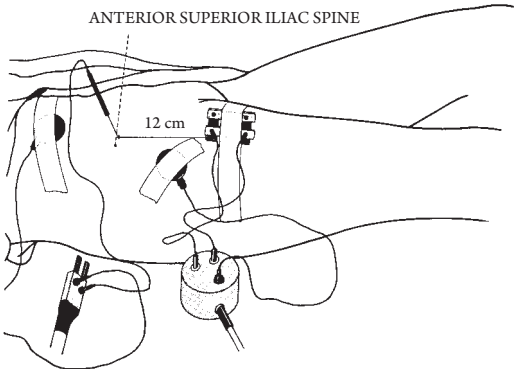


FIGURE 6-33 Antidromic sensory nerve conduction study of the lateral femoral cutaneous nerve. The diagram shows stimulation above the inguinal ligament, and recording from the nerve over the thigh, 12 cm below the anterior-superior iliac spine (E1) and 2–3 cm distally (E2). (From Butler, Johnson and Kaye,[13] with permission.)

Pudendal Nerve

The technique consists of stimulating the pudendal nerve and recording a CMAP from the external anal sphincter.[169] A specially constructed disposable electrode, when properly mounted onto the gloved right hand, has the stimulating cathode at the tip of index finger and recording electrodes near the base of the same finger. Locating the ischial spine and lateral margin of the sacrum with the finger tip inserted into the rectum helps place the cathode near the pudendal nerve. Methodical exploration then identifies the optimal location, which elicits maximal and reproducible muscle response. A latency value, positively correlated with age,[99] exceeds 2.2 ms in pudendal neuropathy.[21] Magnetic coil stimulation of the pudendal nerve also elicits a sphincter response recordable from the perianal surface electrodes.[115,157]

Dorsal Nerve of the Penis

Stimulation with a pair of electrodes placed at the base of the penis, cathode 2 cm distal to anode, gives rise to an antidromic sensory nerve potential recordable at the distal shaft along the dorsal midline with the active electrode (E1) placed 2 cm proximal to the reference electrode (E2).[11,24] The latency measured to the peak of the negative wave after averaging the response 20 times yielded conduction velocity of 26. 9 m/s for flaccid and 29.7 m/s for stretched shaft.[194] A specially constructed urinary catheter electrode placed in the urethra also registers sensory potential following stimulation of the dorsal nerve of the penis.[193]

Other Nerves

Other nerves tested infrequently include medial femoral cutaneous nerve[94,97] and genitofemoral nerve.[7,35]

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PART III

Late Response, Reflex, and Other Methods

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7

The F Wave and the A Wave

Abbreviations: ALS—amyotrophic lateral sclerosis, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CTS—carpal tunnel syndrome, E1—active electrode, E2—reference electrode, EMG—electromyography, FWCV—F-wave conduction velocity, GBS—Guillain-Barré syndrome, HMSN I & II—hereditary motor sensory neuropathy, M—muscle, MEP—motor evoked potential, MNCV—motor nerve conduction velocity, NCS—nerve conduction studies, SD—standard deviation, SFEMG—single fiber electromyography, TRH—thyrotropin-releasing hormone

1. INTRODUCTION

In nerve conduction studies, optimal selection of technique based on the available clinical findings improves its sensitivity and utility. A short segmental stimulation, inching across the affected site, detects a focal lesion better than the ordinary study covering a longer distance, which tends to dilute a localized change (see Chapter 11-7). In contrast, studies of a longer segment, accumulating abnormalities in proportion to the nerve length, uncover diffuse or multisegmental involvement better than a short segment. Measurement errors also diminish for a longer, as compared to

shorter, segment, improving reproducibility of the results.

The F wave results from backfiring of antidromically activated anterior horn cells. It, thus, helps assess motor conduction along the entire length of the peripheral axons, including the most proximal segment. The inherent variability of the latency and waveform makes its use technically more demanding than that of the compound muscle action potential (CMAP), or muscle (M) response. Nonetheless, F wave usefully supplements the conventional nerve conduction studies (NCS) in characterizing neuropathic disorders in general and polyneuropathies in particular. Explored first in patients with Charcot-Marie-Tooth disease (CMT)[61] and motoneuron diseases,[106] the method has since gained popularity in evaluation of a variety of neurologic conditions as part of routine nerve conduction studies.[15,38,40,67,71,102,111,120,128,162] In a diffuse process, F-wave latencies, reflecting accumulated conduction delay, often clearly exceed the normal range even in patients with a borderline conduction abnormality. In addition, the calculation of F-wave velocities and F ratios permits comparison of conduction in the proximal versus the distal nerve segments.[61,66–68]

Motoneuron excitability dictates the probability of backfiring in individual axons.[104,143,144] Thus, F-wave amplitude and persistence serve as a measure of this domain as does the H reflex. Theoretically, comparison between the two modes of motoneuron activation may help differentiate whether the observed change involves the presynaptic or postsynaptic pathway. Possible differences in inherent sensitivity between antidromic and reflexive activation, however, might bias the result.[39,58,85] This section will review the currently available methods of F-wave determination and discuss its clinical value and limitations.

2. PHYSIOLOGY OF THE F WAVE

Recurrent Activation of the Motoneuron

A supramaximal electric shock delivered to a nerve often elicits a late muscle response that follows the direct M response in men and animals.[105] Since the original description by Magladery and McDougal,[92] who coined the term *F wave* (presumably to indicate a response recorded from "foot" muscles, or "following" M response), different authors have debated its neural source. With more proximal stimulation, the latency of the M response increases, whereas that of the F wave decreases (Fig. 7-1). Thus, the F-wave impulse must first travel away from the recording electrodes toward the spinal cord before it returns to activate distal muscles. This finding supports either reflex hypothesis[92] or recurrent discharge of antidromically activated motoneurons[96,97] or both as the source of this response. The presence of the F wave in deafferentated limbs[47,96,97] implies that it depends on backfiring of motoneurons. Studies using single fiber electromyography (SFEMG)[150] also showed that the occurrence of the F wave requires prior activation of the motor axon.

Frequency of Backfiring

Subject to recurrent activation, F waves appear only infrequently after a series of supramaximal stimuli eliciting direct motor responses.[134] Thus, although antidromic and orthodromic activation of motoneurons usually follow the same physiologic principles,[26] additional mechanisms must prevent the generation of the late response with every stimulus.[26,124] Recurrent discharges develop in only a limited number of motor units in part because the antidromic impulse fails to enter the somata in some of the motoneurons.[88] This type of block often takes place at the axon hillock, where membrane characteristics change, but it may also occur more distally in the myelinated segment of the axons. The spike potential, if generated in the soma-dendrite membrane, faces a very narrow window for the generation of recurrent discharges. The impulse, if activated too early, cannot travel back the same axon hillock for about 1 ms during its refractory period after the passage of the antidromic impulse. In addition, the antidromic impulse near its entry to the axon hillock also activates the Renshaw cell, which in turn inhibits the motoneuron, with a slight delay.[95] Thus, any chance of generating a recurrent discharge may abate under the effect of Renshaw inhibition, which begins with a delay of some 2 ms through a couple of synapses.

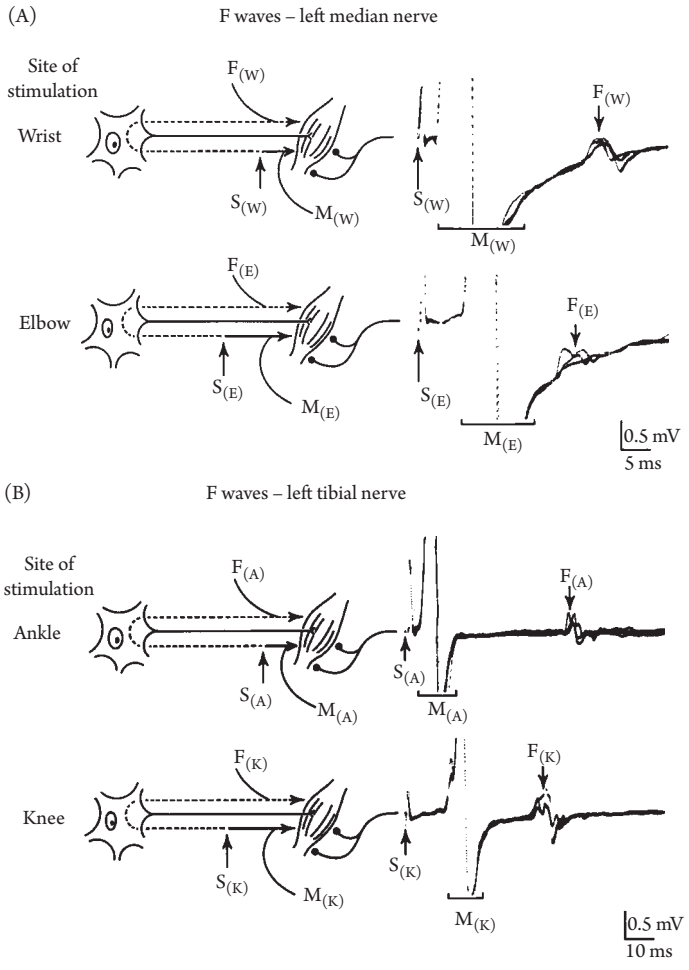

FIGURE 7-1 (***A***) Normal M-response (horizontal brackets) and F wave (small arrows) recorded from the thenar muscles after supramaximal stimulation of the median nerve at the wrist (*top*) and elbow (*bottom*). The shift of stimulus point proximally increased the latency of the M response and decreased that of F wave. The schematic diagrams illustrate the centrifugal (solid arrows) and centripetal impulses (dotted arrows). (Modified from Kimura.[61]) (***B***) Normal M response (horizontal brackets) and F wave (small arrows) recorded from the abductor hallucis after supramaximal stimulation of the tibial nerve at the ankle (*top*) and knee (*bottom*). With a shift of stimulus site proximally, the latency of the M response increased, whereas that of the F wave decreased. (Modified from Kimura, Bosch, and Lindsay.[70])

Overall, only a small percentage of the recurrent discharges can clear this narrow window with a turnaround time of greater than 1 ms and less than 2 ms after the entry of antidromic impulse. This explains, at least in part, why most antidromic impulses that invade the motoneuron pool fail to induce the F wave. A particular set of physiologic conditions required for generation and propagation of a recurrent discharge makes the latency of successive F waves from a single motor axon vary only narrowly between 10 and 30 s.[134] Parenthetically, the latency of consecutive H reflexes from a single motor axon may fluctuate by as much as 2.5 ms, primarily reflecting variation in synaptic transmission (see Chapter 9-2).

Subliminal excitation of soma-dendrite membrane facilitates antidromic activation of the SD spike, resulting in increased probability of a recurrent response. Thus, slight voluntary muscle contraction or even mental imagery without actual

motion usually enhances F-wave activation[55] Further efforts, however, often have no additional effect for a number of reasons. If the descending central drive to the anterior horn cell generates an action potential, it will block antidromic impulse by collision, thus eliminating the F wave from this motoneuron. An H reflex, if elicited by simultaneous stimulation of the group IA afferent fibers, also prevents antidromic impulse by collision. A higher motoneuron excitability, which induces a greater reflexive activation, therefore, may reduce the F wave amplitude and frequency. In addition, subliminal depolarization of the soma-dendrite membrane may also generate recurrent discharge too quickly to overcome the refractory period of the axon hillock induced by passage of antidromic impulse. These findings suggest volitional facilitation beyond a certain level increases the chance of backfiring in some motoneurons and reduces it in others, rendering the overall effect of effort-induced excitability change rather unpredictable.

Large and Small Motoneurons

Up to 5% of antidromically invaded motoneurons give rise to an F wave regardless of their peripheral excitability or conduction characteristics.[23,145] In normal subjects, F-wave frequency varies with a mean of 79%, most responses occurring only once during a train of 200 stimuli.[117] Partial excitation of the nerve generates recurrent discharges in either larger anterior horn cells with lower threshold motor axons or smaller cells with higher thresholds.[36] After progressive block of the fast-conducting axons by a collision technique, the F wave continues to appear in proportion to the slow-conducting motor axons that have escaped the collision.[75] Studies of twitch contraction by intramuscular microstimulation also show that recurrent discharges occur not only in the larger but also smaller motoneurons with greater and lesser twitch force.[21,145]

When stimulating both the large and small axons simultaneously in clinical studies, anatomic or physiologic properties predispose a given fraction of the more excitable motoneurons to backfiring.[54] The smaller, lower threshold motoneurons, which rapidly depolarize, probably encounter blockage at the initial segment more frequently[56] and receive Renshaw inhibition more effectively.[27] Hence, the incidence of the F wave may, at least in theory, favor the larger motoneurons with faster conducting axons. In fact, preferential activation of a few motor units with very strong twitch forces may generate the repeater F waves, identified by recurrence of the identical waveforms. The incidence of repeater F waves increases with loss of motor axons, as seen, for example, in median nerve studies of the CTS.[90]

Minimal-latency F waves selected from a number of trials usually serve as a measure of the fastest conducting fibers. A few-millisecond interval between the earliest and latest F wave, or chronodispersion, results, in part, from the difference between fast and slow motor conduction.[115] If the backfiring of the anterior horn cells occurs randomly, then distribution of F-wave latencies may indicate the range of motor nerve conduction velocities.[122] Among various F-wave measures, however, only the minimal latency reflects pure motor conduction as reflex inputs affect other indices such as mean latency, maximal latency, and chronodispersion.[32]

To further compound the interpretation of F-wave latencies, nerve conduction time changes as a function not only of the speed of the propagated impulse but also of the length of the fine terminal fibers innervating each muscle fiber. The terminal length determined by the location of endplates probably varies only on the order of a few millimeters between the longest and shortest nerve fibers. A slight change in the length of the thinly myelinated or unmyelinated terminal segment, however, may result in a substantial latency difference. Another unknown variable includes the distance between the recording electrodes and the motor endplate, where the muscle action potential originates. Because of these factors, the F wave from the fastest conducting fibers may not necessarily show the shortest latency, and vice versa.[75]

Measure of Anterior Horn Cell Excitability

Motoneuron excitability influences the amplitude and persistence of the F wave based on complex physiologic mechanisms. The F wave fails

in hypoexcitable cells if an antidromic impulse produces only subliminal depolarization or Renshaw inhibition suppresses the backfiring. During moderate volitional muscle contraction, a voluntarily or reflexively evoked discharge may eliminate the antidromic invasion by collision. In addition, backfiring may occur too rapidly to clear the refractory period of the initial axon segments in hyperexcitable states.

Systematic administration of anesthetic agents intravenously affected F-wave excitability only a little, if at all.[82] Intrathecal baclofen application, however, altered F-wave mean and maximum amplitude as well as mean duration in a quantifiable manner.[24] Intravenous or subcutaneous injections of thyrotropin-releasing hormone (TRH) rapidly increased the amplitude of the F waves.[9] Stimulation of afferent fibers may inhibit F waves ipsilaterally and facilitate them contralaterally.[152] Subthreshold transcranial magnetic stimulation (see Chapter 20-3), if appropriately timed to collide at the motoneuron, enhances the F wave. A second facilitatory phase seen 2–3 ms later presumably represents the sequential arrival of I waves. A subsequent phase of suppression probably signals the arrival of inhibitory postsynaptic potentials generated by the cortical stimulus.[98] Electrical stimulation of the dentate nucleus also reduces the size of the F wave in human.[46] Other factors that affect F-wave excitability include caffeine intake,[153] sleep and related alteration of alertness,[60] administration of sedatives, level of consciousness,[16] muscle vibration, contraction of a distant muscle, remote botulinum toxin application[159] and high-intensity stimulation of fingers.[86]

In healthy subjects simulating paresis for a few hours by immobilizing the target muscle, F waves as well as transcranial motor evoked potential (MEP) show rest-dependent declines in amplitude and persistence.[49,69,104,127,144,132,149] Both responses recover quickly upon a brief, standardized voluntary muscle contraction (Fig. 7-2A). If the subject periodically simulates muscle contraction without actual movement, F-wave persistence and amplitude show little change despite immobilization.[50,59,143] These findings indicate (1) MEP amplitude commonly used as a measure of cortical excitability reflects, at least in part, a reversible suppression of the anterior horn cell; (2) the absence of F wave, usually taken as a sign of conduction block of the peripheral motor axons, may also result from inexcitability of spinal motoneurons after volitional inactivation; and (3) mental imagery without overt motor output suffices to counter the rest-induced suppression by maintaining the subliminary central drive. Thus, this maneuver helps differentiate motoneuron hypoexcitability from peripheral conduction failure in interpreting absent F waves seen in a paretic limb. In our experience, motor imagery enhances F-wave persistence and amplitude, which further increase with a slight muscle contraction but show no additional change with a stronger effort (Fig. 7-2B).[55]

As a test of excitability, F wave provides a less sensitive measure than the H reflex.[57] Nonetheless, patients with upper-[6] and lower-limb[10,32] spasticity show increased mean amplitude of the ulnar and tibial nerve F waves, respectively. In patients with spasticity, the F wave became more persistent, making the average amplitude of 32 F waves significantly greater than 1% of the M response seen in normal subjects.[29] A higher rate of stimulation tends to increase F-wave amplitude and persistence in normal persons and to a lesser degree in patients with spasticity.[35] Patients with upper motoneuron disorders show less facilitation of F wave with voluntary muscle contraction, partly because already enhanced baseline values have no room for further increase.[100] Unusually large F waves may appear in association with clinical spasticity (Fig. 7-3), but reflex components may contribute to the late response, especially if the patient has prominent hyperreflexia. The amplitude of the F wave also increases in peripheral nerve disorders presumably because regenerated axons supply a greater number of muscle fibers.[37,136]

3. F-WAVE ANALYSIS

Recording and Measurement

A supramaximal stimulus applied at practically any point along the course of a nerve elicits the F wave. The use of submaximal stimulation,

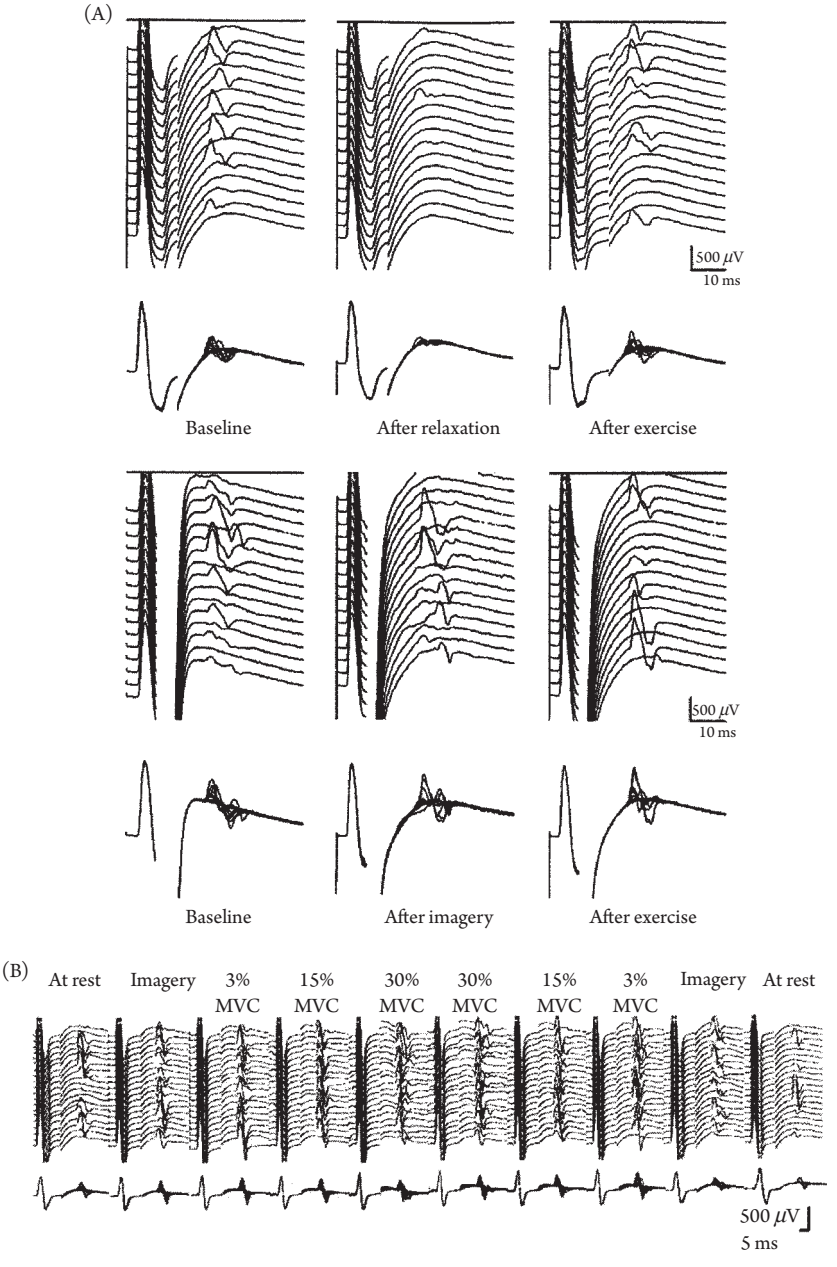

FIGURE 7-2 (***A***) Raster mode display of 16 consecutive traces showing M responses and F waves recorded from the abductor pollicis brevis muscle before (*left*) and after (*middle*) 3 hours of muscle immobilization, and after subsequent exercise (*right*) in a 26-year-old healthy woman. (*Top*) Analyses of 100 traces showed a change from 49% to 23% and 35% in persistence and from 102 μV to 49 μV and 80 μV in trial average of amplitude with relaxation task. (*Bottom*) Corresponding values consisted of 51%, 62%, and 50% and 98 μV, 110 μV, and 101 uV with motor imagery task (Modified from Taniguchi, Kimura, Yamada, et al.[143]) (***B***) A typical time course of F-wave changes in one subject from baseline at rest to motor imagery, followed by progressive increase and decrease of force to and from 30% maximal voluntary contraction (MVC), and back to imagery and baseline at rest. Motor imagery enhanced F-wave persistence and amplitude, which further increased with a slight muscle contraction, showing no additional change with a stronger effort. (Modified from Hara, Kimura, Walker, et al.[55])

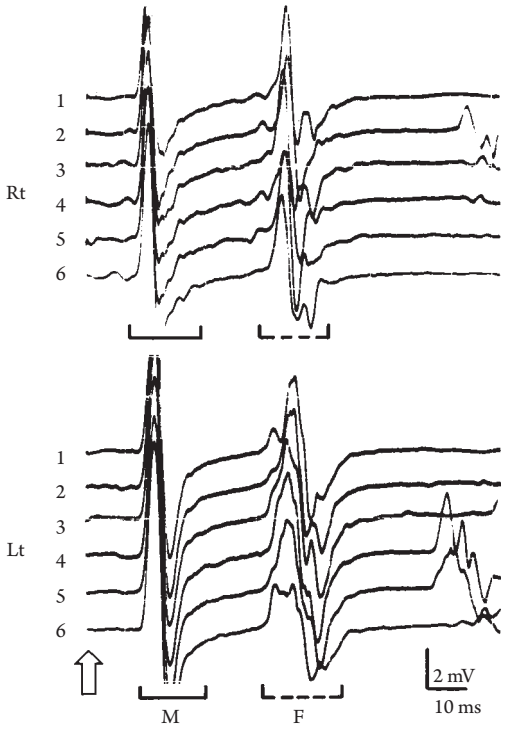

FIGURE 7-3 A 39-year-old man with chronic tetanus, diffuse hyperreflexia, and rigidity. Supramaximal stimulation of the peroneal nerve at the knee elicited large F waves in the extensor digitorum brevis. Note consistency of the response in six consecutive trials obtained on each side showing F-wave amplitude of 57% compared to the corresponding M response on the right and 43% on the left. Reflex components may have contributed to the late response despite the use of supramaximal stimulation. (From Risk, Bosch, Kimura et al.,[125] with permission.)

although not universally approved, may have a role in patients who tolerate the procedure poorly.[22] Some advocate placing the cathode proximal to the anode, which, if located rostrally, could block the antidromic impulse, although, in clinical practice, anodal hyperpolarization mostly abates before the arrival of the impulse.[163] The reversal of stimulator orientation also circumvents the possibility of anodal activation known to occur with the use of excessively high-intensity stimulation.[157,161] In routine clinical studies, we use the conventional cathode distal stimulation to avoid any ambiguity in maintaining the same cathodal position in eliciting M response and F wave. Cathodal monopolar stimulation with the anode placed slightly off the nerve also eliminates the concern. A surface electrode over the motor point of the tested muscle serves as the active electrode (E1) with the reference electrode (E2) placed over the tendon.

An optimal display of F waves consists of an amplifier setting of 200 or 500 μV/cm and an oscilloscope sweep of 5 or 10 ms/cm, depending on the nerve length and stimulus point. A high amplification and slow sweep truncate and compress the simultaneously recorded M response into the initial portion of the tracing. Most commercially available instruments offer an option to display the M response and F wave simultaneously, but independently, using two optimal gains. For clinical studies, routine procedures include stimulation of the median and ulnar nerves at the wrist and of the tibial and peroneal nerves at the ankle. Stimulation of the facial nerve also elicits F waves, although superimposition of the M response may make its recognition difficult. Inadvertent stimulation of the neighboring trigeminal afferent fibers may simultaneously activate reflex responses, which may mimic the F wave.

Automatic vertical shifting of successive sweeps helps identify the number of F waves out of 10 to 15 trials and other characteristics of the waveform (Fig. 7-4). The level of motoneuron excitability and the number of functional axons dictate the measure called persistence, or the percentage of the trials with a detectable F wave. F-wave latencies measured from the stimulus artifact to the beginning of the evoked potential normally vary by 2–4 milliseconds from one stimulus to the next depending on the nerve length. Determination of the minimal and maximal latencies reveals not only the fastest and slowest conducting fiber but also the degree of scatter among consecutive responses, or temporal dispersion. Electronic averaging of a large number of responses permits easy analysis of mean latency, although phase cancellation sometimes defeats its own purpose. An automated analysis, though not tested adequately, may shorten the analysis time.[41]

Slight voluntary contraction or even mental imagery without actual movement enhances the incidence of the F wave, thus facilitating the analysis,

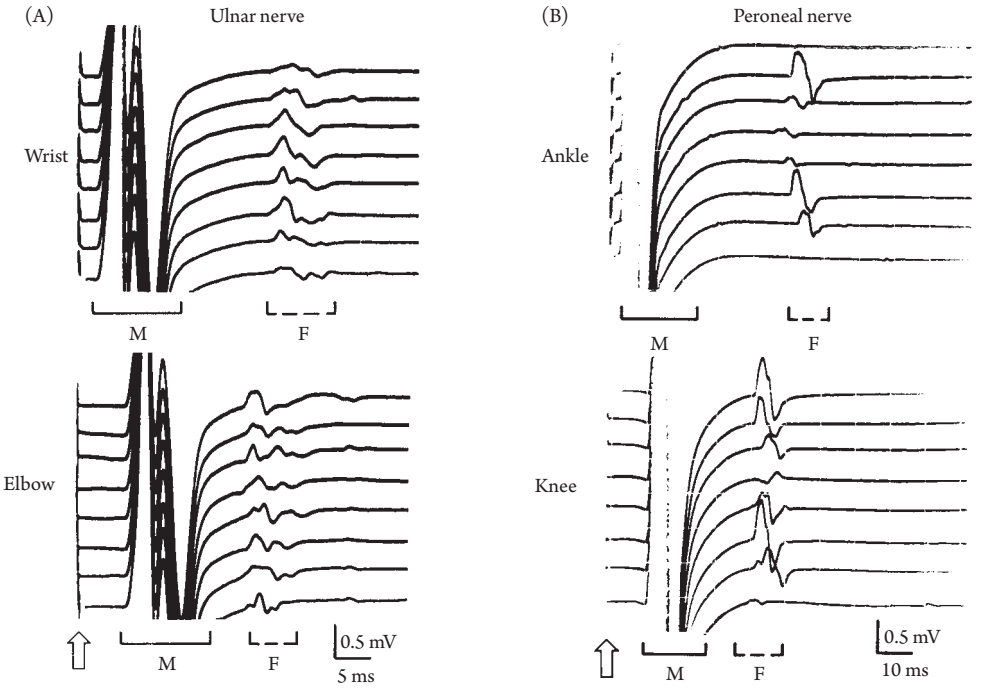

FIGURE 7-4 (***A***) Normal M responses and F waves recorded from the hypothenar muscles after eight consecutive stimulations of the ulnar nerve at the wrist and elbow. (***B***) Normal M responses and F waves recorded from the extensor digitorum brevis after eight consecutive stimulations of the peroneal nerve at the ankle and knee.

especially if the trial at rest proves unsatisfactory.[55] Muscle contraction induces orthodromic impulses along the motor axons, which would block the stimulus-induced antidromic impulse by collision, although with slight volitional effort, it involves only a few motor fibers.[64] A greater muscle contraction induces more voluntary impulses, which collide with antidromic activity in many axons, inhibiting the generation of the F wave. In addition, with such facilitation, subliminally excited motoneurons may discharge reflexively with input from the group IA afferents, blocking the antidromic impulse. In this case, reflexively activated impulses may propagate along the motor axons cleared of the antidromic impulse, eliciting the H reflex not normally seen after supramaximal stimulation.

Distal versus Proximal Stimulation

The F wave, generated by antidromic impulse propagating toward the spinal cord, has a longer latency than the M response evoked by the orthodromic impulse toward the muscle. With distal stimulation at the wrist, for example, the long-latency F wave follows the short-latency M response with clear separation between the two. With a shift of stimulus site, proximally the latency of F wave decreases, whereas that of M response increases, moving these responses closer toward each other. So much so that F wave elicited by very proximal stimuli, like at the axilla, superimposes on the tail end of the M response.[61,62] In this instance, simultaneous stimulation at the axilla and wrist helps to isolate the F wave. With this technique, the orthodromic impulse from the axilla and the antidromic impulse from the wrist collide, eliminating the M response from the axilla and the F wave from the wrist (Fig. 7-5). This leaves the clearly separated M response from the wrist and F wave from the axilla for latency measurement.[61]

Assuming that the latency of the F wave, like that of M response, measures the fastest conducting motor fibers, the sum of these two latencies

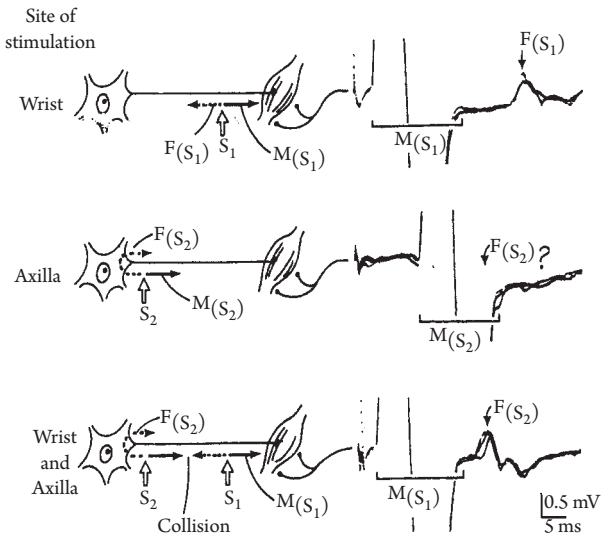

FIGURE 7-5 Normal M-response (horizontal brackets) and F-wave (small arrows) recorded from abductor digit minimi through surface electrodes. From top to bottom, supramaximal stimulation to the ulnar nerve at the wrist (S1), at the axilla (S2) and simultaneous paired stimuli at the wrist and axilla (S1 and S2). Three consecutive traces superimposed for each tracing show M response and F-wave elicited by wrist stimulation but only M-response with stimulation at the axilla because F wave occurred before the completion of the former. In this instance, simultaneous stimulation at the axilla and wrist help to isolate the F wave. With paired stimuli, the orthodromic impulse from axilla and the antidromic impulse from the wrist collide, leaving the M response, M (S1), from the wrist and F-wave, F (S2), from the axilla intact. Schematic diagrams on the left show the orthodromic (solid arrows) and antidromic (dotted arrows) impulses carrying the M response and the F wave, respectively. (From Kimura.[61])

remains the same regardless of the site of nerve stimulation. This value equals twice the conduction time along the entire length of the axon plus the central activation time of about 1.0 ms. As an inference, F-wave latency from the axilla must equal the sum of the latencies of the F wave and M response elicited by distal stimulation minus the latency of the M response evoked by axillary stimulation.[8] Or, $F(A) = F(W) + M(W) - M(A)$, where $F(A)$ and $F(W)$ represent the latencies of the F wave with stimulation at the axilla and wrist, and $M(A)$ and $M(W)$, latencies of the corresponding M response.[71]

Central Latency

Central latency or conduction time from the stimulus point to and from the spinal cord equals F – M, where F and M represent latencies of the F wave and the M response (Fig. 7-6). Subtracting an estimated delay of 1.0 ms for the turnaround time at the cell and dividing by two, $(F - M - 1)/2$, yields the conduction time along the proximal segment from the stimulus site to the spinal cord. Although no studies measured the central activation time at the anterior horn cells in humans, animal data indicate a delay of nearly 1.0 ms.[124] The absolute refractory period of the fastest human motor fibers lasts about 1.0 ms or slightly less.[63,73] Thus, the recurrent discharge cannot propagate distally beyond the initial segment of the axon during the absolute refractory period lasting 1.0 ms after the passage of antidromic impulse. The impulse, however, would abate after the inhibition of Renshaw cells activated by an antidromic impulse with two synaptic delays of some 2.0 ms. In evaluating the minimal latency, therefore, it seems appropriate to assume a turnaround time of 1.0 ms.[61]

The minimal-latency F wave selected out of many trials usually, although perhaps not always,

reveals the conduction properties of the fastest fibers. In some diseased nerves with proximal conduction block, for example, some fast-conducting motor axons that contribute to the M response may not propagate antidromic impulses centripetally. In this instance, the stimuli that elicit an M response evoke no F waves from the same axons, making comparison between the M response and the F wave inappropriate. In doubtful cases, the sums of the F latency and M latency at distal and proximal stimulus sites can test this relationship.[61,70] If they add up, then the increase in latency of the M response elicited by a proximal stimulus equals the decrease in latency of the F wave. If so, the F wave and the M response come from the same group of motor fibers. This, in turn, provides a rationale for equating the conduction characteristics of these two muscle potentials in various formulas for assessments of proximal versus distal nerve segments.[65]

F-Wave Conduction Velocity

In the upper limbs, the surface distance measured from the stimulus point to the C7 spinous process via the axilla and midclavicular point approximates the nerve length under consideration.[61,66] In the lower limb, surface measurement follows the nerve course from the stimulus site to the T12 spinous process by way of the knee and greater trochanter of the femur.[70] The estimated nerve length divided by the conduction time to and from the spinal cord derives the F-wave conduction velocity (FWCV) in the proximal segment as follows:

$$\text{FWCV} = (2D)/(F - M - 1)$$

where D represents the distance from the stimulus site to the cord, and $(F - M - 1)/2$, the time needed to cover the length (Fig. 7-6).

The estimated length of a nerve segment by surface measurement correlates well with its F-wave latency. Observations in five cadavers showed good agreement between surface determinations and actual lengths of nerves in the upper limbs[87] as well as the lower limbs.[70] F-wave latencies may provide a useful measure in studying limbs of average length or in documenting sequential changes in the same subjects. Otherwise, clinical assessment of F-wave latency calls for determination of a surface distance to adjust for differing nerve lengths[142] or the patient's height with the use of a nomogram.[102,120,147] For unilateral lesions affecting one nerve, comparison between the right and left sides in the same subject or one nerve with another in the same limb improves the yield of abnormality.[65,160]

$$\text{F ratio} = \frac{(F - M - 1)/2}{M} = \frac{F - M - 1\ (\text{ms})}{M \times 2\ (\text{ms})}$$

$$\text{FWCV} = \frac{D}{(F - M - 1)/2} = \frac{D \times 2\ (\text{mm})}{F - M - 1\ (\text{ms})}$$

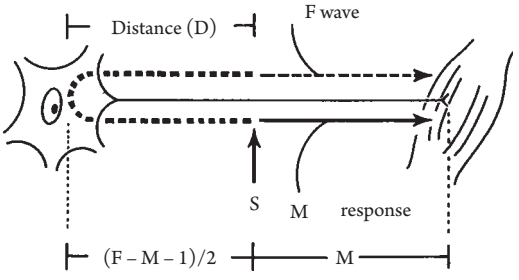

FIGURE 7-6 The latency difference between the F wave and the M response, (F – M), equals the time for passage of a motor impulse to and from the cord through the proximal segment. Considering an estimated minimal delay of 1.0 ms at the motoneuron pool, $(F - M - 1)/2$ yields the proximal latency from the stimulus site to the cord. Thus, $\text{FWCV} = (D \times 2)/(F - M - 1)$, where D represents the distance from the stimulus site to the cord; $(F - M - 1)/2$, the time required to cover the length D; and FWCV, F-wave conduction velocity in the proximal segment. Dividing the conduction time in the segment to the cord by that of the remaining segment to the muscle, the F-ratio $= (F - M - 1)/2M$, provides a proximal to distal latency comparison. (From Kimura,[66] with permission.)

F Ratio

Similar to the F/M ratio[30,31] where F and M represent the latency of the F wave and M response elicited by stimulation at the elbow and knee, the F ratio, defined as $(F - M - 1)/2M$, compares the conduction time from the cord to the stimulus site to the remaining distal nerve segment to the muscle.

Circumventing the need for determining the nerve length, the F ratio serves as a simple means of comparing the conduction characteristics between proximal and distal segment (Fig. 7-6). Clinical use of this ratio assumes the same proportion for the proximal and distal segments regardless of the limb length.[65] Because of a wide variability, the F ratio has proven less useful than theoretically expected as a diagnostic test in individual patients. Nonetheless, it plays an important role in characterizing the conduction abnormalities of various neuropathic conditions as a group based on statistical comparison between patients and control subjects.

In our normative data, average F ratios approach unity with stimulation of the median nerve at the elbow, ulnar nerve 3 cm above the medial epicondyle, tibial nerve at the popliteal fossa, and peroneal nerve immediately above the head of the fibula. With stimulation at these sites, therefore, the latency of the F wave roughly equals three times the latency of the M response plus 1.0 ms for the turnaround time. Also, the stimulus sites at the elbow or knee, as described earlier, dissect the total length of the axon into two segments of approximately equal conduction time despite the considerably longer proximal segment compared with the distal segment.[70] This finding implies that the proximal segment conducts faster than the distal segment, thus compensating for the difference in nerve length to make the F ratio a unity. In fact, calculated FWCV over the proximal segment exceeds motor nerve conduction velocity (MNCV) along the distal segment.[61,70,71]

4. USE OF F WAVES AS A CLINICAL TEST

Principles and Practice

Clinical uses of F wave suffer from inherent latency variability from one trial to the next. Determination of the shortest latency after a large number of trials can minimize this uncertainty. In one study of the normal ulnar nerves,[16] a sample size of 10, as compared with 100, overestimated the F-wave latency by a maximum of 2.4 ms, whereas sampling 40 provided an equal value. In another series, results following 10 stimuli compared with 100 stimuli gave mean latency measurements within 1 ms, whereas 20 stimuli provided mean latencies within 0.5 ms.[42] In group comparison of ulnar nerve F waves, the lower limit of sample size showing valid results included 16 stimuli or 10 waves for minimal and maximal latencies and 20 stimuli or 16 waves for chronodispersion.[101] Recording as many as 40–100 F waves at each stimulus site proved useful in special studies,[108] but not in a routine clinical test where 10–15 stimuli suffice for practical purposes,[102,120] especially if tested with facilitation by motor imagery or a slight voluntary contraction of the target muscle.[55]

Determining the latency differences between two sides or between two nerves in the same limb serves as the most sensitive means of examining a patient with a unilateral disorder affecting a single nerve. Absolute latencies serve well for evaluating the same subjects sequentially for follow-up studies (see Chapter 11-7). Calculation of the central latency, FWCV, and F ratio provides additional information not otherwise available to compare the proximal and distal segments. Other measures, advocated by some,[109] include F chronodispersion, or scatter between minimal and maximal latencies, and F tacheodispersion, or distribution of the conduction velocities estimated from a large number of consecutively recorded F waves.[14,122]

Normal Values

Tables 7-1 and 7-2 (see also Appendix Table 1-6) summarize the ranges and the upper and lower limits of F-wave values defined as 2 standard deviation (SD) around the mean established in the same control subjects described for nerve conduction studies (see Tables 6-1, 6-4, 6-11, and 6-13 in Chapter 6).

Reported normal values include those of more commonly tested muscle such as extensor digitorum brevis, abductor hallucis, abductor pollicis brevis, and adductor digiti minimi[5,19,29,44,61,65,70–72,76,96,103,107,147,162] and of the less commonly tested such as the gastrocnemius and soleus muscles,[110,147] flexor carpi radialis,[93] flexor hallucis brevis,[147] vastus lateralis,[158] nasalis,[155]

Table 7-1 F Waves in Normal Subjects*

NO. OF NERVES TESTED	SITE OF STIMULATION	F-WAVE LATENCY TO RECORDING SITE (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CENTRAL LATENCY† TO AND FROM THE SPINAL CORD (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CONDUCTION VELOCITY‡ TO AND FROM THE SPINAL CORD (m/s)	F RATIO§ BETWEEN PROXIMAL AND DISTAL SEGMENTS
122 median nerves from 61 subjects	Wrist	26.6 ± 2.2 (31)**	0.95 ± 0.67 (2.3)**	23.0 ± 2.1 (27)**	0.93 ± 0.62 (2.2)**	65.3 ± 4.7 (56)††	
	Elbow	22.8 ± 1.9 (27)	0.76 ± 0.56 (1.9)	15.4 ± 1.4 (18)	0.71 ± 0.52 (1.8)	67.8 ± 5.8 (56)	0.98 ± 0.08
	Axilla¶	20.4 ± 1.9 (24)	0.85 ± 0.61 (2.1)	10.6 ± 1.5 (14)	0.85 ± 0.58 (2.0)		
130 ulnar nerves from 65 subjects	Wrist	27.6 ± 2.2 (32)	1.00 ± 0.83 (2.7)	25.0 ± 2.1 (29)	0.84 ± 0.59 (2.0)	65.3 ± 4.8 (55)	
	Above elbow	23.1 ± 1.7 (27)	0.68 ± 0.48 (1.6)	16.0 ± 1.2 (18)	0.73 ± 0.52 (1.8)	65.7 ± 5.3 (55)	1.05 ± 0.09
	Axilla¶	20.3 ± 1.6 (24)	0.73 ± 0.54 (1.8)	10.4 ± 1.1 (13)	0.76 ± 0.52 (1.8)		
120 peroneal nerves from 60 subjects	Ankle	48.4 ± 4.0 (56)	1.42 ± 1.03 (3.5)	44.7 ± 3.8 (52)	1.28 ± 0.90 (3.1)	49.8 ± 3.6 (43)	
	Above knee	39.9 ± 3.2 (46)	1.28 ± 0.91 (3.1)	27.3 ± 2.4 (32)	1.18 ± 0.89 (3.0)	55.1 ± 4.6 (46)	1.05 ± 0.09
118 tibial nerves from 59 subjects	Ankle	47.7 ± 5.0 (58)	1.40 ± 1.04 (3.5)	43.8 ± 4.5 (53)	1.52 ± 1.02 (3.6)	52.6 ± 4.3 (44)	
	Knee	39.6 ± 4.4 (48)	1.25 ± 0.92 (3.1)	27.6 ± 3.2 (34)	1.23 ± 0.88 (3.0)	53.7 ± 4.8 (44)	1.11 ± 0.11

*Mean ± standard deviation (SD) in the same patients shown in Tables 6-1, 6-4, 6-11, and 6-13.

†Central latency = F – M, where F and M represent latencies of the F wave and M response.

‡Conduction velocity = 2D/ (F – M –1), where D indicates the distance from the stimulus point to C7 or T12 spinous process.

§F ratio = (F – M – 1) /2M with stimulation with the cathode on the volar crease at the elbow (median), 3 cm above the medial epicondyle (ulnar), just above the head of the fibula (peroneal), and in the popliteal fossa (tibial).

¶F (A) = F (E) + M(E) – M(A), where F(A) and F(E) represent latencies of the F wave with stimulation at the axilla and elbow, and M(A) and M(E), latencies of the corresponding M response.

**Upper limits of normal calculated as mean +2 SD.

††Lower limits of normal calculated as mean –2 SD.

Table 7-2 Comparison between Two Nerves in the Same Limb*

NO. OF NERVES TESTED	SITE OF STIMULATION	F-WAVE LATENCY TO RECORDING SITE			CENTRAL LATENCY† TO AND FROM THE SPINAL CORD		
		MEDIAN NERVE	ULNAR NERVE	DIFFERENCE	MEDIAN NERVE	ULNAR NERVE	DIFFERENCE
70 nerves from 35 patients	Wrist	26.6 ± 2.3 (31)‡	27.2 ± 2.5 (32)‡	1.00 ± 0.68 (2.4)‡	23.3 ± 2.2 (28)‡	24.5 ± 2.4 (29)‡	1.24 ± 0.75 (2.7)‡
	Elbow	22.9 ± 1.8 (26)	23.0 ± 1.7 (26)	0.84 ± 0.55 (1.9)	15.5 ± 1.4 (18)	16.0 ± 1.2 (18)	0.79 ± 0.65 (2.1)
		PERONEAL NERVE	TIBIAL NERVE	DIFFERENCE	PERONEAL NERVE	TIBIAL NERVE	DIFFERENCE
104 nerves from 52 patients	Ankle	47.7 ± 4.0 (55)	48.1 ± 4.2 (57)	1.68 ± 1.21 (4.1)	43.6 ± 4.0 (52)	44.1 ± 3.9 (52)	1.79 ± 1.20 (4.2)
	Knee	39.6 ± 3.7 (47)	40.1 ± 3.7 (48)	1.71 ± 1.19 (4.1)	27.1 ± 2.9 (33)	28.0 ± 2.7 (33)	1.75 ± 1.07 (3.9)

*Mean ± standard deviation (SD) in the same patients shown in Tables 6-2 and 6-12.
†Central latency = F – M, where F and M represent latencies of the F wave and M response.
‡Upper limits of normal calculated as mean +2 SD.

triangularis,[164] extensor digitorum communis,[164] and extensor indicis.[112]

F-wave persistence varies widely depending on the degree of central drive not only at the time of[55] but also immediately prior to the study[104,143] In general, the peroneal nerve supplying only extensor digitorum brevis below the ankle gives rise to a low value as compared to the tibial nerve, which innervates the remainder of the intrinsic foot muscles. Similarly, the median nerve, controlling a smaller number of muscles, has less persistence compared to the ulnar nerve with more intrinsic hand muscles. The excitability of the motoneuron population also varies among different nerves. A motor imagery or slight voluntary muscle contraction increases the chance of recording the fastest conducting fibers.[55]

Of all the measures of NCS in healthy subjects F-wave latency shows the best reproducibility.[4,77,118] Latency difference between the two sides and between two nerves in the same limb serves as the best measure in detecting a lesion affecting only one nerve. In diffuse process, the use of height nomogram serves well as an acceptable means to adjust F latencies for the limb length. Latency-height nomograms (see Appendix Figs. 1-1, 1-2, 1-3) show linear relationships for upper- and lower-limb nerves.[119] Our data, based on F waves elicited by 32 stimuli in 100 healthy subjects[102] indicate the need of at least 10 stimuli to determine the mean latency and 15 stimuli for the minimal and maximal latencies. Similar to other nerve conduction studies, cold limb calls for temperature correction to 32° by subtracting 4% of the measured value per degree to achieve adjusted latency.

In addition to the commonly used minimal latency, FWCV and persistence, clinically relevant measures with a narrow variability include mean and maximal latencies, chronodispersion, and mean duration. In particular, mean latency obtained with 10 stimuli give accurate results either for group or individual analysis.[102]

Disorders Associated with F-Wave Abnormalities

Studies of the F wave help characterize polyneuropathies in general and those associated with prominent proximal abnormalities in particular (Figs. 7-7, 7-8, and 7-9). In the diagnosis of more localized nerve lesions such as radiculopathies, the remaining normal segment dilutes a conduction delay across the much shorter segment. Thus, relatively mild abnormalities over restricted segments rarely alter the F-wave latency beyond its inherent variability (see Chapter 11–7). In fact, in experimental allergic neuritis with demyelination of the ventral roots, only 14% of the guinea pigs and 7% of the rabbits showed an abnormal increase in F-wave latency in fibers with normal MNCV.[151] The latency of an F wave elicited after a proximal stimulation close to the lesion can isolate a relatively short central loop that contains the site of involvement. The F wave elicited here, however, overlaps with the M response, unless combined with a collision method (see Chapter 7-3), which, in effect, separates the two components for latency determination.[71] Further, this relatively short central pathway still dilutes a very focal slowing of a radicular lesion, which constitutes only a small portion compared to the remaining normally conducting unaffected portions of this loop.

The F-wave studies show consistent abnormalities in patients with hereditary motor sensory neuropathy (Panayiotopoulos, 1978),[61,70,107] acute or chronic demyelinating neuropathy,[66,71,76] diabetic neuropathy,[19,74] uremic neuropathy,[1,110] alcoholic neuropathy,[83] and a variety of other neuropathies.[81] Other categories of disorders associated with F-wave changes include entrapment neuropathies,[30,160] large-fiber sensory neuropathy,[129] amyotrophic lateral sclerosis,[5] neurogenic thoracic outlet syndrome,[52] and radiculopathies.[31,45] Some patients with cervical syringomyelia may have increased F-wave latencies of the median or ulnar nerve with normal peripheral conduction velocities.[116,129] A number of disorders show characteristic F-wave abnormalities as summarized in the following sections.

HEREDITARY MOTOR SENSORY NEUROPATHY

Patients with advanced illness often have small M responses and absent F waves in the lower limbs (Panayiotopoulos, 1978)[70,107] with relatively

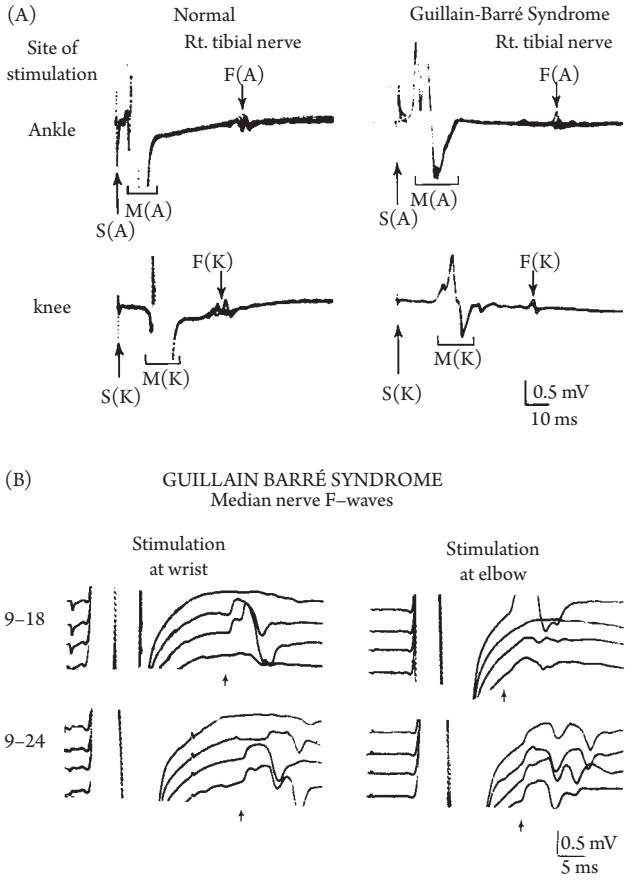

FIGURE 7-7 M response (open brackets) and F wave (small arrows) recorded from the abductor hallucis in two patients with the Guillain-Barré syndrome. (***A***) The first subject had an increased F-wave latency. The M response remained normal in latency, although reduced in amplitude. (***B***) The second subject, a 26-year-old man with progressive generalized weakness for 2 weeks had difficulty rising from the chair or climbing stairs. F-wave latency, normal on September 18, became prolonged on September 24 by 4 ms from the previous measures with stimulation of the median nerve either at the wrist or at the elbow, suggesting a proximal conduction delay.

preserved responses in the upper limbs. These findings support the clinical impression that the disease affects the lower limb more severely (Table 7-3). Mildly diseased nerves may show slow motor conduction in the distal segment and normal conduction in the proximal segment.[61] In advanced cases, conduction abnormalities affect both segments equally. A bimodal distribution of MNCV[146] and F-wave latencies supports the dichotomous separation into hypertrophic and neuronal types, or hereditary motor sensory neuropathy Type I and II (HSM I and II) (see Chapter 24-5). Intermediate F-wave latencies seen in some series probably reflect extreme variability of conduction over a wide spectrum in each group (Fig. 7-10).

GUILLAIN-BARRÉ SYNDROME

Conduction abnormalities may involve any segment of the peripheral nerve in Guillain-Barré syndrome (GBS) (Table 7-4). The disease commonly affects the most proximal, possibly radicular, portion of the nerve and the most distal or terminal segment, relatively sparing the main nerve trunk during early stages (see Chapter 24-3).[48,66,71,76] The routine conduction studies may show normal results in 15%–20% of cases tested within the first few days of onset.[28] Some of these patients may have axonal neuropathies, but others probably have the lesion too proximal for detection with the use of ordinary techniques.

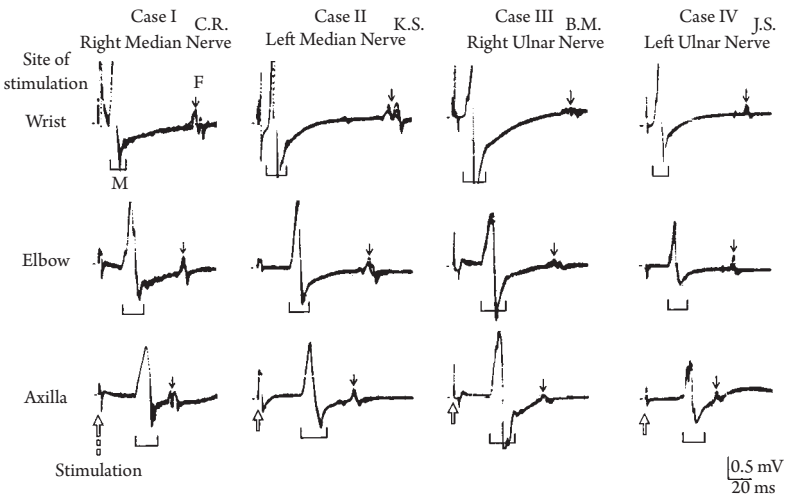

FIGURE 7-8 M response (horizontal brackets) and F wave (small arrows) recorded from the thenar muscles (cases 1 and 2) and hypothenar muscles (cases 3 and 4) in patients with demyelinative form of Charcot-Marie-Tooth disease, or hereditary motor sensory neuropathy Type I. Three consecutive trials in each showed markedly increased M-response and F-wave latencies requiring a slower sweep speed of 20 ms/cm instead of the usual 5 ms/cm. Note clear separation of M response and F wave even with proximal stimulation at the axilla because of slowed conduction, rendering the collision technique unnecessary (cf. Fig. 7-5). (Modified from Kimura.[61])

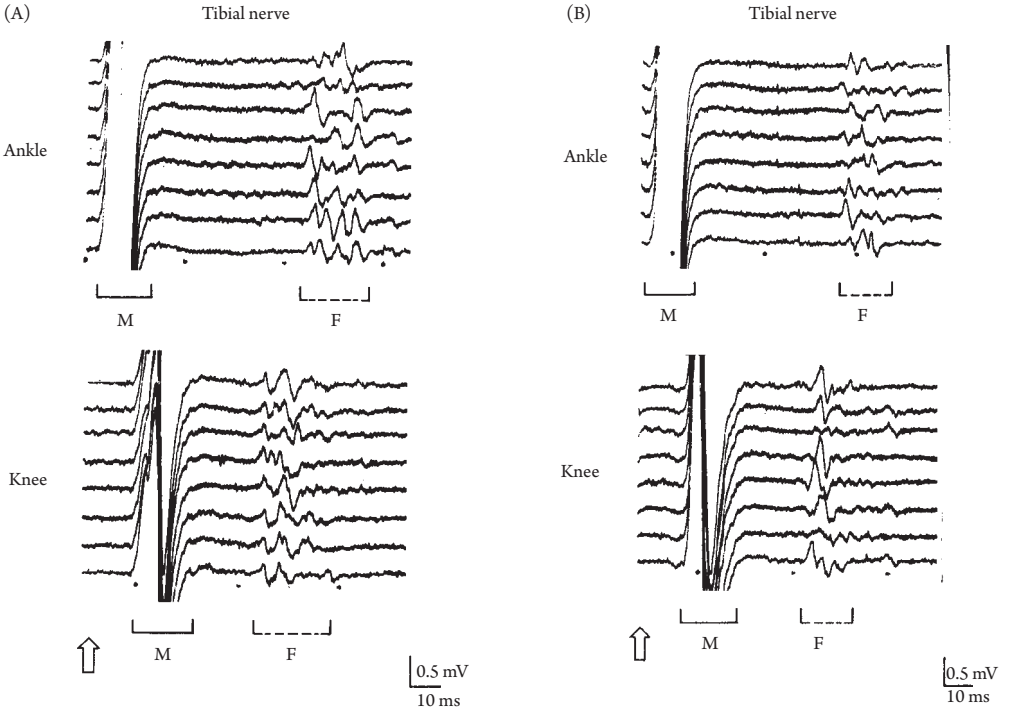

FIGURE 7-9 A 44-year-old man with adrenoleukodystrophy and diffuse weakness. Stimulation of the tibial nerve at the ankle and knee on the right (***A***) and left (***B***) elicited the F waves in the abductor hallucis, showing an increase in latency and marked temporal dispersion. These findings indicate proximal conduction abnormalities in sharp contrast to the normal M response, indicating integrity of the distal segment.

Table 7-3 Hereditary Motor Sensory Neuropathy (mean ±SD)

NO. OF NERVES TESTED	SITES OF STIMULATION	M LATENCY (ms)	F LATENCY (ms)	MNCV BETWEEN TWO STIMULUS SITES (m/s)	FWCV FROM CORD TO STIMULUS SITE (m/s)
36 median nerves	Wrist	6.4 ± 3.0	55.6 ± 26.1	30.4 ± 14.6 38.9 ± 20.2	33.7 ± 14.6
	Elbow	15.6 ± 7.8	46.1 ± 21.4		36.4 ± 14.9
	Axilla	22.2 ± 10.6	39.3 ± 17.8		38.4 ± 16.8
31 ulnar nerves	Wrist	5.2 ± 2.9	55.5 ± 35.1	38.0 ± 18.3 36.6 ±19.3 42.5 ± 22.1	39.2 ± 18.7
	Below elbow	13.1 ± 7.9	48.2 ± 29.8		40.2 ± 19.0
	Above elbow	18.0 ± 10.6	40.7 ± 27.2		42.3 ± 20.8
	Axilla	21.3 ± 14.0	37.3 ± 23.6		43.7 ± 18.9
10 peroneal nerves	Ankle	5.6 ± 1.3	52.8 ± 10.6	40.7 ± 15.2	47.2 ± 6.9
	Knee	15.0 ± 4.8	50.8 ± 19.1		41.6 ± 6.8
22 tibial nerves	Ankle	5.4 ± 1.4	62.8 ± 21.3	40.3 ± 14.9	42.9 ± 14.2
	Knee	16.2 ± 6.3	52.5 ± 15.3		43.9 ± 12.3

FWCV, F-wave conduction velocity; MNCV, motor nerve conduction velocity.

These cases typically show absent F waves initially during acute stages of illness. The return of the previously absent F wave indicates recovery of conduction across the proximal segment. The considerably increased F-wave latency usually suggests a demyelinative lesion (Fig. 7-10).

Many patients have a normal F ratio, which indicates an equal slowing of conduction above and below the stimulus site at the elbow and knee. This does not necessarily mean uniform abnormalities along the entire length of the peripheral nerve. In our series, the cord-to-axilla segment showed slowing more frequently than the elbow-to-wrist segment for both the median and ulnar nerves. In calculating the F ratio, a marked slowing at the common compression site in the distal segment compensates for the prominent proximal abnormalities.

DIABETIC, UREMIC, AND OTHER NEUROPATHIES

Clinical observations of a glove and stocking distribution of neuropathic symptoms do not necessarily imply a distally dominant pathologic process (see Chapter 24-2) because probability models can reproduce the same sensory deficit on the basis of randomly distributed axonal dysfunction.[154] In fact, most diabetic neuropathies show conduction abnormalities along the entire length of the nerve,[19,25,48,74,148] although not as a universal finding in mild cases.[99] Thus, minimal F-wave latency serves as the most sensitive and reproducible measure of conduction slowing in neuropathies associated with diabetes mellitus (see Chapter 11-7).[4,77] The average value and distribution of the F ratio indicate distally prominent conduction abnormalities, as expected in this type of neuropathy (Fig. 7-11). In contrast, patients with proximal amyotrophy may have an increased F ratio in the lower limbs.[13]

Patients undergoing hemodialysis for chronic renal[94]or hepatic[34] failure have an increased F-wave latency with greater than normal differences between the minimum and maximum values. In some of these patients an increased F ratio implies predominant affection of the proximal nerve segment[12] but in others, slowing of nerve conduction involves both segments to the same extent.[33]

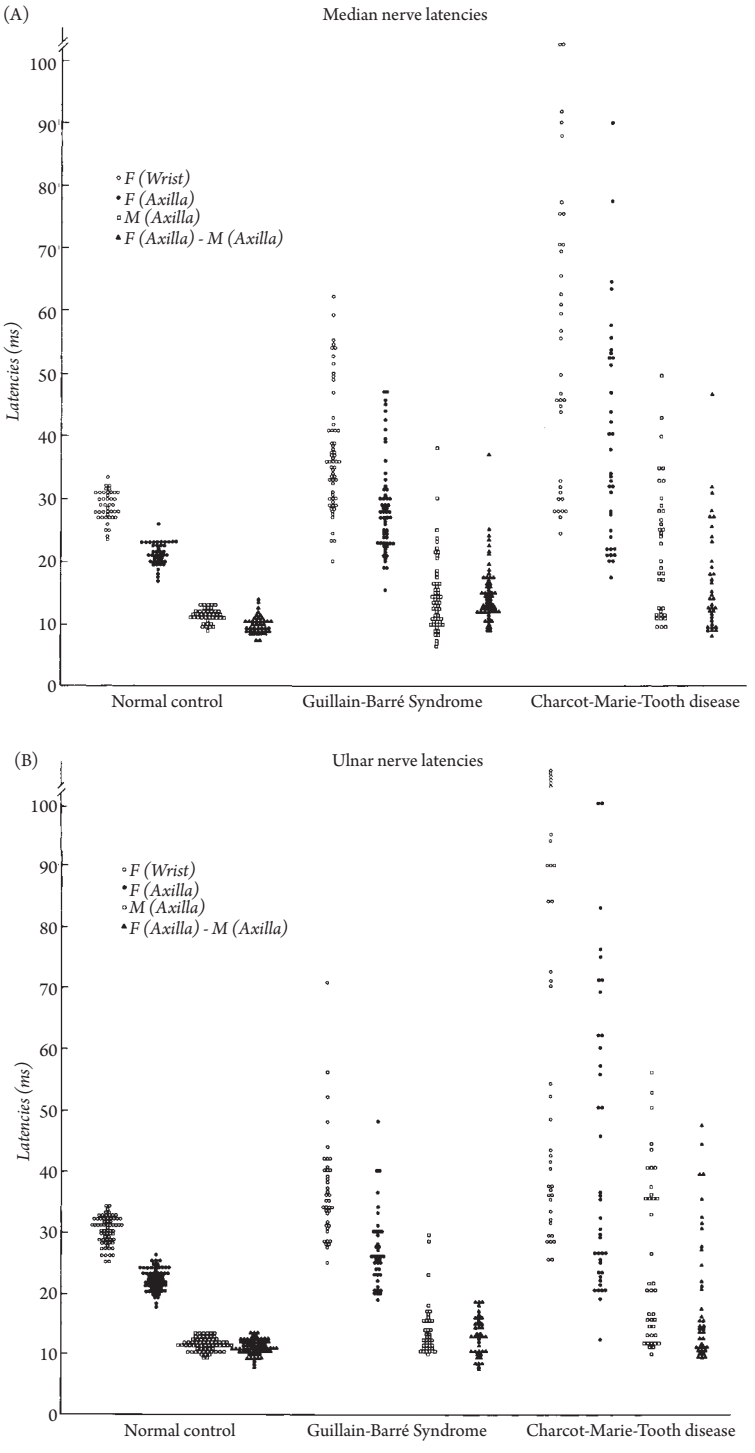

FIGURE 7-10 Latencies of F wave and M response for median (***A***), ulnar (***B***), peroneal (***C***), and tibial nerves (***D***) in control, Guillain-Barré syndrome, and Charcot-Marie-Tooth disease. The histogram includes only those nerves whose stimulation elicited both an M response and F wave at the sites of stimulation indicated in the key. The difference in latency between F wave and M response (triangles) equals the central latency required for passage of the impulses to and from the spinal cord. (Modified from Kimura.[68])

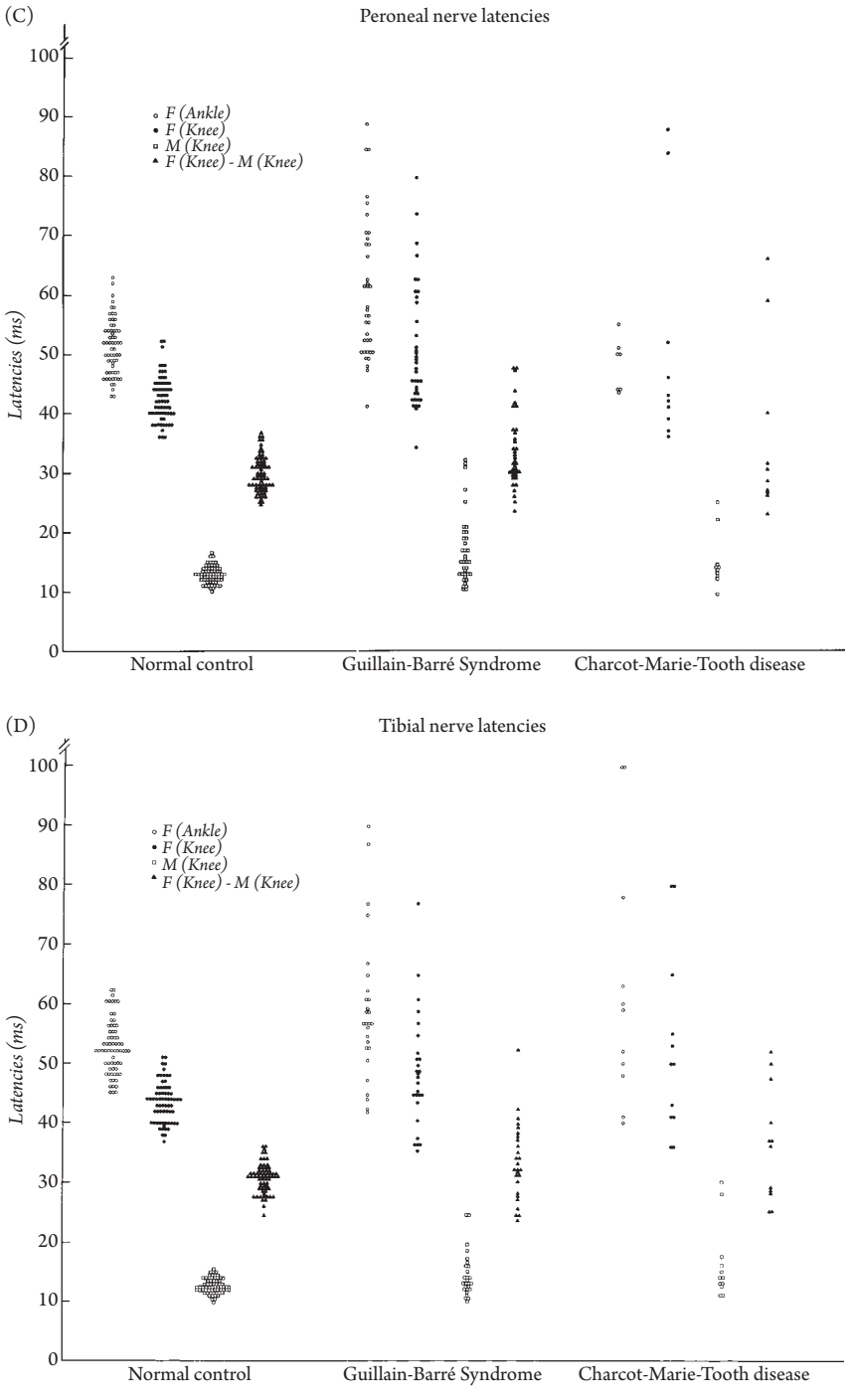

FIGURE 7-10 *(Continued)*

Table 7-4 Guillain-Barré Syndrome (mean ± SD)

NO. OF NERVES TESTED	SITES OF STIMULATION	M LATENCY (ms)	F LATENCY (ms)	MNCV BETWEEN TWO STIMULUS SITES (m/s)	FWCV FROM CORD TO STIMULUS SITE (m/s)
58 median nerves	Wrist	5.8 ± 3.1	38.1 ± 12.7	48.2 ± 12.1	48.6 ± 11.1
	Elbow	11.2 ± 4.8	32.6 ± 9.9	55.5 ± 14.1	49.1 + 11.4
	Axilla	14.5 ± 5.7	29.4 ± 9.5		47.5 ± 14.5
40 ulnar nerves	Wrist	4.0 ± 2.0	36.8 ± 8.6	52.2 ± 10.7	48.1 ± 9.7
	Belσw elbow	8.3 ± 2.5	32.1 ±7.1	47.7 ± 12.0	47.4 ± 9.6
	Above elbow	11.2 ± 3.5	29.7 ± 8.7	56.8 ± 14.9	47.4 ± 10.7
	Axilla	13.7 ± 4.8	27.2 ± 6.2		48.0 ± 12.3
39 peroneal nerves	Ankle	7.6 ± 4.8	59.9 ± 11.5	43.0 ± 8.2	42.5 ± 8.7
	Knee	16.9 ± 5.8	50.6 ± 10.3		43.9 ± 11.8
29 tibial nerves	Ankle	5.6 ± 2.3	56.4 ± 10.6	43.3 ± 9.0	42.7 ± 8.8
	Knee	14.6 ± 3.8	47.9 ± 9.4		43.8 ± 9.9

FWCV, F-wave conduction velocity; MNCV, motor nerve conduction velocity.

ENTRAPMENT AND COMPRESSION SYNDROMES

In general, F wave studies fail to provide a sensitive measure for the evaluation of entrapment syndromes because disproportionately longer unaffected segments tend to dilute the focal conduction abnormalities (see Chapter 11–7). An increased F-wave latency, if seen in entrapment or compression neuropathies[137,138] has no localizing value as it covers the entire length of the motor axons. A reduced F ratio of the median nerve in the carpal tunnel syndrome (CTS) rivals that in diabetic neuropathy, indicating distally prominent abnormalities in both conditions (Fig. 7-11).[74] With loss of axons, unaffected neurons backfire at higher than normal frequencies, resulting in an increased percentage of repeater F waves as reported in CTS.[90]

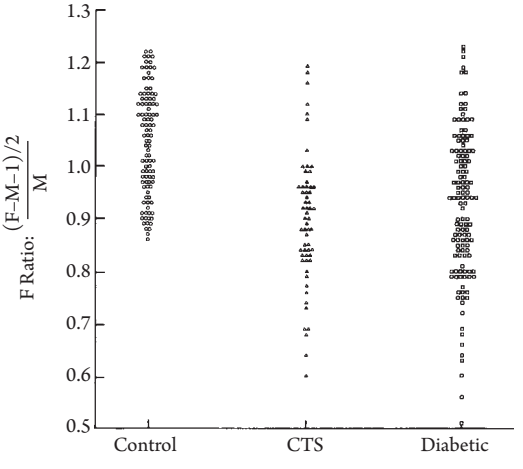

FIGURE 7-11 F ratio of the median nerve in 57 control subjects, 44 patients with carpal tunnel syndrome (CTS), and 93 patients with diabetic polyneuropathy. Statistical analysis showed significantly ($p < .01$) reduced ratios in both disease groups, indicating disproportionate distal slowing of motor conduction. (Modified from Kimura.[67])

Plexopathy

F-wave latency may increase in the neurogenic,[160] but not in the vascular, type of the thoracic outlet syndrome.[65,137,138] F-wave changes render useful information in some children with brachial plexus injury at birth,[80] but the results may remain normal in clinically established cases of brachial or lumbosacral plexopathy.[2]

An unequivocal delay or absence of the F wave in conjunction with normal motor conduction distally indicates a proximal lesion (Fig. 7-12).

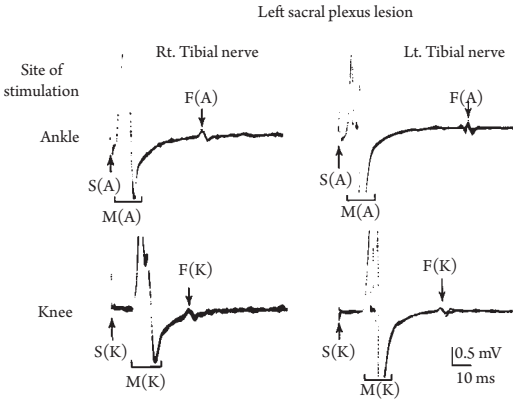

FIGURE 7-12 A patient with a sacral plexus lesion on the left. Stimulation of the tibial nerve at the ankle and knee elicited an M response (open brackets) and F wave (small arrows) in the abductor hallucis. Note the increased F-wave latency on the affected side despite a normal M response.

Right-to-left difference usually serves as a reliable means of assessing unilateral lesions, although even this measure often falls short of documenting small latency change.[65] The F-wave persistence declines on the affected side, compared with the normal side, when the proximal lesion induces partial conduction block. In some patients with neurogenic claudication, serial studies before and after ambulation reveal dynamic alterations in F-wave persistence and latency.[89,92,113,118,141,146] A reversible suppression of F waves with exercise seen in this condition stands in contrast to the contraction-induced physiologic excitation of the anterior cells[55] This finding, which suggests an ischemic conduction block, corroborates a neurogenic origin of the symptoms.

RADICULOPATHY

A number of reports have suggested clinical value of F-wave study in assessing patients with root injuries.[30,31,43,53,114,149] Theoretical considerations discussed earlier, however, clearly imply its limitation as an electrodiagnostic measure of radiculopathies. Other reasons for failure of F waves to provide clinically useful information in this condition include the following: (1) a surviving fast-conducting neuron gives rise to a normal F-wave latency in an incomplete lesion; (2) the F waves recorded from the intrinsic hand and foot muscles mostly originate from C8-T1 and S1–2 roots, excluding more commonly affected C7 and L5 levels from evaluation; (3) normal F waves derived from an unaffected root or rootlet mask possible abnormalities of the affected roots; (4) F-wave abnormalities, which indicate slowing somewhere along the length of the axon, cannot localize the lesion, if seen in a patient with radiculopathy.

Consistent with the theoretical limitation stated earlier, most reported studies show disappointingly low yields. In one well-controlled study of cervical radiculopathy,[126] sensitivity of the F wave ranged only from 10% to 20%. More specifically, 10% of 2093 patients who had clinical symptoms of cervical radiculopathy and 3% of 1005 patients with normal examinations showed F-wave abnormalities. In the same series, 7% of patients with clinical and electromyographic (EMG) evidence of radiculopathy had increased F-wave latencies. Thus, the F wave showed abnormalities twice as often in patients with clinical symptoms of radiculopathy as compared to those with normal examination. The likelihood of finding an increased F-wave latency approached 20% in patients with an abnormal needle examination, indicating a C8 radiculopathy. Thus, F-wave studies add little in patients showing EMG changes consistent with radiculopathy. F-wave abnormalities, if seen in conjunction with normal needle studies, have a limited clinical value in diagnosing radiculopathy for the lack of localizing value. Finally, F-wave studies may show statistically significant changes in patients with radiculopathies compared to the control subjects. A group difference, however, means little for an electrophysiologic technique used to confirm a clinical diagnosis in individual patients.

FLACCID PARALYSIS

Spinal shock suppresses the H reflex and F wave below the lesion very early after injury. Although H reflexes tend to recover within days, F waves may remain absent for weeks.[84] In one series,[20] 50% of the acute spinal cord injury patients had no F waves below the lesion site despite the preservation of M responses. The F wave returned during the chronic

stage, suggesting the effect of spinal shock on the excitability of the motoneurons. These types of F-wave changes can also occur in an evolving spinal cord or conus medullaris lesion,[3,18,140] mimicking the abnormalities seen in early stages of GBS.[48] Reduced F-wave excitability in acute flaccid hemiparesis generally recovers toward the normal range during chronic stages.[20,140] In our experience, some patients with hysterical paresis also show reduced F-wave excitability, probably by inhibitions of the facilitatory central drive (see Chapter 7-2). Clinical use of F wave should take all these possibilities into consideration.

Other Disorders

Other entities associated with F-wave abnormalities include amyotrophic lateral sclerosis (ALS)[7] and acoustic neuroma.[156]

5. A WAVES AND OTHER RELATED RESPONSES

Basic Types of A Wave

If a submaximal stimulus excites one branch of the axon but not the other, the antidromic impulse propagates up to the point of branching and turns around to proceed distally along a second branch. This gives rise to a late response, which, unlike F waves, remains constant in latency and waveform. The designation, A waves, has replaced the traditional name, axon reflex, to avoid the implication of its reflexive origin. Its initial description, the intermediate latency response,[51] also has fallen in disrepute as the A waves do not necessarily appear between the M response and the F wave. Possible pathophysiologic mechanisms include, in addition to collateral sprouting, ephapsis, or a cross talk from a neighboring axon, and ectopic discharges generated in the hyperexcitable portion of the motor axon after the passage of an impulse (Fig. 7-13).[11,91]

The A wave has a constant latency and waveform because it originates from the same portion of a single motor unit, either at a branching point of a collateral sprout or at an unstable site vulnerable to ephaptic or ectopic discharge. Regardless of the underlying physiologic mechanisms, A-wave latencies decrease with more proximal stimulation, indicating, analogous to the F wave, an initially antidromic passage of the impulse. The point of origin and conduction velocity of the two branches of the axon determine the latency of the

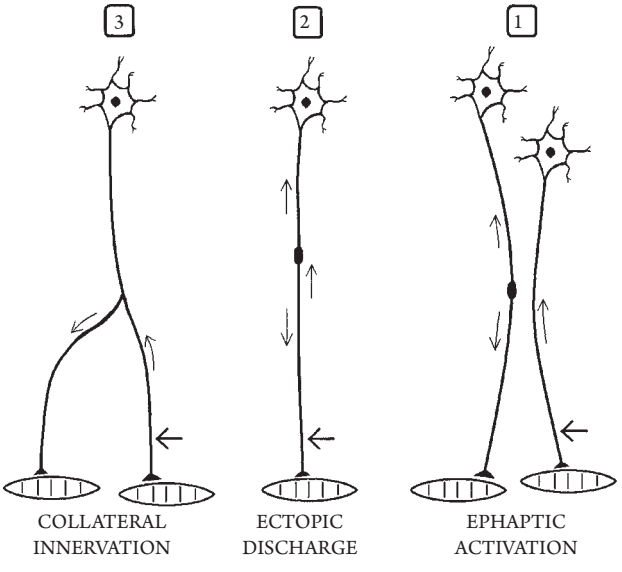

FIGURE 7-13 Pathophysiologic mechanisms for three types of A wave: (1) ephaptic activation of hyperexcitable segment by a nerve impulse of the neighboring axons, (2) an ectopic discharge triggered by a propagating impulse, and (3) turnaround at a branching point of collateral innervation.

A wave. The regenerating unmyelinated collateral sprout may conduct the ascending or descending impulses much more slowly than the neighboring intact axons that relay the F wave. Hence, A waves, despite a shorter pathway may follow rather than precede the F wave (Fig. 7-13).

Physiologic Characteristics

With the A waves generated by collateral sprouting, shocks of higher intensity, activating both branches distally, eliminate the response because two antidromic impulses collide as they turn around at the branching point (Fig. 7-14). Thus, supramaximal stimuli normally abolish the collateral A wave altogether. In contrast, an ephaptic A wave will persist if slow-conducting antidromic impulse induces ephaptic transmission of the neighboring fast-conducting axon after the passage of its antidromic impulse, thereby escaping the collision. An increase in shock intensity also fails to inhibit the ectopic A wave induced by antidromic passage of an impulse across a hyperexcitable segment of an axon. In this case, paired shocks abolish the A wave because the second antidromic impulse collides with the ectopically generated orthodromic impulse. With repetitive shocks, only

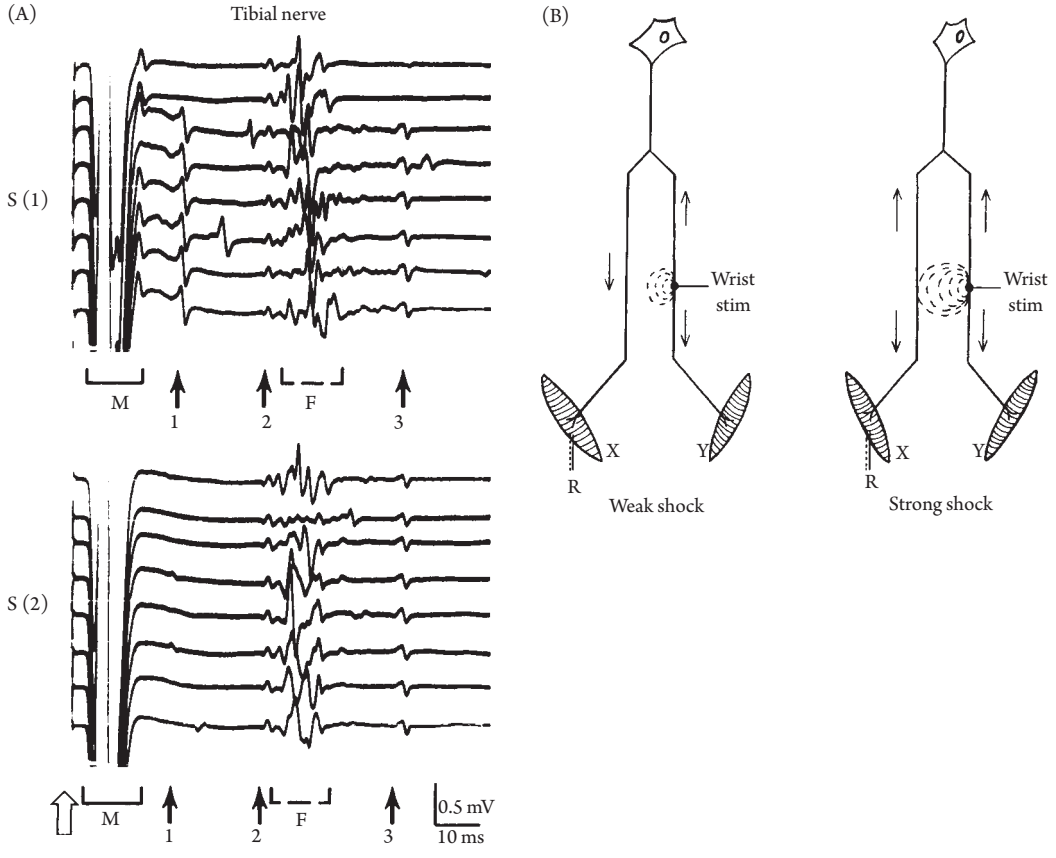

FIGURE 7-14 (***A***) A 51-year-old man with low-back pain. Stimulation of the right tibial nerve at the ankle elicited a number of A waves. A series of eight tracings, displayed with stepwise vertical shift of the baseline, confirm the consistency. This type of display not only facilitates the selection of the F wave with minimal latency but also allows individual assessments of all the late responses. Of the three A waves (small arrows, 1, 2, and 3) elicited by a weak shock, S(1), a stronger shock S(2), eliminated only the earliest response. (***B***) Collateral sprouting in the proximal part of the nerve. A strong shock, activating both branches, can eliminate the A wave generated by weak stimulation by collision. (Modified from Fullerton and Gilliatt, 1965.[51])

every other stimulus gives rise to an ectopic A wave because even-numbered shocks cause collision. Analyses of recorded responses using various maneuvers usually prove or disprove the ephaptic hypothesis in each case.[91]

Distal stimulation of the median or ulnar nerve at the wrist or the peroneal or tibial nerve at the ankle most commonly evokes an A wave. In contrast, proximal stimulation above the origin of the collateral sprout or the point of ephaptic or ectopic discharges induces only an M response. Thus, a series of stimuli applied along the course of the nerve may localize the site of origin. Collateral sprouting, however, does not always develop at the level of the lesion but frequently well below the actual site of involvement.[51] Distal and proximal stimuli may elicit the same A wave, allowing determination of conduction velocity for the short intersegment of that particular motor fiber.

Late Motor Response

A late motor response presumably mediated by an axon loop along the nerve may mimic an A wave.[131] A late potential may also result from a scattered motor response with slow conduction in pathologic nerves. Again, with proximal stimulations the latency of the A wave decreases, whereas that of a temporally dispersed M response increases (Figs. 7-15). If repetitive potentials originate distally by the orthodromic impulse, their latencies change with M response, shortening with more distal stimulation. The electric field of the muscle action potential could also ephaptically re-excite an intramuscular axon, producing a muscle-nerve

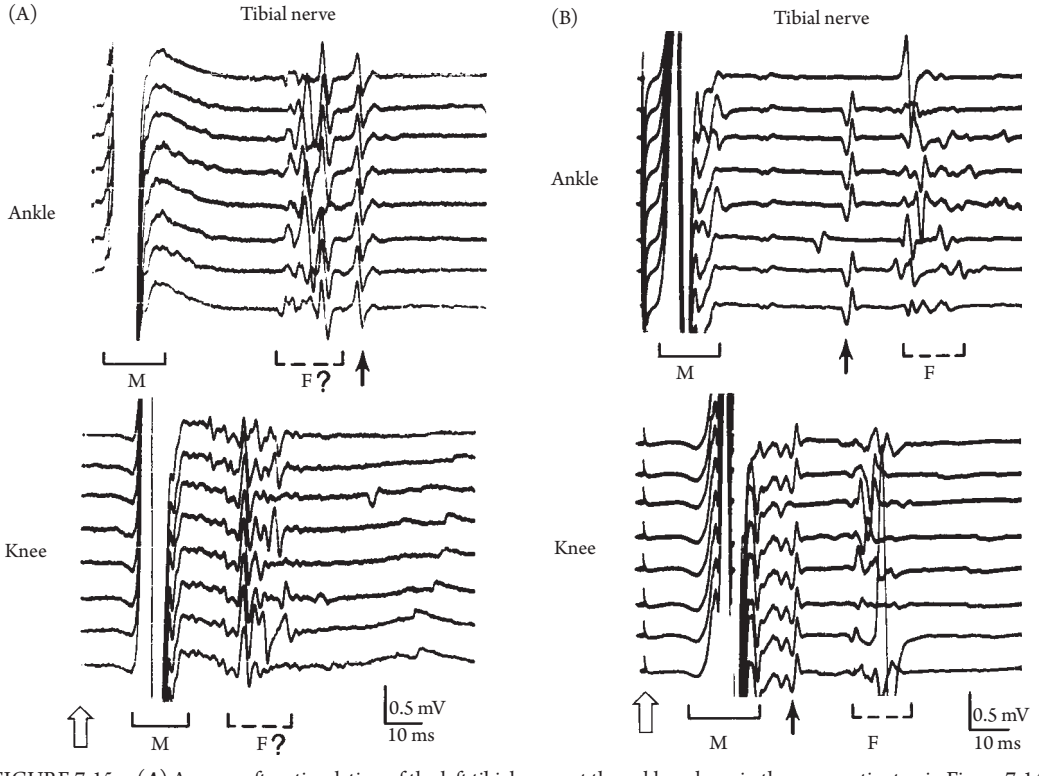

FIGURE 7-15 (***A***) A waves after stimulation of the left tibial nerve at the ankle or knee in the same patient as in Figure 7-14. Proximal stimulation eliminated the A wave (arrow) that followed the F wave with distal stimulation. This finding suggests the generation of the A wave at a site between the distal and proximal stimulation point. (***B***) A 50-year-old man with recurrent backaches following laminectomy. Stimulation of the tibial nerve at the ankle or knee elicited the A wave (arrow). Like the F wave, the latency of the A wave decreased with proximal site of stimulation. This indicates that the impulse first propagates in the centripetal direction.

reverberating loop.[135] In these cases, the original muscle potential and the repetitive discharge maintain the same interval regardless of the nerve stimulation point.

Repetitive Discharges

Less frequently, repetitive A waves, or A-wave multiplex, occur after the M response (Fig. 7-16).[78] In the absence of synaptic connection along the pathway, the impulse can usually follow a high rate of repetitive stimulation up to 40 Hz. Repetitive A waves, however, usually fail at high rates of stimulation and tend to vary in latency and waveform even if they originate from a single axon. High-frequency responses probably result from reverberating ephaptic or ectopic discharge at a focal point of an axon, leading to repetitive re-excitation of the same site through complex neural pathways.[131,139]

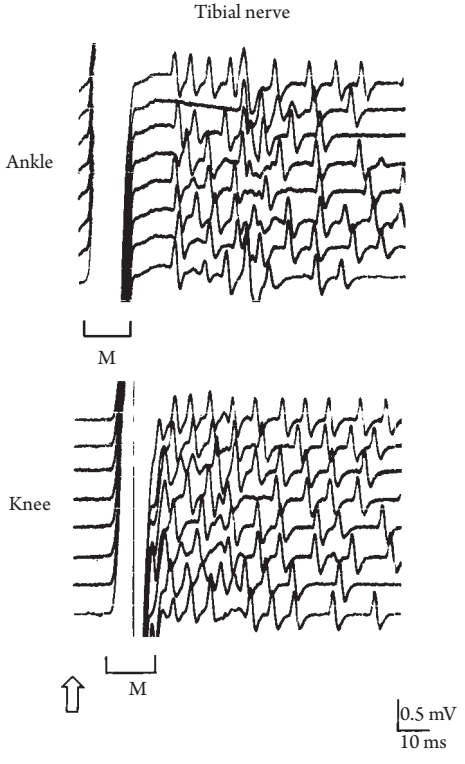

FIGURE 7-16 Incidental finding in a 38-year-old man with a history of right pelvic fracture. Stimulation of the right tibial nerve at the ankle and knee elicited the repetitive discharge. Its onset latency shortened with proximal as opposed to distal stimulation, as expected for an A-wave multiplex.

Disorders Associated with A Waves

A heterogeneous group of patients develop A waves as a sign of peripheral neurogenic disorders. Occasionally some healthy individuals, particularly in old age, may also show this discharge, especially when studying the tibial nerve. The A waves abound in acute and chronic neuropathies, widely varying in pathophysiology from nerve regeneration to demyelination. The commonly associated disease entities include various entrapment syndromes, tardy ulnar palsy, brachial plexus lesions, diabetic neuropathy, HSMN I and II, facial neuropathy, ALS, GBS, and cervical root lesions, to mention only a few.[51,79,132] In one series,[133] A waves prevailed in demyelinating neuropathy, often showing a complex waveform. In another study of diabetic subjects,[121] A waves occurred in 25% of the tibial and 14% of peroneal nerves but only in 2% of median and ulnar nerves, probably as subclinical abnormalities.

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8

Studies of the Facial Nerve and the Blink Reflex

Abbreviations: CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, D—direct response, E1—active electrode, E2—reference electrode, EMG—electromyography, GBS—Guillain-Barré syndrome, HMSN—hereditary motor sensory neuropathy, R/D ratio—rate of R1 to direct response, REM—rapid eye movement

1. INTRODUCTION

Commonly tested cranial nerves in an electromyographic (EMG) laboratory include the facial and trigeminal nerves.[2,126] Surface stimulation of the facial nerve as it exits from the stylomastoid foramen or more distally (see Chapter 11-3) gives rise to compound muscle action potentials (CMAPs) in various facial muscles on the same side. A reduction in size of this direct response (D), so called to distinguish it from the reflexive contraction after stimulation of the trigeminal nerve, signals the loss of distal axons, which in turn determines the prognosis for recovery.

Electrical stimulation of the supraorbital nerve elicits two or more temporally separate responses of the orbicularis oculi muscles, an ipsilateral early component (R1) via a short latency pontine pathway and bilateral late component (R2) and sometimes later component (R3) through a complex route, which includes the pons, lateral medulla, and reticular formation (Fig. 8-1). A contralateral R1, which usually remains inactive, may also appear under some

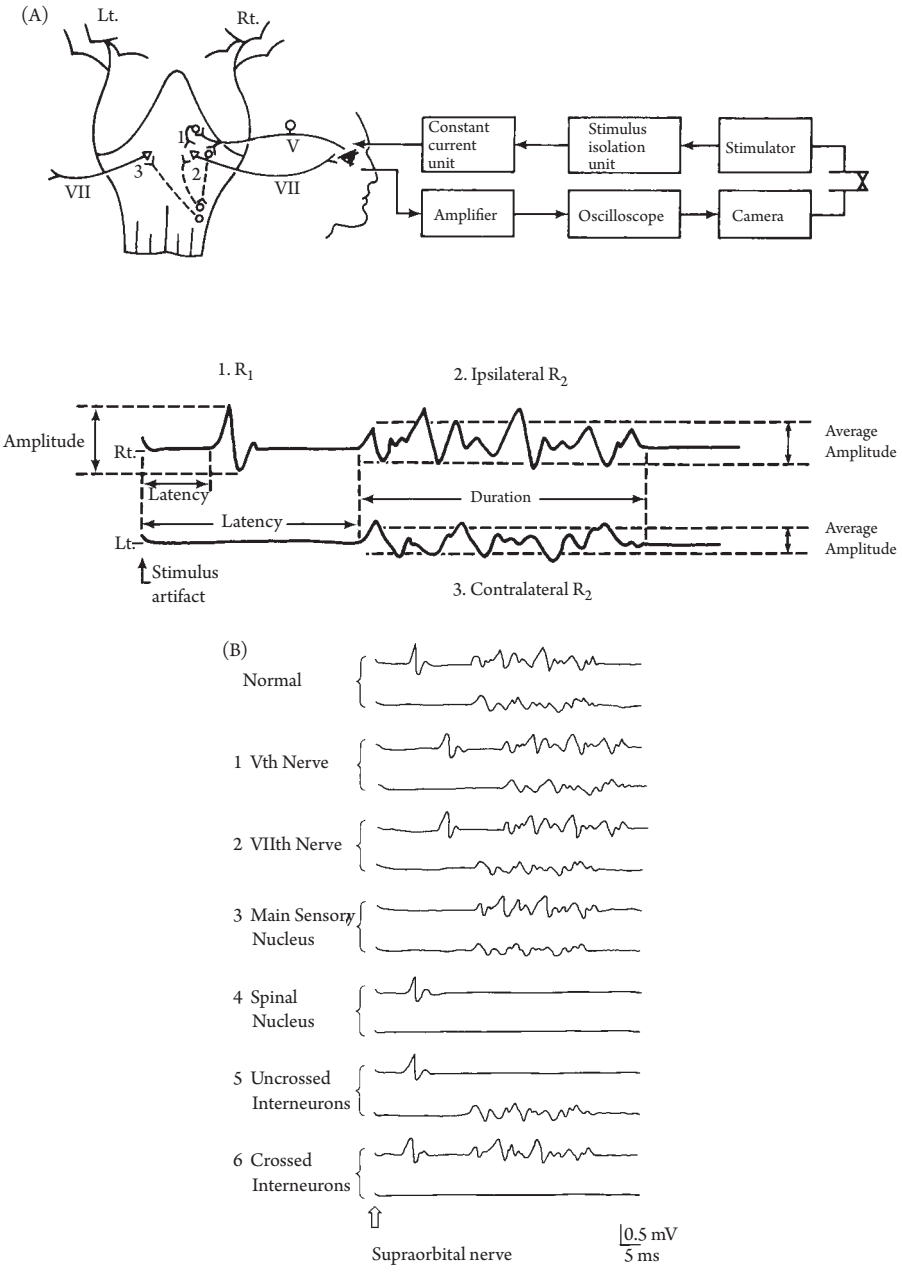

FIGURE 8-1 (***A***) (Top) Stimulation and recording arrangement for the blink reflex, with the presumed pathway of R1 through the pons (1) and ipsilateral and contralateral R2 through the pons and lateral medulla (2 and 3). The schematic illustration shows the primary afferents of R1 and R2 shown as one fiber, but details of polysynaptic central connections of these reflexes remain unknown. (Bottom) A typical blink reflex after right-sided stimulation, with an ipsilateral R1 response and bilateral simultaneous R2 responses. (Modified from Kimura.[53]) (***B***) Five basic types of blink reflex abnormalities. From top to bottom, the finding suggests the conduction abnormality of (1) afferent pathway along the trigeminal nerve (V in ***A***); (2) efferent pathway along the facial nerve (VII in ***A***); (3) main sensory nucleus or pontine interneurons relaying to the ipsilateral facial nucleus (1 in ***A***); (4) spinal tract and nucleus or medullary interneuronal pathways to the facial nuclei on both sides; (5) uncrossed medullary interneurons to the ipsilateral facial nucleus (2 in ***A***); and (6) crossed medullary interneurons to the contralateral facial nucleus (3 in ***A***). Increased latencies of R1 usually indicate the involvement of the reflex arc itself, whereas the loss or diminution of R1 or R2 may result not only from lesions directly affecting the reflex pathway but also those indirectly influencing the excitability of the interneurons or motoneurons.

circumstances often associated with absent ipsilateral R1 as in some cases of Bell's palsy.[83] These findings suggest unmasking of a crossed pathway for R1 similar to the mechanism proposed for enhanced R2 contralateral to the paralyzed side of the face.[78]

Of the two main components, R1 serves as a more reliable measure of nerve conduction along the reflex pathway. Analysis of R2 helps localize the lesion to the afferent or efferent reflex arc. Involvement of the trigeminal nerve causes an afferent pattern with delays or diminution of R2 bilaterally after stimulation of the affected side. Diseases of the facial nerve give rise to an efferent pattern with alteration of R2 only on the affected side regardless of the side of trigeminal nerve stimulation. In this type of analysis, we can draw an analogy to the two types of abnormality for pupillary light reflex. In an afferent defect, light stimuli given to the affected eye constrict neither pupil, whereas in an efferent defect, stimuli to either side fail to constrict the pupil only on the affected side.

2. STIMULATION OF THE FACIAL NERVE

Table 8-1 (see also Appendix Table 1-7) summarizes the normal latencies measured to the onset of the negative deflection of the evoked potential in 78 subjects divided into different age groups.[134]

Table 8-1 Facial Nerve Latency in 78 Subjects Divided into Different Age Groups

AGE	MEAN (ms)	RANGE (ms)
0–1 month	10.1	6.4–12.0
1–12 months	7.0	5.0–10.0
1–2 years	5.1	3.5–6.3
2–3 years	3.9	3.8–4.5
3–4 years	3.7	3.4–4.0
4–5 years	4.1	3.5–5.0
5–7 years	3.9	3.2–5.0
7–16 years	4.0	3.0–5.0

Modified from Waylonis and Johnson.[134]

Stimulating the facial nerve trunk just below the ear and anterior to the mastoid process or over the stylomastoid foramen elicits a D response in all the mimetic muscle on that side (Fig. 8-2A). Selective stimulation of a given branch of the facial nerve more distally elicits a relatively isolated response with a shorter latency from the muscle innervated by this branch (Fig. 8-2B,C). An active electrode (E1) placed on the ipsilateral nasalis with reference electrode (E2) on the inactive, contralateral nasalis suits best for assessment of D response, although other possible recording sites include orbicularis oculi, orbicularis oris, and quadratus labii.[35] Recording from distant facial muscles following a stimulus delivered to a single facial motor branch helps identify an ephaptic impulse transmitted between different facial motor branches (see Chapter 28-10).[82] Selective recording from a target muscle may require a coaxial needle placed in the orbicularis oris just superior to the corner of the mouth or in the orbicularis oculi at the lateral epicanthus. The use of a monopolar needle calls for a surface or a second needle electrode in the vicinity as a reference. A larger electrode placed on the forehead or under the chin serves as the ground.

With a facial nerve lesion as in Bell's palsy, the onset latency of D response rarely shows a clear abnormality even after substantial axonal degeneration because the surviving axons conduct normally. A proximal section of the nerve, however, results in a gradual loss of distal excitability toward the end of the first week with initial failure of the neuromuscular junction followed by the emergence of wallerian degeneration (Fig. 8-3). Amplitude reduction of the distally elicited D response reflects the degree of axonal loss, which determines the prognosis. Despite a substantial intra-individual side-to-side variability, a 50% reduction compared to the unaffected side usually indicates unequivocal nerve degeneration. A normal or near-normal response 1 week after injury suggests a good prognosis. Serial determinations may, however, reveal further decline in amplitude thereafter, indicating

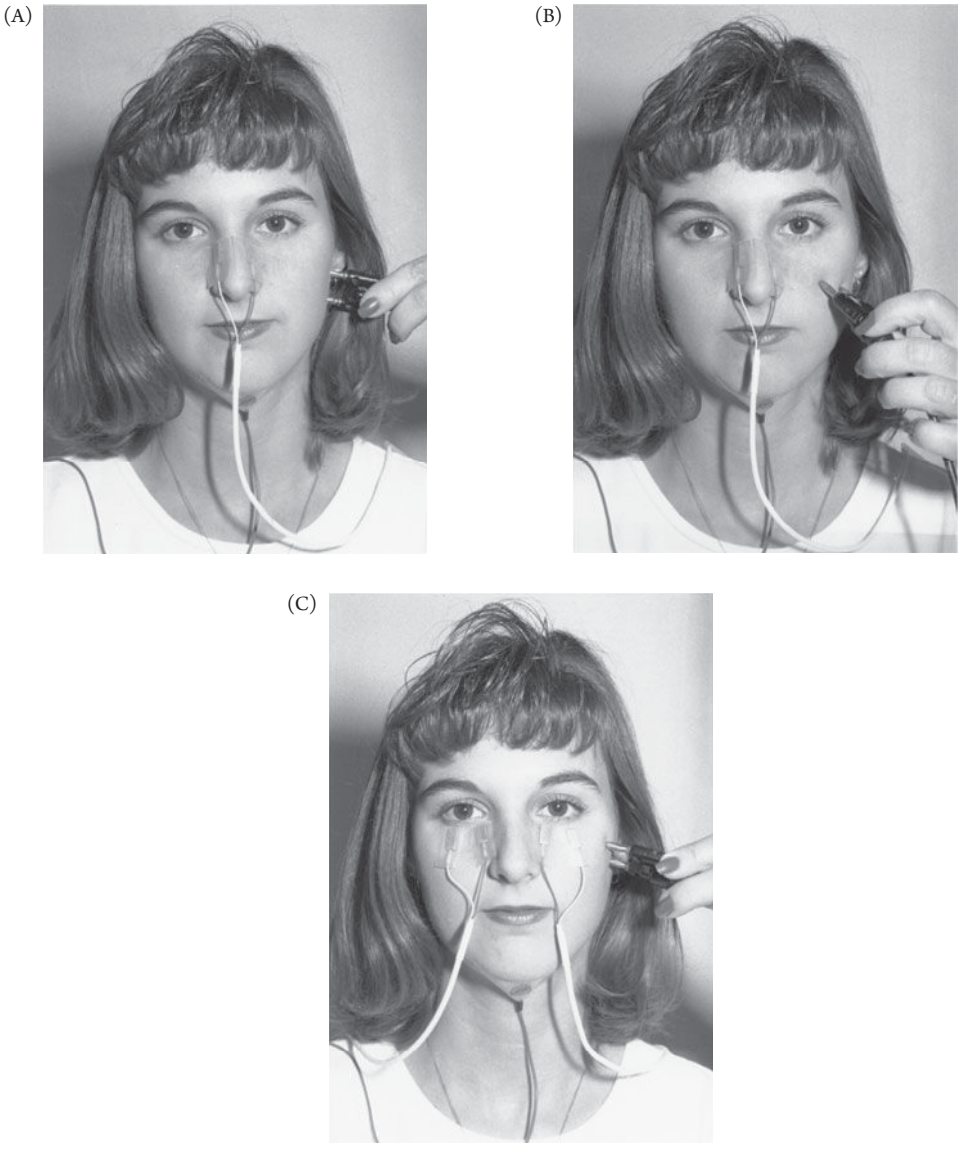

FIGURE 8-2 Technique for recording the direct response. Stimulation of the facial nerve trunk (***A***) with the cathode placed just anterior to the mastoid process elicits compound muscle action potentials in all mimetic muscles of the face ipsilaterally. Stimulation of buccalis (***B***) or zygomaticus (***C***) activates the target muscle more selectively, minimizing movement artifact. Recording from the nasalis with E1 placed ipsilateral to the side of stimulation and E2 contralaterally often gives rise to a discrete compound muscle action potential (***B***). The test performed in conjunction with the blink reflex uses E1 medially and E2 laterally on the lower portion of the orbicularis oculi (***C***) (cf. Fig. 1-3).

progressive wallerian degeneration over the span of 5–10 days involving different motor axons sequentially. High-intensity shocks may inadvertently activate the motor point of the masseter muscle (see Fig. 11-1). Visual inspection of the induced twitch helps confirm the source of the response.

3. STIMULATION OF THE TRIGEMINAL NERVE

Components of Blink Reflex

Stimulation of the supraorbital nerve elicits reflex contraction of the orbicularis oculi. In contrast

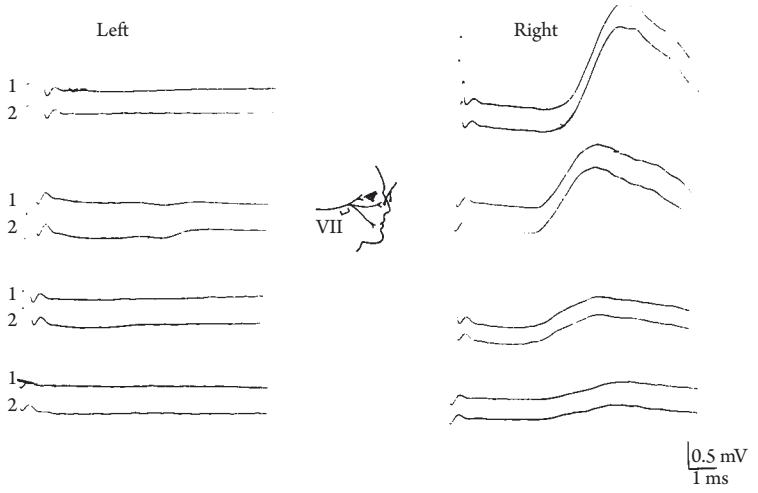

FIGURE 8-3 A 63-year-old man with acute facial palsy on the left in November, and on the right in March. Stimulation of the left facial nerve elicited no response in the nasalis at the initial evaluation with no recovery thereafter. Stimulation on the right evoked a normal response in November but progressive reduction in amplitude of the compound muscle action potential in March. This finding indicates axonal degeneration during the first few days after the onset of illness.

to the direct stimulation of the facial nerve that measures distal nerve excitability, the blink reflex tests the integrity of the afferent and efferent reflex pathways, including the proximal segment of the facial nerve. Stimulation of the infraorbital or mental nerve with the cathode placed over the respective foramen on one side also elicits blink reflex of the orbicularis oculi but less consistently.

Of the two separate responses of the orbicularis oculi evoked by a single shock to the supraorbital nerve, R1 represents the conduction along the trigeminal and facial nerves and pontine relay. In comparison, the latency of R2, elicited bilaterally with unilateral stimulation, reflects, in addition to the axonal conduction time, the excitability of interneurons. Changing excitability of synaptic transmission probably accounts for the inherent latency variability of R2 from one trial to the next. A greater shock may activate small-diameter, high-threshold afferent fibers, evoking R3.[6,72] Bilateral responses at around 70 ms and occasionally also at 130 ms elicited by painful laser stimulation[27] fall within the range of electrically evoked R2 and R3, assuming the nociceptor activation time of about 40 ms.

Electrically Elicited Responses

The subject lies supine with the eyes gently closed for surface stimulation by the cathode placed over the supraorbital foramen with the anode, 2 cm rostrally, and ground electrode under the chin or around the arm (Fig. 8-4).[62] Shocks applied here evoke R1 and R2, easily recordable with a pair of recording electrodes, E1 medially and E2, 2 cm laterally on the lower aspect of the orbicularis oculi muscle on each side. The latency of R1, measured to the initial deflection of the earliest evoked potential after several trials, yields the minimal conduction time of the reflex pathway. The R/D ratio, defined as the latency ratio of R1 to the D response, compares the conduction time of the distal segment of the facial nerve to that of the entire reflex arc, which includes the trigeminal nerve and the proximal segment of the facial nerve.

To elicit a reproducible R1 with repeated trials, optimal intensity for shocks of 0.1 ms duration, ranges from 50 to 150 V or 5–15 mA, assuming the impedance of 10 KΩ. A small number of healthy subjects may have an absent or unstable R1 at rest, usually bilaterally. In this situation, where the use of higher shock intensity only causes the patient's

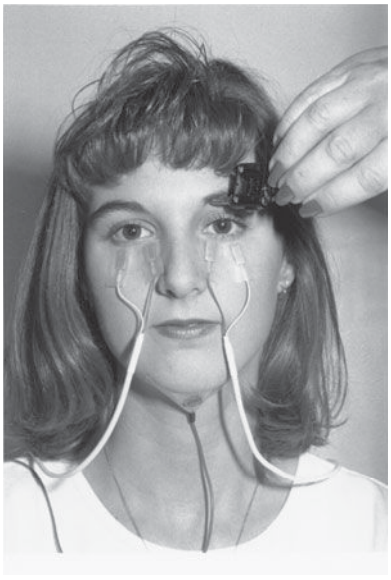

FIGURE 8-4 Technique for recording the blink reflex. Unilateral stimulation of the supraorbital nerve with the cathode placed at the supraorbital foramen elicits R1 ipsilaterally and R2 bilaterally in the orbicularis oculi muscles. Recording leads consist of the active electrode (E1) placed over the inferior portion of the orbicularis oculi near the inner canthus and the reference electrode (E2) 2 cm laterally. Rotation of the anode around the cathode helps establish the optimal position of the stimulating electrodes to minimize the shock artifact.

discomfort without satisfactory results, mild voluntary contraction of the orbicularis oculi may facilitate the response. Applying paired stimuli, with an interstimulus interval of 3–5 ms, also elicits a detectable R1 for latency measurement from the second shock artifact.[48] Hence, a subthreshold conditioning shock subliminally excites the motoneurons, then discharge in response to a supramaximal test stimulus to evoke the response (Figs. 8-4, 8-5, and 8-6a,b).

Because E1 and E2 lie only a few centimeters away from the cathode, R1 tends to overlap with the stimulus artifact, which can last more than 10 ms. Usual care in reducing surface spread of stimulus current helps accomplish optimal recording of this short-latency response. A specially designed amplifier (see Chapter 3-3) with a short blocking time (0.1 ms) and low internal noise (0.5 μV root mean square at a bandwidth of 2 KHz) minimizes the stimulus artifact.[133,149] Most modern instruments offer a similar fast recovery feature, requiring no additional special devices for routine recording of R1. A frequency response in the range of 10 Hz–10 KHz suffices for recording either the R1 or R2 component.

Mechanically Evoked Responses

A mechanical tap,[65,70,73,78,116,128] given by a specially constructed reflex hammer with a built-in microswitch or other pressure-sensitive device, triggers a sweep on impact. A gentle tap over the glabella causes a cutaneous reflex, rather than a stretch reflex, probably relayed by the same polysynaptic reflex pathways as the electrically elicited blink reflex. A mechanical tap on one side of the forehead evokes an R1 only ipsilaterally, similar to unilateral electrical stimulation. In contrast, a glabellar tap, stimulating the trigeminal nerves on both sides, elicits the R1 and R2 bilaterally, allowing instantaneous comparison of the two sides (Fig. 8-6c). A mechanically elicited R1 has a latency 2–3 ms greater than the electrically evoked response, in part reflecting an additional length of the afferent arc from the glabella to the supraorbital foramen, averaging 2 cm. Activation time of the cutaneous receptors probably accounts for the remaining difference. In contrast, mechanically elicited R2 has a shorter latency compared to the electrically elicited counterpart for a yet undetermined reason. Thus, R1 and R2 induced by a glabellar tap tend to merge without clear separation seen in electrically induced blink reflex.

The R2 component elicited by a glabellar tap provides confirmation of an afferent or efferent abnormality of the electrically elicited R2. A glabellar tap stimulates the right and left trigeminal nerves simultaneously, both activating the facial nuclei on both sides to elicit bilateral R2 responses. A consistent latency or amplitude difference between simultaneously recorded right- and left-sided R2 indicates a delay or block in the facial nerve, or the final common path. A lesion affecting the afferent arc unilaterally does not alter R2 on either side, because the crossed afferent input from the unaffected side compensates for the loss (Fig. 8-6C). Magnetic coil stimulation also elicits R1 bilaterally with latencies equal to those following electrical shocks.[9] A glabellar tap or magnetic coil stimulation renders less

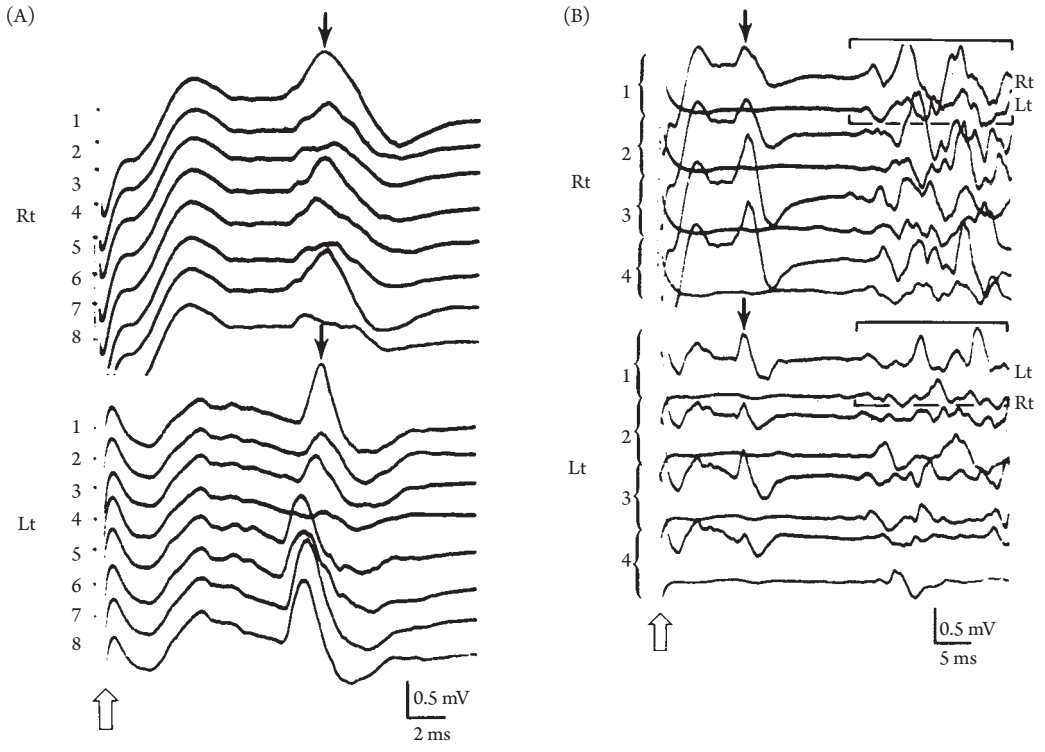

FIGURE 8-5 (***A***) R1 components recorded from the orbicularis oculi after stimulation of the supraorbital nerve by single supramaximal stimuli (top four trials on each side) or by paired stimuli with interstimulus interval of 5 ms (bottom four trials on each side). The paired stimuli consist of the first shock of subthreshold intensity, which subliminally primes the motoneuron pool, and the second shock of supramaximal intensity, which activates the reflex and triggers the sweep. (Modified from Kimura.[54]) (***B***) Simultaneous recording from ipsilateral (upper tracing in each frame) and contralateral (lower tracing) orbicularis oculi after unilateral stimulation of the supraorbital nerve either with single shocks (top two trials on each side) or with paired shocks (bottom two trials on each side). The paired stimuli consist of the first shock of subthreshold intensity and the second stimulus of a supramaximal shock that triggers the sweep. Note unilateral R1 (arrows) recorded only in the upper tracing in each frame and bilateral R2 (brackets) in both upper and lower tracings. (Modified from Kimura.[54])

discomfort to patients and causes no shock artifacts. In our experience, however, electrical stimulation of the supraorbital nerve generally yields more precise information.

Other Types of Stimuli

Various nociceptive stimuli give rise to pain induced blink reflex,[17,26,42,131] for various physiologic studies,[91] but its clinical applications remain largely untested. In addition to the trigeminal blink reflex by electrical stimulation of the supraorbital nerve, mechanical, visual, and auditory stimuli as well as electrical shocks applied remotely[71] induce the blink reflex.

4. ABNORMALITIES OF THE R1 COMPONENT

Direct Involvement of the Reflex Arc

A substantial increase in latency of R1 usually implies demyelination of either the central reflex pathway in the pons[39,47,50,53,73,85] or of the peripheral pathway along the trigeminal nerve,[37,64,93] the facial

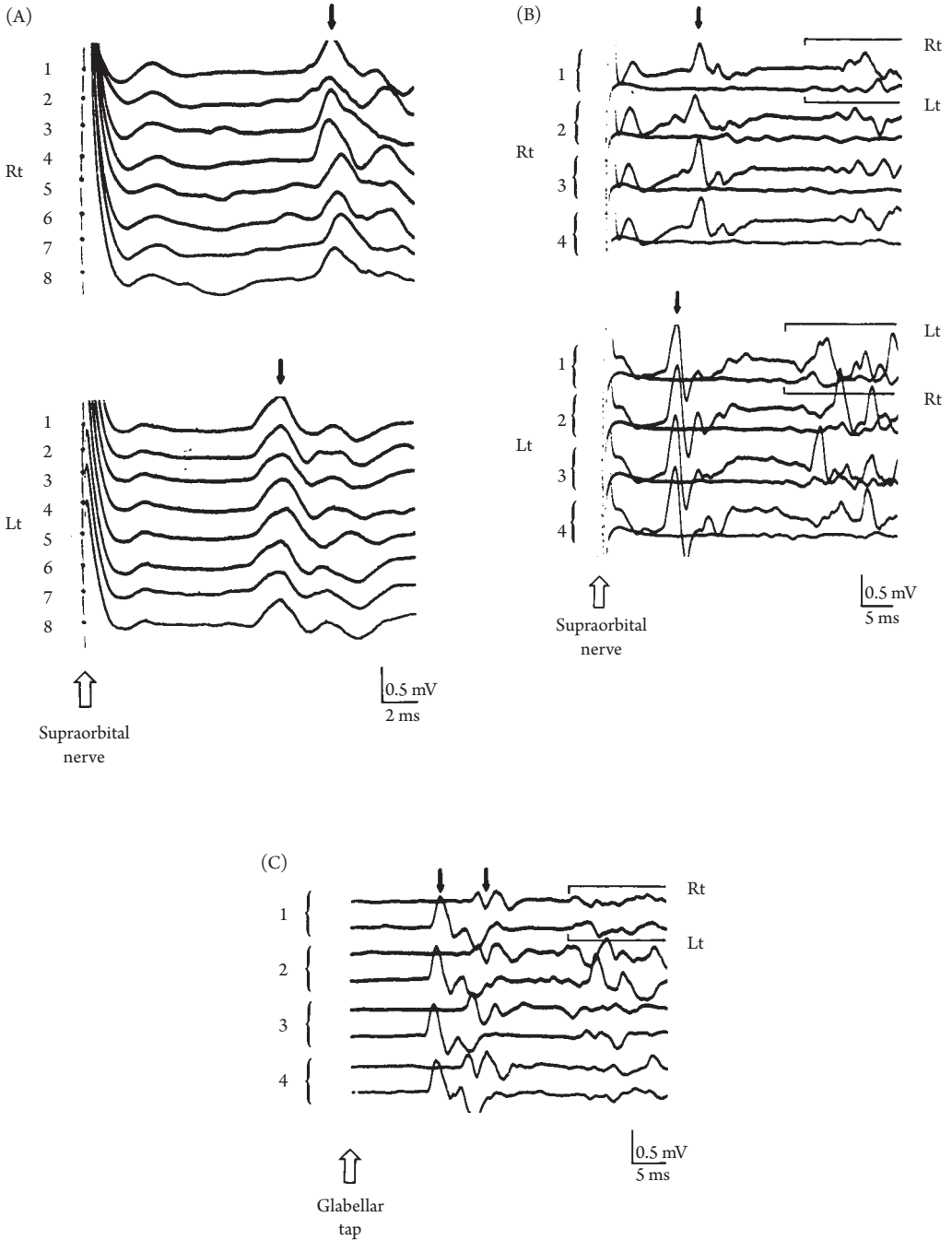

FIGURE 8-6 (***A***) Delayed R1 (arrows) in a 68-year-old man with a mass lesion involving the right anterior cavernous sinus (cf. Fig. 8-5). (***B***) Delayed and diminished R2 (bracket) on both sides after stimulation on the right in the same patient as in (***A***). Stimulation on the left elicited normal R2 on both sides. These findings suggest a lesion involving the afferent arc of the reflex pathway on the right (cf. Fig. 8-16). (***C***) R1 (arrow) and R2 (bracket) after a midline glabellar tap in the same patient. Note a delayed R1 on the right in conjunction with a normal R2, bilaterally. Because of crossed input from the intact trigeminal nerve, a unilateral lesion involving the afferent arc results in little alteration of R2 when elicited by a midline glabellar tap.

nerve,[57,62,102,112] or both.[7,25,49,61,77] Posterior fossa tumors may affect R1 either by compressing the cranial nerves extra-axially or by involvement of the brainstem itself.[15,48,61]

Effect of Lesions outside the Reflex Pathway

Alteration of R1 may also result from central lesions suppressing the brainstem, thus inhibiting the reflex pathway.[53] A reversible block of R1 usually indicates the effect of anesthesia, acute supratentorial lesions, or massive drug intoxication in comatose patients.[75] In some of these patients, single electric shocks may elicit R1 only partially or not at all on the affected side of the face contralateral to the hemispheric lesion or bilaterally with a diffuse process. An apparent increase in R1 latency results if such a stimulus fails to activate the fastest conducting fibers. In this instance, paired or a train of stimuli with an interstimulus interval of 3–5 ms usually elicit a maximal R1 with a normal latency.[22,48,52,53]

The latency of R1 elicited by a glabellar tap shows a mild increase in patients with acute hemispheric strokes but recovers almost completely within a few days.[31] In contrast, electrically elicited R1 has a normal latency even during acute stages of hemispheric disease, when elicited by paired or multiple stimuli or with other facilitatory maneuvers to compensate for reduced excitability.[52] As an inference, the latency of a fully activated R1 indicates the conduction characteristics of the reflex arc itself, and a delay of fully activated R1 beyond the normal range implies a lesion directly involving the pathway, rather than a remote process altering excitability. In these cases, a mild delay of R1 may result from axonal degeneration of the larger myelinated fibers, leaving the smaller, slow-conducting fibers intact. A substantial delay exceeding 120% of the upper limit indicates a conduction abnormality across a demyelinated segment.

Degree of Slowing and R/D Ratio

In multiple sclerosis, central demyelination increases the R1 latency to 12.3±2.7 ms (mean±SD) compared with 15.1 ± 5.9 ms in Guillain Barré syndrome (GBS) and 17.0 ± 3.7 ms in hereditary motor sensory neuropathy type I (HMSN I). The degree of latency prolongation presumably reflects the difference in length of the demyelinated segment in the pons and along the peripheral reflex arc. In support of this view, the latency of R1 increases only to 12.8 ± 1.6 ms in Bell's palsy with focal involvement of the facial nerve. Patients with compressive lesions of the trigeminal nerve have a similar delay of R1 latency.

Despite the same degree of delay (Figs. 8-7 and 8-8), a decreased R/D ratio suggests distal slowing of facial nerve in HMSN I, whereas a slightly increased R/D ratio indicates proximal involvement of the facial nerve in GBS, assuming a normal conduction of the trigeminal nerve. Other disorders associated with an increased R/D ratio include multiple sclerosis with pontine involvement, compressive lesions of the trigeminal nerve, and Bell's palsy without distal degeneration of the facial nerve.

5. ABNORMALITIES OF R2 COMPONENT

Involvement of Polysynaptic Pathways

Analysis of the R2 component allows classification of the reflex abnormality as either afferent or efferent. Some brainstem lesions may give rise to a more complex pattern of reflex change (Fig. 8-1B). Stimulation on one side may reveal unilateral abnormality of R2 either ipsilaterally or contralaterally to the stimulus, whereas stimulation on the opposite side shows normal, absent, or delayed R2 bilaterally or unilaterally, but not necessarily on the same side, as implicated by the contralateral stimulation.

Like R1, changes of R2 may imply lesions directly affecting the reflex pathways, as in the case of the Wallenberg syndrome, or lesions elsewhere indirectly influencing the excitability of the polysynaptic connections (Fig. 8-9).[39,60,94] For example, any comatose states render R2 unelicitable or markedly diminished in size (Fig. 8-10) regardless of the site of the lesion.[75,113] A hemispheric lesion (Fig. 8-11) also suppresses R2, producing either an afferent or an efferent pattern of abnormality, perhaps based on the

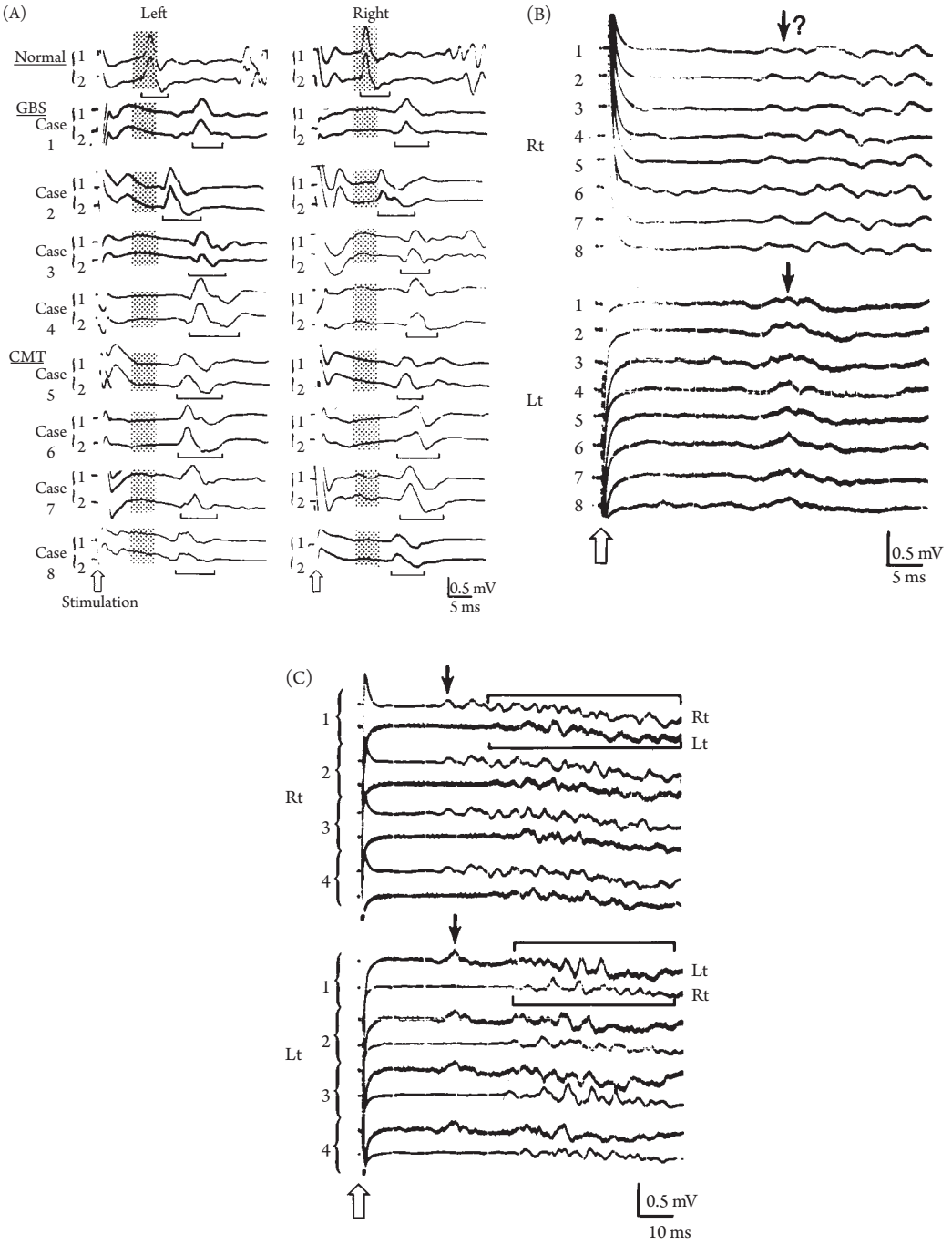

FIGURE 8-7 (***A***) Bilateral delay of R1 in four patients with Guillain-Barré syndrome (GBS) and four patients with hereditary motor sensory neuropathy type 1 (CMT). Two tracings recorded on each side in each subject show consistency. The top tracings from a healthy subject serve as a control, with shaded areas indicating the normal range. (Modified from Kimura.[55]) (***B***) R1 in a 55-year-old woman with chronic peripheral neuropathy and a monoclonal gammopathy (cf. Fig. 8-5). Note a substantially delayed and temporally dispersed R1 recorded by the slower 5 ms/division sweep instead of the 2 ms/division normally used to obtain this response. (***C***) R1 and R2 in the same patient. Note delayed R2 recorded by slower 10 ms/division sweep instead of usual 5 ms/division. The continuity between R1 and R2 precluded accurate latency determination of R2 on the right. Nonetheless, the contralateral R2 recorded simultaneously allows approximate separation between R1 and R2.

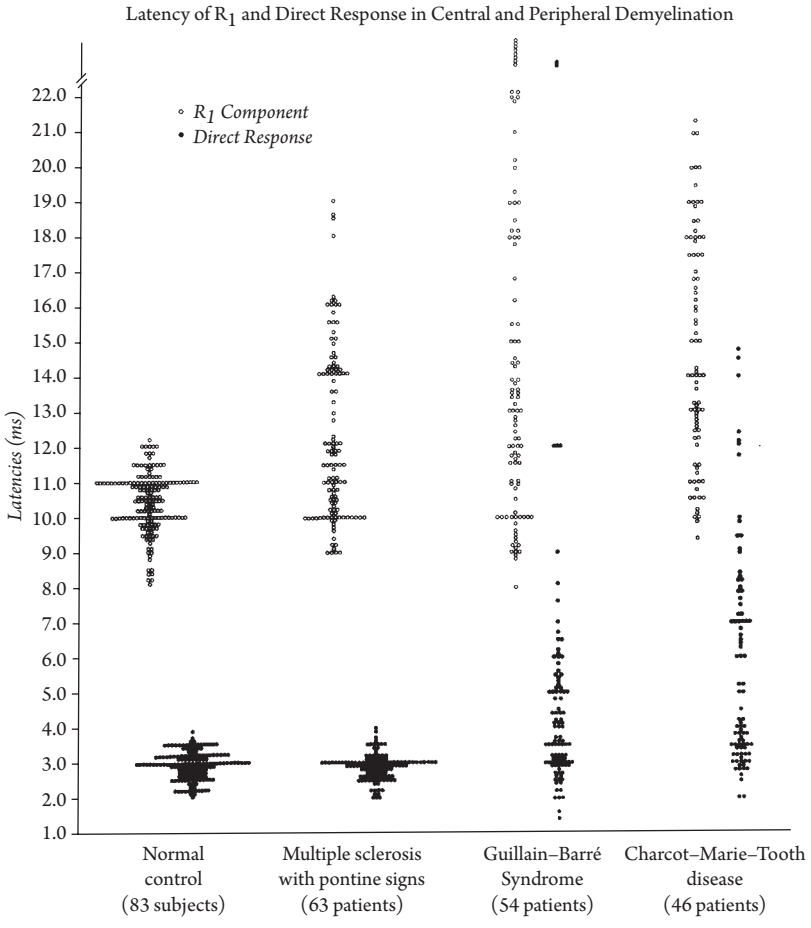

FIGURE 8-8 Latency distribution of the direct response and R1 of the blink reflex in normals and in patients with central or peripheral demyelination of the reflex pathways. The histogram indicates delayed direct responses in Charcot-Marie-Tooth disease, and to a lesser extent in Guillain-Barré syndrome, but normal values in multiple sclerosis. The R1, delayed equally in the two polyneuropathies, showed similar but less prominent changes in multiple sclerosis. (Modified from Kimura.[55])

site of involvement.[31,52,65] After peripheral facial palsy, blink reflex circuit sensitized to inputs from the paralyzed side may render contralateral R2 unusually large.[78]

Level of Consciousness and Perception

A state of arousal alters the excitability of R2 and, to a much lesser extent, R1.[30,58,59,115,118] All-night sleep analysis shows a marked reduction of R2 in stages II, III, and IV and substantial recovery during rapid eye movement (REM) sleep, approaching the level of full wakefulness, with some unusual discharge characteristics. Blink reflex studies may show absent R2 with normal or nearly normal R1 in some alert but immobile patients with features of the locked-in syndrome, in alert and ambulatory patients with pseudobulbar palsy, and in alert patients given therapeutic dosages of diazepam (Valium), which presumably blocks the multisynaptic reflex arc.[50] Complex psychological events may also selectively affect different reflex pathways.[111]

Stimulation on a hypesthetic area of the face elicits a smaller R2 than that evoked by a shock of the same intensity applied to the corresponding area on the normal side. Sensory deficits of the

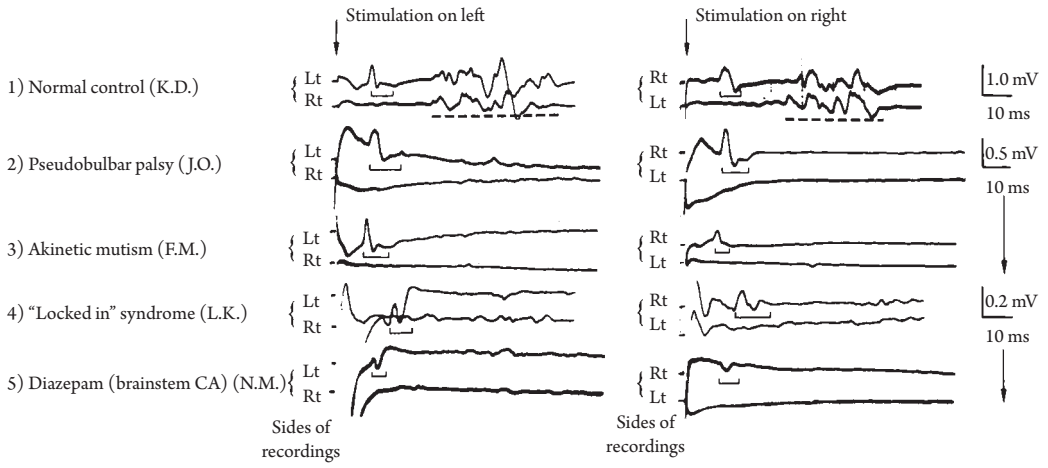

FIGURE 8-9 Various neurologic disorders associated with absent R2 after stimulation of the supraorbital nerve with shock intensity slowly advanced up to 40 mA and 0.5 ms duration. Note virtual absence of R2 regardless of the side of stimulation in cases 2 through 5, with normal R1 in cases 2, 3, and 5 and delayed R1 in case 4. (Modified from Kimura.[50])

face often cause alteration of R2; the reverse, however, does not hold, because a similar reduction of R2 occurs in pure motor hemiplegia.[5,11,21,31,52] In such cases, clinical evaluation may have overlooked minor sensory deficits, or supratentorial lesions outside the somatosensory pathways may have inhibited or disfacilitated the reflex pathway.

Altered Excitability of Interneurons

Of the two components, R2 habituates readily in normal subjects but not in patients with Parkinson's disease, whether tested clinically, as with the glabellar taps, or by electrophysiologic means.[68,74] Similarly, the blink reflex fails to show physiologic habituation in patients with migraine

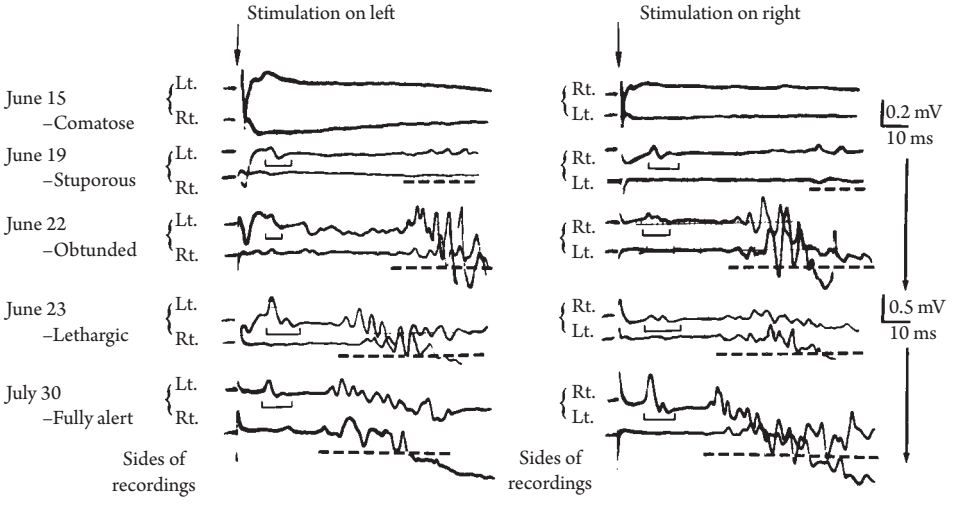

FIGURE 8-10 R1 and R2 in a patient recovering from herpes simplex encephalitis. The stimulus delivered to the supraorbital nerve elicited neither R1 nor R2 on June 9 (not shown) and on June 15 with the patient in coma. A repeat study on June 19th showed a normal R1 but markedly delayed and diminished R2. Note the progressive recovery in amplitude and latency of R2 contemporaneous with the patient's improvement to full alertness in July. (Modified from Kimura.[50])

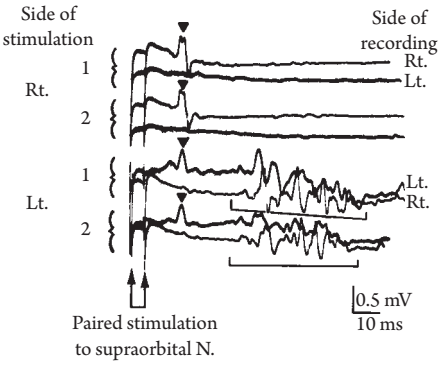

FIGURE 8-11 Left cerebral stroke (cf. Fig. 8-17). Paired stimuli delivered to the right supraorbital nerve elicited normal R1 but no R2 on either side. Stimulation on the left, however, evoked an ipsilateral R1 and bilateral R2. (Modified from Kimura.[52])

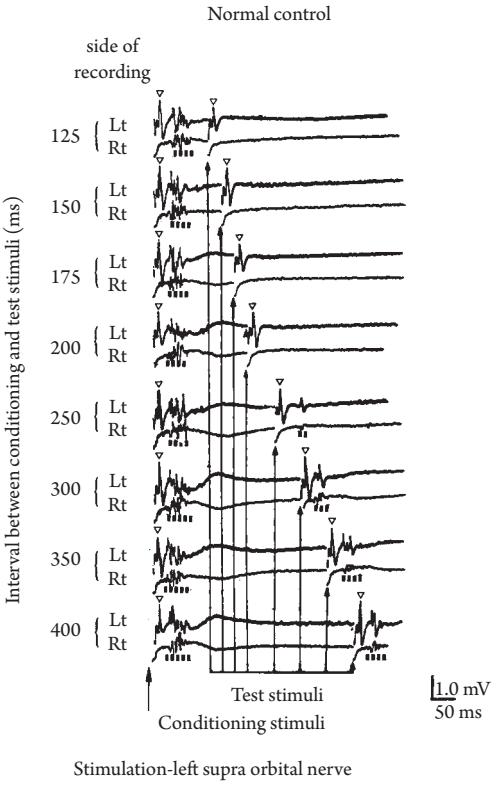

FIGURE 8-12 Normal responses to paired shocks (arrows) delivered to the left supraorbital nerve with time intervals ranging from 125 to 400 ms between test and conditioning stimuli. R1 of the test response, although slightly suppressed at time intervals of 125 to 175 ms, remained relatively constant thereafter with the amplitude equal to the conditioning response. The test stimuli failed to elicit R2 up to the time interval of 200 ms with gradual recovery subsequently. (Modified from Kimura.[51])

if tested during the premonitory phase[19] or in nocturnal myoclonus, a syndrome associated with additional reflex components after R2. These findings suggest that a disorder of the central nervous system may produce increased excitability of segmental reflexes.[135]

The paired-shock technique reveals the intensity-dependent[119] effect of a single cutaneous conditioning stimulus on this reflex (Fig. 8-12). A conditioning stimulus normally suppresses R2 more than R1, presumably based on excitability changes of interneurons in the brainstem[51,127] and the intracortical inhibitory mechanisms.[120] A conditioning stimulus delivered anywhere on the face or neck suppresses R2 elicited by a subsequent stimulus applied to the same or different, ipsilateral or contralateral trigeminal cutaneous fields.[51] Thus, the physiologic inhibition must involve the interneuronal network diffusely, even in response to a conditioning input given to a remote segment.[129]

In Parkinson's disease, R1 follows a normal time course of recovery, whereas the R2 shows little physiologic suppression substantially deviating from the normal range.[61,79] Additional evidence of an excitability change includes an abnormally shortened R2 latency with a single maximal stimulus in advanced cases. These findings indicate that a cutaneous conditioning stimulus fails to inhibit interneurons in Parkinson's disease. Interestingly, dyskinetic patients show physiologic inhibition of R2, presumably reflecting the reinstatement of dopaminergic suppressive control over the multisynaptic pathway.[40] These changes imply facilitation or disinhibition of interneurons, rather than motoneurons as the primary cause of motor dysfunction in this disease.

In contrast, diminution of R2 in Huntington's chorea represents the opposite extreme, probably implicating a decrease in interneuronal reactivity.[20] The recovery curves show reduced inhibition in premature infants[36]; stiff-person syndrome[80]; cranial, cervical, and generalized dystonia[23]; and blepharospasm,[41] but not in those with extracranial segmental dystonia[97]

or presumed psychogenic blepharospasm.[13,114] The test may also provide an objective means for evaluating the reactivity in brainstem pathways in such conditions as olivopontocerebellar atrophy,[128] mitochondrial myopathy,[69] hemifacial spasm[24] chronic migraine,[18] adaptive excitability changes after facial weakness,[122] and contralateral reorganization caused by peripheral facial palsy.[108]

6. CLINICAL APPLICATIONS

Normal Values

Table 8-2 (see also Appendix Table 1-7) shows the normal latency range of electrically elicited D response, R1, R/D ratio, and R2 in 83 healthy subjects 7–86 years of age (average age, 37 years),[53] and R1 elicited by a midline glabellar tap in another group of 21 healthy adult subjects.[65]

The upper limits of normal, defined as the mean latency plus 2.5 SD, include 4.1 ms for direct response, 12.5 ms for electrically elicited R1, and 16.7 ms for mechanically evoked R1. Additionally, the latency difference between the two sides should not exceed 0.6 ms for direct response, 1.2 ms for electrically elicited R1, and 1.6 ms for mechanically evoked R1. The R/D latency ratio should not fall outside the range of 2.6 to 4.6, 2 SD above and below the mean in normal individuals. With stimulation of the supraorbital nerve, R2 latency should not exceed 40 ms on the side of the stimulus and 41 ms on the contralateral side. In addition, the ipsilateral and the contralateral R2 simultaneously evoked by stimulation on one side should not vary more than 5 ms in latency. A latency difference between R2 evoked by right-sided stimulation and corresponding R2 evoked by left-sided stimulation may show a slightly greater value but not more than 7 ms. Both direct and reflex responses vary considerably in amplitude from one individual to the next. In 60 nerves from 30 healthy subjects, 7 to 67 years of age, the values averaged 1.21 mV for D response, 0.38 mV for R1, 0.53 mV for ipsilateral R2, and 0.49 mV for contralateral R2.[62]

In another 50 healthy subjects, 12 to 77 years of age (average age, 40 years), stimulation of the supraorbital nerve elicited both R1 and R2 regularly, whereas that of the infraorbital nerve evoked R1 in some cases and R2 in all. Both R1 and R2 had similar latencies regardless of the nerve tested. Shocks applied to the mental nerve elicited R1 rarely and R2 inconsistently, showing considerably prolonged latency. Stimulation of the lingual nerve on one side also elicits R2 in the orbicularis oculi bilaterally, as a possible test for lingual neuropathy.[81,98]

Tables 8-3 and 8-4 summarize our own experience with the blink reflex at the University of I owa.[48,49,50,51,53,56,57,60,62,76,77] A brief summary of each category follows.

Lesions of the Trigeminal Nerve

The blink reflex serves as a test of the trigeminal nerve, the afferent arc of the reflex pathways.[16,64,101] In our own series, only 7 of 93 patients with trigeminal neuralgia had absent or slowed R1 (Table 8-3). Excluding three patients who had undergone nerve avulsion before the test, only four patients had abnormalities attributable to the disease. These findings suggest that the impulse conducts normally along the first division of the trigeminal nerve in most patients with this disorder. Usual sparing of the first division and minimal compression of the nerve, if any, probably account for this finding. Conduction abnormalities, however, may appear after surgery.

In contrast, 10 of 17 patients with tumor, infection, or other demonstrable causes for facial pain showed an unequivocal delay of R1 on the affected side (Fig. 8-6A). In these patients, reproducible delay of R2 bilaterally with stimulation on the affected side indicated involvement of the afferent arc of the blink reflex (Fig. 8-6B). An increased R/D ratio often seen in this category reflects normal conduction along the distal segment of the facial nerve, combined with a delay along the trigeminal nerve. Other disorders showing blink reflex abnormalities include trigeminal neuropathy from perineural spread of an amyloidoma.[136]

Bell's Palsy

Blink reflex latencies reflect conduction along the entire length of the facial nerve, including the interosseous portion involved in Bell's palsy.[57,62]

Table 8-2 Blink Reflex Elicited by Electrical Stimulation of Supraorbital Nerve in Normal Subjects and Patients with Bilateral Neurologic Disease (Mean ± SD)

CATEGORY	NO. OF PATIENTS	DIRECT RESPONSE RIGHT AND LEFT COMBINED			R_1 RIGHT AND LEFT COMBINED			DIRECT RESPONSE (ms)	R_1 (ms)	R/D RATIO	IPSI-LATERAL R_2 (ms)	CONTRA-LATERAL R_2 (ms)
		ABS	*DELAY*	*NI*	*ABS*	*DELAY*	*NI*					
Normal	83 (glabellar tap 2l)*	0	0	166	0	0	166	2.9 ± 0.4	10.5 ± 0.8 (12.5 ± l.4)	3.6 ± 0.5	30.5 ± 3.4	30.5 ± 4.4
Guillain-Barré syndrome	90	12	63	105	20	78	82	4.2 ± 2.1	15.1 ± 5.9	3.9 ± 1.3	37.4 ± 8.9	37.7 ± 8.4
Chronic inflammatory polyneuropathy	14	4	13	11	7	13	8	5.8 ± 2.6	16.4 ± 6.4	3.1 ± 0.5	39.5 ± 9.4	42.0 ± 10.3
Fisher syndrome	4	0	0	8	0	1	7	2.7 ± 0.2	10.7 ± 0.8	3.9 ± 0.4	31.8 ± 1.3	31.4 ± 1.9
Hereditary motor sensory neuropathy type 1	62	9	88	27	0	105	19	6.7 ± 2.7	17.0 ± 3.7	2.8 ± 0.9	39.5 ± 5.7	39.3 ± 6.4
Hereditary motor sensory neuropathy type II	17	0	0	34	1	0	33	2.9 ± 0.4	10.1 ± 0.6	3.6 ± 0.6	30.1 ± 3.8	30.1 ± 3.7
Diabetic polyneuropathy	86	2	20	150	1	17	154	3.4 ± 0.6	11.4 ± 1.2	3.4 ± 0.5	33.7 ± 4.6	34.8 ± 5.3
Multiple sclerosis	62	0	0	124	1	44	79	2.9 ± 0.5	12.3 ± 2.7	4.3 ± 0.9	35.8 ± 8.4	37.7 ± 8.0

Abs, absent response; Nl, normal.

*R_1 elicited bilaterally by a midltae glabellar tap in another group of 21 healthy subjects.

All 144 patients studied showed either absence or slowing of R1 during the first week, although abnormalities did not necessarily emerge at the onset. Delayed or absent R2 on the paretic side, regardless of the side of stimulation, indicated an efferent involvement. A few other patients not included in this series had a normal blink reflex despite minimal unilateral facial weakness lasting 1–2 days, perhaps representing an unusually mild form of Bell's palsy.

In 100 of 127 patients tested serially, the previously absent R1 or R2 returned, with preservation of the D response throughout the course (Table 8-3). This finding implied recovery of conduction across the involved segment without substantial distal degeneration (Fig. 8-13). These patients generally showed a good clinical recovery within a few months after onset. The latency of R1, initially delayed by more than 2 ms on average, showed a gradual recovery during the second month, returning to normal during the third or fourth month (Fig. 8-14). The magnitude of latency change at the onset and the subsequent time course of recovery indicate a demyelinative lesion involving the proximal segment of the facial nerve as evidenced by increased R/D ratios.

In the remaining 27 patients, marked diminution of the D response without return of the reflex response during the first 2 weeks indicated axonal degeneration.[63] This group of patients had a slow and usually incomplete recovery associated with synkinesis. In some of them,

Table 8-3 Blink Reflex Elicited by Electrical Stimulation of Supraorbital Nerve on the Affected and Normal Sides in Patients with Unilateral Neurologic Disease (Mean ± SD)

CATEGORY AND SIDE OF STIMULATION	NO. OF PATIENTS	DIRECT RESPONSE (ms)	R_1 (ms)	R/D RATIO	IPSILATERAL R_2 (ms)	CONTRALATERAL R_2 (ms)
Trigemlnal neuralgia						
Affected side	89	2.9 ± 0.4	10.6 ± 1.0	3.7 ± 0.6	30.4 ± 4.4	31.6 ± 4.5
Normal side	89	2.9 ± 0.5	10.5 ± 0.9	3.7 ± 0.6	30.5 ± 4.2	31.1 ± 4.7
Compresslve lesion of the trigeminal nerve						
Affected side	17	3.1 ± 0.5	11.9 ± 1.8	3.9 ±1.0	36.0 ± 5.5	37.2 ± 5.7
Normal side	17	3.2 ± 0.6	10.3 ± 1.1	3.4 ± 0.6	33.7 ± 3.5	34.8 ± 4.1
Bell's palsy						
Affected side	100	2.9 ± 0.6	12.8 ± 1.6	4.4 ± 0.9	33.9 ± 4.9	30.5 ± 4.9
Normal side	100	2.8 ± 0.4	10.2 ± 1.0	3.7 ± 0.6	30.5 ± 4.3	34.0 ± 5.4
Acoustic neuroma						
Affected side	26	3.2 ± 0.7	14.0 ± 2.7	4.6 ± 1.7	38.2 ± 8.2	36.6 ± 8.2
Normal side	26	2.9 ± 0.4	10.9 ± 0.9	3.8 ± 0.5	33.1 ± 3.5	35.3 ± 4.5
Wallenberg syndrome						
Affected side	23	3.2 ± 0.6	10.9 ± 0.7	3.6 ± 0.6	40.7 ± 4.6	38.4 ± 7.1
Normal side	23	3.2 ± 0.4	10.7 ± 0.5	3.4 ± 0.4	34.0 ± 5.7	35.1 ± 5.8

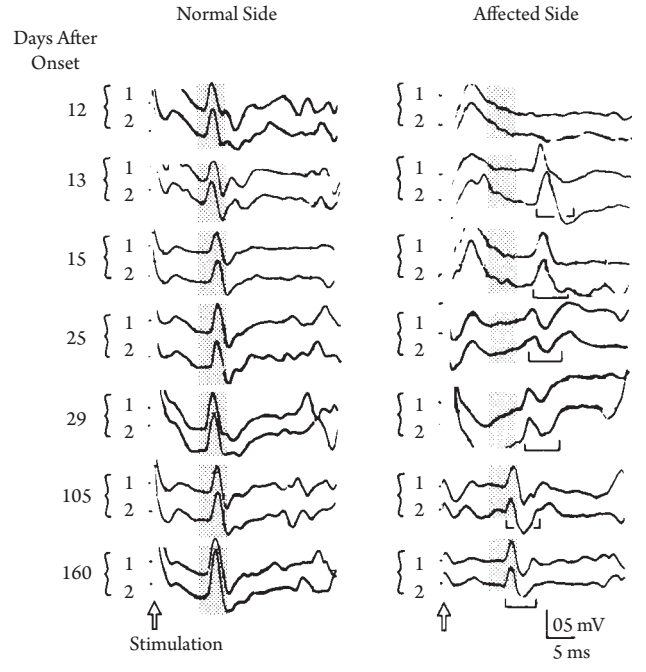

FIGURE 8-13 Serial changes of R1 in a 16-year-old girl with Bell's palsy on the right. Two consecutive tracings recorded on each side show consistency of R1. On the affected side, delayed R1 first appeared on the 13th day of onset, recovering progressively thereafter. Shaded areas indicate the normal range (mean +3 SD in 83 subjects). (Modified from Kimura.[55])

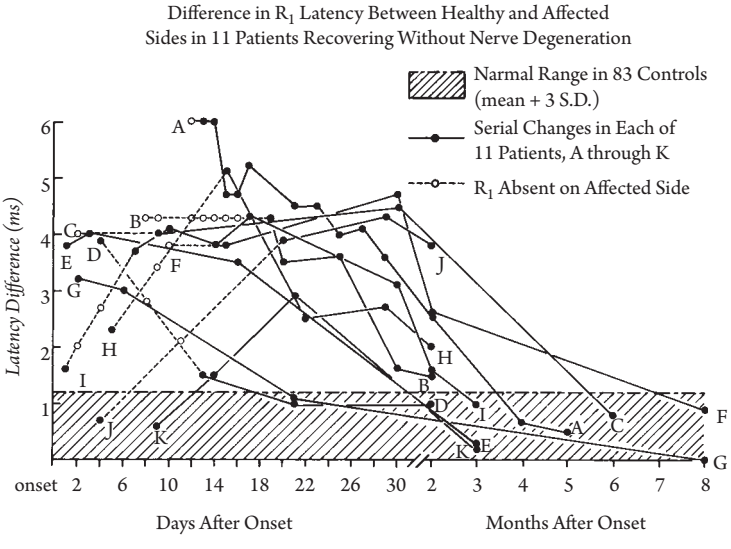

FIGURE 8-14 Serial changes in latency difference of R1 between normal and paretic sides in 11 patients recovering without nerve degeneration (A through K). Shaded area indicates the normal range (mean +3 SD in 83 subjects). The response, if present at onset, showed relatively normal latencies but rapidly deteriorated during the first few days. Delayed R1 usually returned during the second week, plateaued for 2 to 4 weeks, and progressively recovered in latency during the next few months. (Modified from Kimura, Giron, and Young.[57])

R1 may return on the affected side, showing a delay in latency, even though stimulation of the facial nerve fails to evoke a direct response of the orbicularis oculi. Recruitment of motor units with voluntary effort also confirms the passage of impulse across the affected segment of the facial nerve. This discrepancy implies an abnormally increased threshold of the regenerated facial nerve segment to a locally applied stimulus despite the passage of impulses following reflexive or volitional activation of the motoneurons (see Fig. 11-17 in Chapter 11).

Synkinesis of Facial Muscles

As the name implies, the blink reflex results from selective activation of the orbicularis oculi with no involvement of other facial muscles in healthy subjects. During axonal regeneration of degenerated facial nerve, however, the fibers that originally innervated the orbicularis oculi may supply other facial muscles by misdirection.[63] Thus, simultaneous recording from two pairs of recording electrodes, one pair placed over the orbicularis oculi and the other, over the orbicularis oris or platysma on the same side, helps assess facial synkinesis.[3,63] This technique (Fig. 8-15) helps identify the discharge patterns of various facial muscles time-locked to the R1 and R2 evoked in the orbicularis oculi as synkinesis. Associated movements normally seen in most healthy subjects may clinically mimic pathological synkinesis but lack the exact temporal relationship between the two co-contracting muscle. Measurement of the size of the blink reflex elicited in muscles other than orbicularis

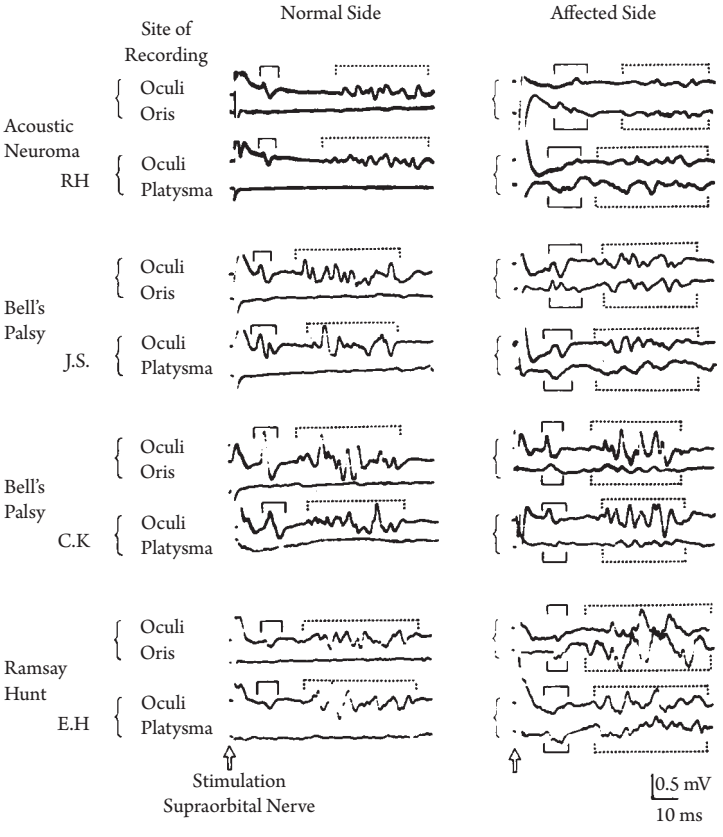

FIGURE 8-15 The blink reflex in the orbicularis oris and platysma in four patients following various diseases of the facial nerve. Stimulation on the affected side of the face elicited both R1 (small bracket) and R2 (dotted bracket) not only in the orbicularis oculi but also in the orbicularis oris and platysma, indicating widespread synkinesis. The blink reflex elicited only in the orbicularis oculi on the normal side served as a control in each patient. (Modified from Kimura, Rodnitzky, and Okawara.[63])

oculi can elucidate the extent and distribution of aberrant reinnervation.

In our series, the blink reflex confirmed synkinetic activation of the orbicularis oris or platysma in 26 of 29 patients tested at least 4 months after total facial nerve degeneration.[63] One of the remaining three had injury only to a peripheral branch of the facial nerve and experienced return of function with no evidence of synkinesis. In the other two patients, the affected side of the face showed total paralysis and no evidence of regeneration. These findings suggest that synkinetic movements ultimately occur in nearly all cases after degeneration of the facial nerve, unless the lesion involves a distal branch or the facial nerve fails to regenerate.

Hemifacial Spasm

Patients with hemifacial spasm (see Chapter 28-10) also exhibit clinical and electrical evidence of synkinetic movements.[3,12,63,92] In these cases the appearance of the blink reflex in muscles other than the orbicularis oculi may indicate hyperexcitability at the facial nucleus, ephaptic activation of motor axons not normally involved in blinking, or aberrant regeneration of the facial nerve fibers.[24,88,124] Unlike the constant responses seen after peripheral facial paresis,[63] successive responses in hemifacial spasm may vary in latency and waveform, a finding supportive of ephaptic transmission.[3] The blink reflex reveals no evidence of synkinesis in essential blepharospasm, focal seizures, or facial myokymia.

Acoustic Neuroma

A cerebellopontine angle tumor frequently compresses the trigeminal nerve, facial nerve, or brainstem. With possible involvement of the afferent, efferent, or central pathways,[25,61,89,98] the blink reflex provides unique diagnostic value. In 33 patients studied, stimulation of the facial nerve elicited no D response in 7, including 5 tested only after surgical sacrifice of the facial nerve. In the remaining 26 patients, studies on the affected side showed absent R1 in 5, delayed R1 in 17, and normal R1 in 4. Analyses of R2 revealed 6 efferent, 6 afferent, 7 mixed patterns, and 7 normal responses (Table 8-3). The test also helps document asymptomatic compression of the facial nerve as a preoperative evaluation, alerting the surgeon of possible facial palsy after the intervention.

Polyneuropathy

Facial or trigeminal nerve involvement in various polyneuropathies affects the blink reflex (Fig. 8-7A). Unlike the two clearly separated components seen normally, a delayed and temporally dispersed R1 tends to merge with R2 in a demyelinative neuropathy (Fig. 8-7B). In such cases, bilateral recording can delineate the onset of R1 as the response clearly preceding the onset of the contralateral R2, which should approximately coincide with the ipsilateral R2 (Fig. 8-7C).

Different category of neuropathy shows distinct abnormalities as briefly described next.[33,55,67,87] Most patients have either absent or delayed D and R1 responses in GBS, CIDP, and HMSN I. Patients with diabetic or alcoholic polyneuropathy have a considerably lower incidence of abnormality. The Fisher syndrome does not regularly affect the blink reflex, except in patients with peripheral facial palsy, who show a delayed R1 on the affected side. The blink reflex usually shows no abnormalities in HMSN II. Patients with chronic renal failure have an abnormal blink reflex, which often improves after hemodialysis.[121] An abnormal blink reflex favors a nonparaneoplastic etiology in patients with sensory neuronopathy.[4] Exposure to trichloroethylene, known to have specific toxic effects on the trigeminal nerve, also affects R1 latency.[29]

Statistical analyses of the D response and R1 latencies revealed a marked increase in GBS, CIDP, and HMSN I; a much lesser degree of slowing in diabetic polyneuropathy; and no change in the Fisher syndrome or HMSN II (Table 8-4). The latency ratio of R1 to the D response, or R/D ratio, showed a mild increase in GBS, a moderate decrease in HSMN I and CIDP, a mild decrease in diabetic polyneuropathy, and a normal valve in HSMN II. The latencies of R2, although commonly within the normal range when analyzed individually, had a significantly greater average value in the neuropathies than in the controls.

Table 8-4 Direct Response and R1 and R2 of the Blink Reflex

DISORDERS	DIRECT RESPONSE	R_1	R_2
Trigemlnal neuralgia	Normal	Normal (95%)	Normal
Compresstve lesion of the trigeminal nerve	Normal	Abnormal on the affected side (59%)	Abnormal on both sides when affected side stimulated (afferent type)
Bell's palsy	Normal unless distal segment degenerated	Abnormal on the affected side (99%)	Abnormal on the affected side regardless of the side of stimulus (efferent type)
Acoustic neuroma	Normal unless distal segment degenerated	Abnormal on the affected side (85%)	Afferent and/or efferent type
Guillain-Barré syndrome	Abnormal (42%)	Abnormal (54%)	Afferent and/or efferent type
Hereditary motor sensory neuropathy type I	Abnormal (78%)	Abnormal (85%)	Afferent and/or efferent type
Diabetic polyneuropathy	Abnormal (13%)	Abnormal (10%)	Afferent and/or efferent type
Multiple sclerosis	Normal	Abnormal with pontine lesion, variable incidence determined by patient's selection	Afferent and/or efferent type
Wallenberg syndrome	Normal	Normal or borderline	Afferent type
Facial hypesthesia	Normal	Abnormal with lesions of the trigemlnal nerve or pons	Afferent type
Comatose state, akinetic mutism, locked-in syndrome	Normal	Abnormal with pontine lesion; reduced excitability in acute supratentorial lesion	Absent on both sides regardless of side of stimulus

Lesions in the Brainstem and Spinal Cord

The blink reflex response to electrical stimulation of the supraorbital nerve may also help evaluate lesions of the brainstem[2,38,95] and spinal cord.[90] We studied 14 cases of intrinsic brainstem lesions (including 2 mesencephalic, 6 pontine, and 4 medullary neoplasms and 2 pontine syrinxes) and 20 cases of lesions extrinsic to the brainstem, including 6 cerebellar and 14 cerebellopontine angle tumors.[61] The R1 showed a delayed latency in all but three cases of medullary tumors and one case of cerebellar tumor. Alteration of R1 by posterior fossa tumors reflects either intrinsic or extrinsic pontine lesions or trigeminal or facial nerve involvement by tumor. The R2 response with its ipsilateral and contralateral components helps

distinguish afferent from efferent abnormalities. Mixed patterns suggest combined involvement of the trigeminal and facial nerves or a relatively widespread brainstem lesion. This simple technique thus provides a useful addition to clinical observation in functional assessment of posterior fossa tumors.

Multiple Sclerosis

Alterations of the electrically elicited blink reflex may result from disorders of the central reflex pathways. Of various lesions affecting the brainstem, multiple sclerosis causes a most conspicuous delay of R1 (Fig. 8-16),[44,47,73,86,96] as expected from the effect of demyelination on impulse propagation. The incidence of blink reflex abnormality varies greatly, depending on the selection of patients. In general, those with a longer history of clinical symptoms have a higher incidence of abnormality. Thus, an earlier study of 260 patients with long-standing disease[53] showed a delayed R1 in 96 of 145 patients (66%) with remission and exacerbation, in 32 of 57 patients (56%) with multiple sites of involvement without relapse, and in 17 of the remaining 58 patients (29%) with suspected diagnosis of multiple sclerosis. In the 63 patients with clinical signs of pontine lesions, the average

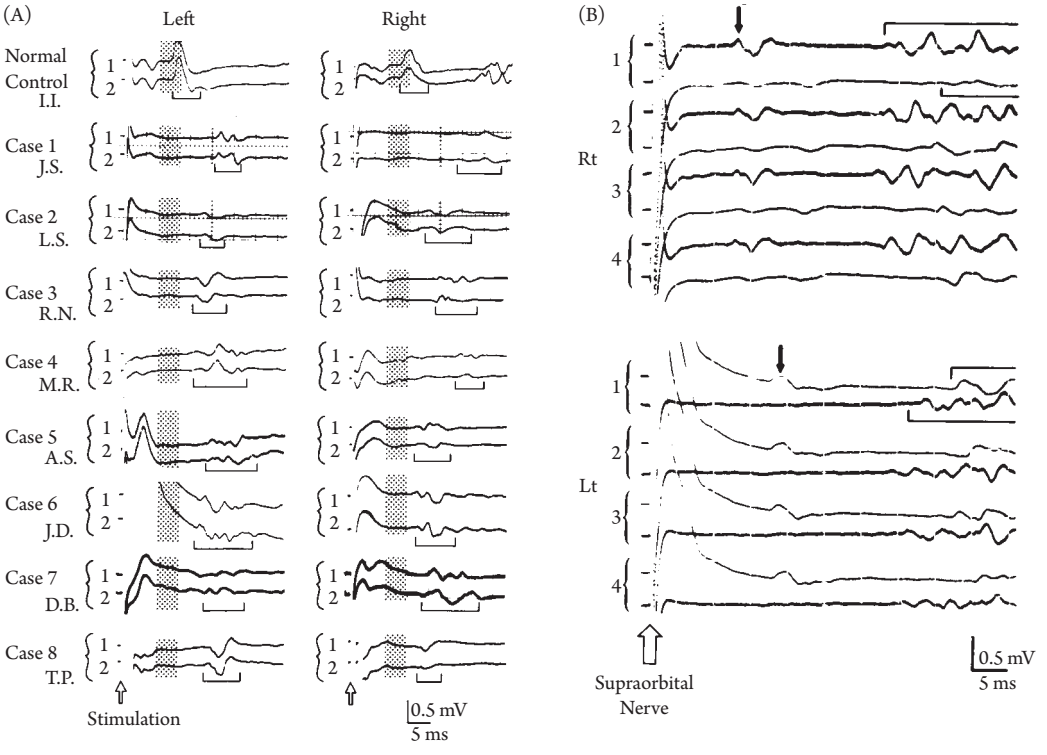

FIGURE 8-16 (***A***) Delayed R1 on both sides in multiple sclerosis. Two tracings recorded on each side in each subject show consistency of R1 response. The top tracings from a healthy subject serve as a control, with shaded areas indicating the normal range (mean +3 SD in 83 subjects). In addition to increased latency, R1 obtained in the patients shows temporal dispersion and very irregular waveform, compared with the normal response. None of these patients had unequivocal pontine signs clinically, except for mild horizontal nystagmus in cases 1, 2, 5, 6, and 7. (Modified from Kimura.[53]) (***B***) R1 and R2 in a 35-year-old woman with multiple sclerosis and mild facial and abducens paresis on the left. Stimulation on the right elicited delayed R2 contralaterally, whereas stimulation on the left evoked delayed R1 and R2 ipsilaterally. This finding suggests a lesion involving the efferent arc of the reflex on the left in the intrapontine portion of the facial nerve (cf. Fig. 8-1). (Modified from Kimura.[55])

latency of R1 substantially exceeded the normal value but fell short of the delay seen in the GBS or HMSN I (Fig. 8-8). The normal D response, combined with delayed R1, resulted in a markedly increased R/D ratio. Hyperthermia did not induce significant changes in mean reflex latency, amplitude, or duration, even in patients with unequivocal blink reflex abnormalities before warming.[106]

Subsequent studies showed comparable results.[86,96,109,125] Another series of patients with a shorter disease duration revealed a lower incidence of abnormalities; a delayed R1 in 41% of patients with definite diagnosis and 18% in those with possible diagnoses.[44] Other investigators reported similar rates of abnormality in patients referred for electrophysiologic testing soon after the onset of their symptoms.[43,110] The blink reflex detects only those lesions that affect the short pontine pathway. Thus, a delayed R1, although less frequent than visual, somatosensory, or brainstem auditory evoked potentials, helps localize the lesion to the pons when establishing subclinical dissemination in multiple sclerosis.[45]

Wallenberg Syndrome

Patients with the Wallenberg syndrome have selective alteration of R2, as expected from lesions affecting the lateral medulla.[32,60,94,130] Unless the infarct extends to the pons, the latency of R1 falls within the normal range; but when analyzed individually, the values on the affected side may slightly exceed those on the normal side (Table 8-3). In a series of 23 typical cases, stimulation on the affected side of the face elicited no R2 on either side in 7, low-amplitude R2 in 6, and delayed R2 in 10 (Fig. 8-17). In contrast, stimulation on the normal side of the face evoked normal R2 bilaterally in 20 of 23 patients. The remaining 3 patients showed normal R2 only on the side of stimulation. Stimulation of the infraorbital nerve or mental nerve gives rise to the same pattern of abnormality. Various types of blink reflex abnormalities reflect different patterns of sensory dysfunction associated with lateral medullary infarction.[46,84,107,132]

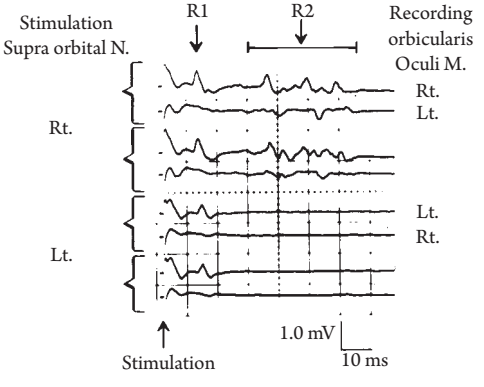

FIGURE 8-17 Left lateral medullary syndrome. Two successive stimuli given on the right (top two pairs) elicited a normal R1 and R2 bilaterally. Two successive stimuli on the left (bottom two pairs) evoked normal R1 but absent R2 bilaterally (cf. Fig. 8-11). (Modified from Kimura and Lyon.[60])

Facial Hypoesthesia

Patients with contralateral hemispheric lesions also develop an afferent delay of R2 indistinguishable from that seen in the Wallenberg syndrome.[21,31,52] This type of abnormality commonly, although not exclusively, accompanies sensory disturbances of the face. Thus, the electrically elicited blink reflex provides a means of quantitating facial sensation. In equivocal cases, alternate stimulation of the right and left sides of the face repetitively every 5–10 seconds reveals consistent asymmetry beyond random variations that follow no predictable pattern. Of 6 patients with bilateral trigeminal neuropathy, 3 had a slowed or absent R1 bilaterally, and 4, delayed or diminished R2 regardless of the side of stimulation. In 19 patients with unilateral disease of either the trigeminal nerve or the brainstem,[14,15] stimulation on the affected side of the face elicited absent R1 in 6, delayed R1 in 7, and various combinations of R2 abnormalities in the others (Fig. 8-18). Generally, a smaller response indicates more complete sensory loss, and stimulation on an anesthetic part of the face fails to elicit any response at all.

Other Disorders

A high incidence of blink reflex abnormalities in handicapped children implies the prevalence of brainstem lesion.[123] Blink reflex studies also show abnormalities in Millard-Gubler syndrome caused by a lesion at the level of the facial nucleus.[34] After accessory facial anastomosis, stimulation of the

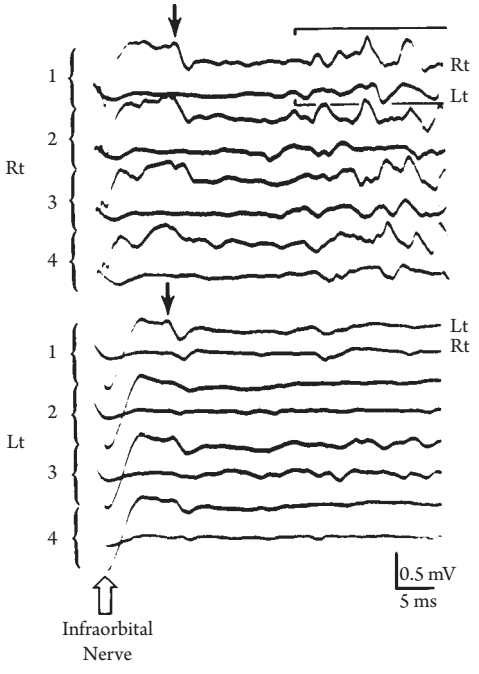

FIGURE 8-18 R1 and R2 elicited by stimulation of the infraorbital nerve in a 39-year-old woman with syringobulbia and facial numbness on the left (cf. Fig. 8-11). Stimulation of the right side of the face elicited normal R1 and R2 bilaterally, but stimulation on the left evoked only the R1 component.

trigeminal nerve may elicit reflex response of the orbicularis oculi, presumably unmasking the trigemino-accessory reflex.[28] An R1-like response observed 4–6 months after hypoglossal-facial anastomosis also suggests central plasticity.[8] Other disorders associated with blink reflex abnormalities, showing a statistical difference when compared to normal values as a group, include Tourette syndrome,[105] systemic sclerosis,[10] tetanus,[104] Chiari II malformation,[66] ALS,[117] primary lateral sclerosis,[103] and chronic tension headache when assessed by nociceptive-specific blink reflex.[100]

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9

H, T, and Masseter Reflexes and the Silent Period

Abbreviations: CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, E1—active electrode, E2—reference electrode, EMG—electromyography, H reflex—Hoffman reflex, Hz—hertz, MEP—motor evoked potential, NCS—nerve conduction study, REM—rapid eye movement, SEP—somatosensory evoked potential, SP—silent period, T max—maximum tendon response, T reflex—tendon reflex

1. INTRODUCTION

Conventional nerve conduction studies (NCSs) primarily assess the distal segments of the peripheral nerves. Techniques to test the more proximal segments and the spinal cord include, in addition to F wave (see Chapter 7) and the blink reflex (see Chapter 8), H reflex, T reflex, tonic vibration reflex, and the silent period (SP). The reflex studies reveal conduction characteristics along the entire course of the sensory and motor axons as well as the excitability of the neuronal pool.[91] This chapter will review their basic mechanisms and possible diagnostic application in evaluating the regions of the nervous system not accessible by the conventional methods. Extensive studies have proven the practical value of the H and T reflexes in certain neurologic disorders. The other techniques mentioned here await further confirmation as a clinical test, although they have contributed substantially for physiologic understanding of the motor and sensory systems.

2. H REFLEX AND T REFLEX

Neurologic examination exploits the muscle stretch reflex to measure motoneuron excitability in spasticity and other related conditions. Clinical observations fall short of quantitatively evaluating briskness, velocity, or symmetry of these responses. Electrophysiologic studies use either a mechanical tap or electric shock to evaluate the degree of abnormality numerically. The electrically elicited spinal monosynaptic reflex, called the H reflex after Hoffmann, bypasses the muscle spindles, though otherwise the same, in many respects, as the stretch reflex induced by a mechanical tap to the tendon, or T reflex. Comparison of the H and T reflexes, therefore, provides an indirect measure of spindle sensitivity controlled by the gamma motor system.

In healthy adults, electrical stimulation elicits an H reflex only when applied to the median or tibial nerve. A short, high-frequency stimulus train enhances the discharge probability of a motoneuron above that observed with a single pulse.[16] Mechanical stretch evokes a T reflex in most muscles, including those not readily accessible to the conventional NCS.[4,15,63] Tapping the voluntarily contracted erector spinae also evokes a two-component stretch reflex, short-latency R1, considered segmental in origin, and long-latency R2, induced by suprasegmental pathway.[139,239]

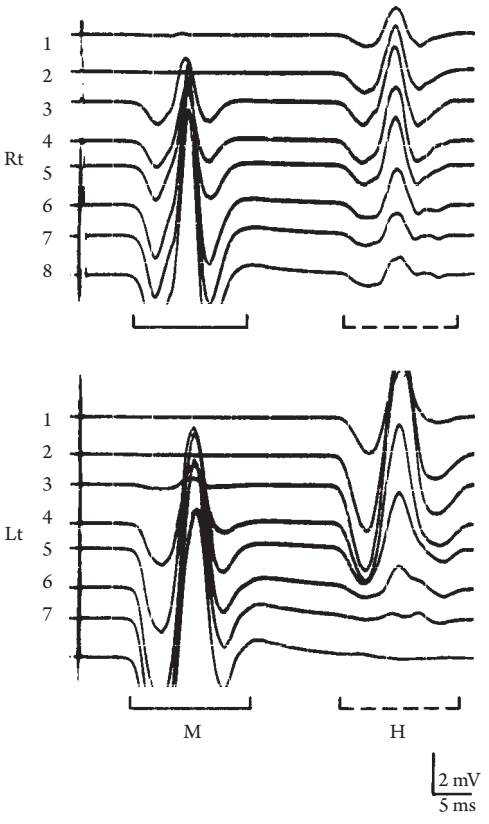

FIGURE 9-1 H reflex recorded from the soleus after stimulation of the tibial nerve at the knee with increasing shock intensities from submaximal (1) to supramaximal level (8). Note initial increase and subsequent decrease in H-reflex amplitude with successive stimuli of progressively higher intensity. Shocks of supramaximal intensity elicited a maximal M response and F wave, with a latency slightly longer than H reflex.

H Reflex versus F Wave

Stimulation of appropriate nerves at rest elicits an H reflex in most limb muscles during the first year of life,[174,243] but only in the soleus and plantar foot muscles[260] and, less consistently, in the flexor carpi radialis[5,216] after 2–3 years of maturation. Stimulation of the femoral nerve also can elicit reflex response of the quadriceps in some but not all adult subjects.[256] This limited distribution stands in contrast to the F wave elicitable in practically any distal limb muscles regardless of age.

With progressively higher stimulus intensity (Fig. 9-1), H-reflex amplitude increases initially and decreases later in portion to the size of preceding muscle (M) response, or compound muscle action potential (CMAP). This pattern results because H-reflex impulses collide, shortly after turning around the motoneurons, with antidromic impulses in the proximal segment of the motor axons, which gave rise to the M response. With supramaximal stimulation, H reflex abates and F wave appears instead with a slightly longer latency, reflecting a slower conduction along the motor fibers as compared to fast-conducting, large-diameter IA afferents, which more than compensate for the synaptic delay of the reflex. Thus, two separate motoneuron populations contribute to the simultaneously elicited M response and H reflex, and the late response elicited in the presence of an M response may contain an F wave.

Other possible mechanisms proposed for progressive extinction of the H reflex with increasing stimulus intensity include refractoriness of the axon hillock after the passage of the antidromic impulse, activation of cutaneous inhibitory neurons, and Renshaw inhibition mediated by axon collaterals via internuncial cells to the same and neighboring alpha motoneurons.[57,199,248] Thus, maximal stimulation of the group IA afferent fibers, without concomitant activation of motor fibers, elicits the H reflex optimally, although few stimuli accomplish such selectivity in practice. In contrast to these human characteristics, studies in rats show a near-maximal H reflex even with the use of supramaximal intensity evoking a maximal M response.[33]

Mild voluntary contraction primes the motoneuron pool sufficiently to allow reflexive activation of some muscles such as biceps brachii, extensor digitorum longus, and tibialis anterior.[169,197] When elicited by this means, the H reflex recorded from the abductor pollicis brevis and tibialis anterior has a longer latency than the corresponding F wave.[22] Thus, the H reflexes, elicitable only when primed by voluntary muscle contraction, may preferentially involve the low-threshold, slow-conducting motoneurons, whereas the minimal-latency F waves represent the high-threshold, fast-conducting pools. Motor units generated reflexively during neuromuscular electrical stimulation also contribute to twitch torque at H-reflex latencies.[50]

Despite the traditional emphasis on homonymous activation, IA afferents have a widespread projection to heteronymous motoneuron pools.[173] For example, stimulation of the median nerve at the elbow elicits a reproducible heteronymous monosynaptic reflex in the contracting biceps brachii, producing a smaller response than the homonymous H reflex evoked by stimulation at Erb's point.[169] Also, the same stimulation elicits the H reflex not only in the flexor carpi radialis, as expected, but also in the flexor digitorum profundus innervated by the ulnar nerve.[190]

Consecutive F waves, derived by recurrent discharges of different groups of motoneurons, characteristically vary in latency and waveform. In contrast, H reflexes elicited by sequential stimuli of the same intensity remain the same,[73] suggesting the activation of the same motoneuron pool each time (Fig. 9-2). The amplitude of the H reflex, however, declines when activated repetitively.[72] The low-frequency depression seen at stimulus rate of 1 Hz may result from processes intrinsic to the presynaptic bouton.

In testing individual axons using single muscle fiber recording, consecutive H reflexes vary in latency more than the F wave. This reflects a greater range of synaptic transmission time at a motoneuron (see Chapter 7–2) compared to a relatively constant turnaround of a recurrent discharge, which must occur within a narrow time window.[108,215,248] In one study, the latency of successive H reflexes recorded from single muscle fibers of the human triceps surae varied up to 2.5 ms.[248] In a similar study, H-reflex jitter showed a direct correlation to H-reflex latency, which, therefore, may serve as an indirect measure of the motor unit size and recruitment threshold.[109]

Recording Procedures of the Soleus H Reflex

The H reflex recorded with the patient supine or prone suffices in clinical determination of reflex

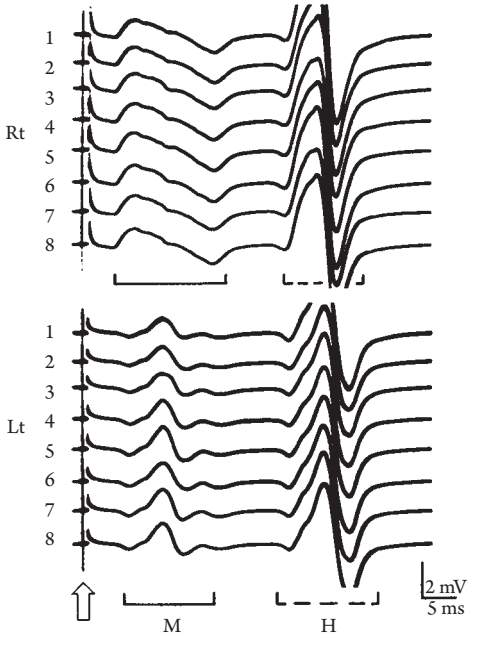

FIGURE 9-2 H reflex recorded from the soleus after series of submaximal stimulation (arrow) of the tibial nerve at the knee. Note consistency of the response on each side (cf. Fig. 9-1).

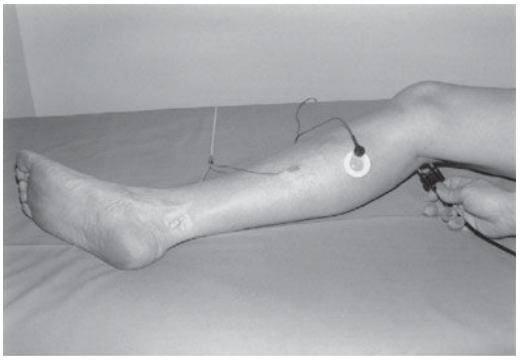

FIGURE 9-3 Recording of H reflex from the soleus muscle with the active electrode (E1) on the medial surface of the leg at the edge of the tibia, one-half to two-thirds of the way from the popliteal fossa to the ankle, and the reference electrode (E2) over the side of Achilles tendon. Shocks of submaximal intensity and 1 ms duration applied at the popliteal fossa optimally activate the group IA afferent fibers of the tibial nerve.

latencies (Fig. 9-3). For an accurate analysis of the amplitude or force of the reflex response, the subject sits upright in a modified dental chair. With this arrangement, a potentiometer monitors the movement of the feet and a force transducer measures the torque. Recorded H reflex varies in amplitude and waveform depending on the placement of the recording electrodes. The traditional setup, with the active electrode (E1) placed 2 cm distal to the insertion of the gastrocnemius on the Achilles tendon and the reference electrode (E2) 3 cm further distally, gives rise to a triphasic potential with initial positivity. An alternative, generally preferred, derivation consists of E1 placed over the soleus just medial to the tibia, half the distance from the tibial tubercle to the medial malleolus, and E2, over the Achilles tendon medial and proximal to the medial malleolus. The response usually appears as a diphasic potential with initial negativity when recorded by this means, suggesting the soleus as the primary source of this potential. Intramuscular studies also reveal a substantially greater contribution of the soleus as compared to either medial or lateral gastrocnemius in the surface recorded H reflex.[160]

The effective modes of stimuli include (1) an electrical or magnetic stimulation applied to the S1 nerve root, sciatic nerve, or tibial nerve at the popliteal fossa (H reflex); (2) a tap of the Achilles tendon with a reflex hammer fitted with a device to trigger the oscilloscope (T reflex); and (3) a mechanical stretch by quick displacement of the ankle (stretch reflex). The ability to elicit the soleus H reflex from stimulation distally and proximally helps localize the site of i nvolvement.[64,121,155,195,274,276] Standardization of stimulus conditions ensures reproducible results. The amplitude of the H reflex and its relationship to M response change with stimulus duration. Based on the recruitment curves, stimulus duration between 0.5 and 1 ms best elicits H reflexes.[142,176] Stepwise changes of shock intensities help determine an optimal electrical stimulus for obtaining the maximal response.

The common evaluation of muscle action potentials recorded reflexively from the soleus includes the onset latencies of the H and T reflexes determined to the initial deflection, either negative or positive, Hmax/Mmax and Tmax/Mmax, where Hmax, Mmax, and Tmax represent the maximal amplitude of the H reflex, M response, and T reflex, respectively. Submaximal M responses closely resemble the waveform of the maximal response,[102] providing a rationale for expressing H- and T-reflex amplitudes as a percentage of the M response. In assessing these indices, the subject must control the degree of muscle contraction, lest variability of baseline tension alters the H-reflex magnitude.[255] As expected from the primary source of the reflex, Hmax/Mmax based on recording from the soleus exceeds that of the gastrocnemius. Kinesiologic studies should measure the force of induced muscle contraction with a transducer placed against the foot plate under isometric conditions and the degree and rate of foot displacement with a potentiometer mounted on the axis of the foot plate.

Studies of Excitability

The selection of an optimal mechanical or electrical stimulus ensures the validity of using the amplitude of the H and T reflexes as a measure of motoneuron excitability.[32,45,113] Suppression of H reflex may result from presynaptic inhibition of Group IA afferents. Thus, the H-reflex

measurement helps in quantitatively evaluating supraspinal and segmental inputs on the alpha motoneurons.[138,148,179,242] Preservation of F waves associated with suppressed H reflex suggests a reduction of excitatory input rather than decreased excitability of motoneurons.[149] Methodological problems (see Chapter 7-2), however, confound the comparison of F wave and H reflex in elucidating the responsible physiologic mechanisms of excitability change.[104] A differential effect on the two responses, therefore, may not serve as an indirect measure of presynaptic inhibition of Group IA fibers mediating the H reflex if changes in motoneuron excitability influence the F wave much less than the H reflex.[103]

Postural changes play an important role.[81,147,178,222] For example, lateral tilting modulates soleus H reflex through vestibular influences, showing ipsilateral suppression and contralateral facilitation.[3] Caloric stimulation of the labyrinth facilitates the H reflex bilaterally.[52] Galvanic vestibular stimulation also modulates the soleus H reflex.[116,154] The background fusimotor activity has little or no influence in eliciting Achilles tendon jerk during complete relaxation,[26,27] although changes of spindle discharges induced by shortening the homonymous muscle depress the monosynaptic reflexes.[266]

A selective voluntary contraction produces H reflex excitability changes by presynaptic and postsynaptic mechanisms.[209,264] Kinesthetic motor images may also facilitate the response.[38] Conversely, volitional relaxation of the target muscle for a few hours suppresses the H reflex (Figs. 9-4 and 9-5).[267] Similarly, contraction history of muscle shortening potentiates, and of muscle lengthening depresses, H-reflex excitability.[251] Sleep, in general, and the rapid eye movement (REM) period, in particular, depress the H-reflex.[93] Descending motor commands induced by pedaling that produce a patterned voluntary activity normally cause facilitation during the downstroke and suppression during the upstroke. Stepping within a robotic exoskeleton preserves phase-dependent modulation of soleus H reflex.[125] Clinical conditions extensively tested by this reflex include periodic limb movement,[200] spasticity,[20,41,66,67,207,245,268] and dystonia.[210]

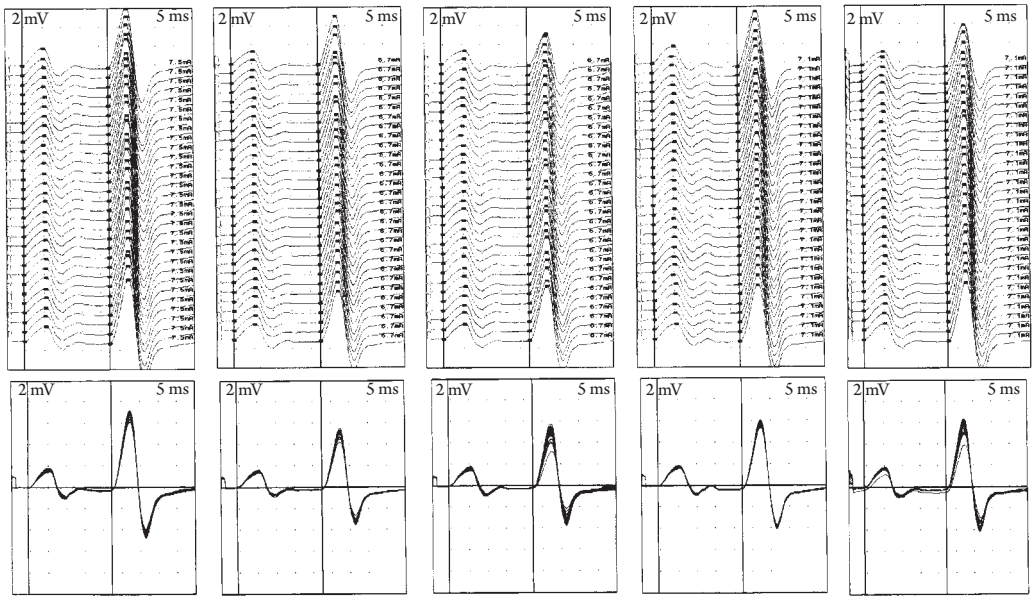

FIGURE 9-4 Thirty consecutive traces of M and H waves evoked in the soleus muscle in a 27-year-old healthy male before and after a 2-hour volitional relaxation. The amplitude of the M wave remained in the range of 2 mV. The amplitude of the H reflex, reduced after a 2-hour rest, recovered on standing. (Modified from Yanagisawa, Kimura, Azuma et al.[267])

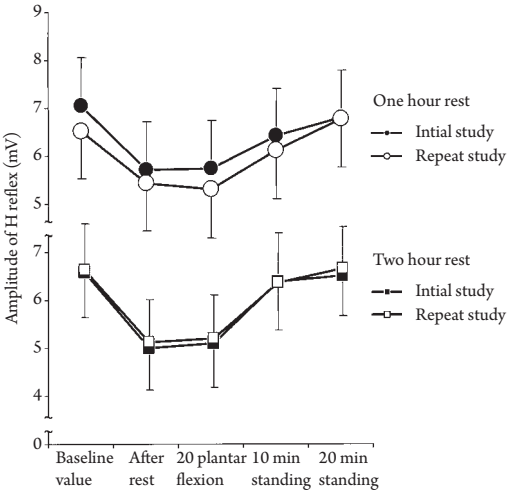

FIGURE 9-5 Rest-induced suppression of H reflex after one and two-hour volitional relaxation, showing a reduction after rest, no change after standardized plantar flexion exercise, and a recovery after standing. A two-hour rest caused a greater amplitude change (mean ± 2SD) compared to a one-hour rest, indicating a duration dependent effect. (Modified from Yanagisawa, Kimura, Azuma et al.[267])

Other factors that influence the excitability of the spinal motoneurons tested by T and H reflex include electrical stimulation of rectus femoris[126] or of contralateral tibial nerve,[235] whole-body vibration,[123] cold stimulation,[184] voluntary teeth-clenching,[238] gait initiation,[247] cycling training,[162] passive rotation of the hip joint,[181] anesthesia,[100,150,233] electrocutaneous stimulation,[117,212] Jendrassik maneuver,[250] posterior root stimulation,[172] high-frequency Group IA afferent stimulation,[16] caffeine intake,[263] and transcutaneous spinal application of direct current.[265]

Paired Shock Techniques

The paired-shock technique reveals the time course of alteration in motoneuron excitability by means of conditioning and test stimuli. Shocks of suprathreshold intensity exert two opposing effects on the excitability of the motoneuron pool: those motoneurons that have discharged in response to the conditioning stimulus become less responsive to a test stimulus during the refractory period and by Renshaw effect and other inhibitory mechanisms. The remaining motoneurons, activated subliminally by the conditioning stimulus, become more responsive to the test stimulus after partial depolarization. The presence of these two competing factors complicates the interpretation of the result. If the conditioning stimulus gives rise to a muscle contraction, motoneuron excitability may change as the secondary effect of Group IA inflows caused by mechanical stretch of the ankle extensor muscles.[111] In experimental studies, single motor unit analysis provides a tool to explore the effect of a conditioning stimulus on a unitary H reflex, without these uncertainties.[229]

The use of a subthreshold conditioning stimulus provides another way of assessing supranuclear control of the H reflex. The excitability curve plotted by this method consists of an early facilitation lasting 25 ms and a period of predominant depression for the next 500 ms before the excitability approaches the control level (Fig. 9-6). The paired-shock technique also reveals the effects of reciprocal inhibition.[13,14,28,40,269] For example, femoral nerve stimulation produces heteronymous reflex responses in tibialis anterior and soleus, inducing short-latency facilitation followed by long-lasting inhibition of the H reflex at appropriate latencies.[166,167] Conversely, a conditioning impulse from sciatic nerve afferents facilitates vastus medialis motoneurons at the joint time of arrival when studied by the test volley via H reflex or corticospinal pathways. Subsequent inhibition seen only in the H reflex implies presynaptic inhibition of the Group IA afferent terminals.[208,256,275]

Clinical Applications

Table 9-1 (see also Appendix Table 1-7) summarizes the normal values for soleus H reflex (mean ± SD), which in our laboratory comprise latency of 29.5 ± 2.4 ms and side-to-side difference of 0.6 ± 0.4 ms with the upper limit of normal of 2.0 ms. The corresponding measures for flexor carpi radialis reflex[62] consist of 15.1 ± 1.0 ms and 0.43 ± 0.39 ms.

As with the F-wave and H-reflex latencies, covering a longer pathway often reveals mild abnormalities early in assessing diffuse or multisegmental pathology.[225] Unlike F wave, however, these studies evaluate conduction abnormalities of both afferent and efferent pathways.[60]

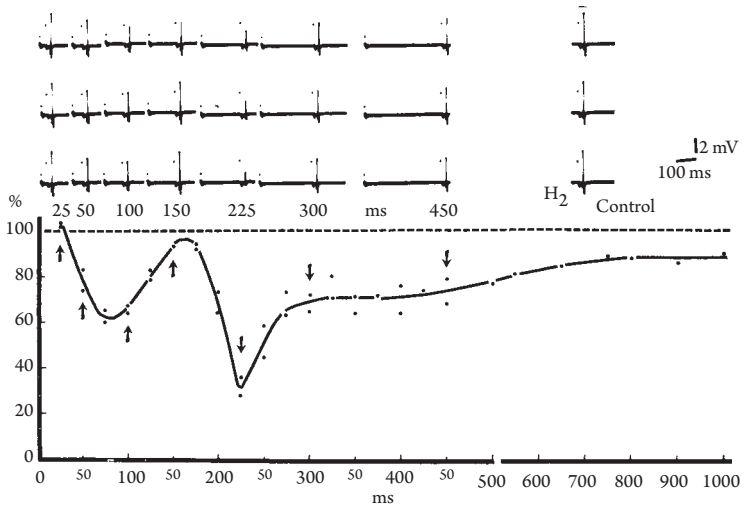

FIGURE 9-6 H-reflex recovery curve after subliminal conditioning stimulus. The upper half shows the test responses arranged in groups of three for each testing intervals of 25, 50, 100, 150, 225, 300, and 450 after conditioning stimulus and control reflexes (H2) before and after the conditioning series. Paired shocks comprise conditioning stimulus just below the threshold for evoking an H reflex and test stimulus just below the threshold for an M response. The lower half shows the plotting of the mean of the three test reflexes at each testing interval (abscissa), expressed in percentages of the mean of the control response. (Modified from Taborikova and Sax.[237])

In patients with diabetes, H-reflex latency rivals the conventional NCS in elucidating early neuropathic abnormalities and a clear-cut proximal-to-distal gradient of conduction slowing. This latency also shows abnormal increases in patients with alcoholic, uremic, and various other polyneuropathies [216] including chronic demyelinating polyneuropathy (CIDP).[140] In contrast, reflex studies have limited utility in detecting a focal slowing, which results in only a small percentage increase of the total conduction time.[158] Nonetheless, a number of studies have demonstrated clinical applications of the H reflex as a test for radiculopathy.[21,195,211] In evaluating a unilateral lesion, the latency difference between the two sides serves as the most sensitive measure of the T and H reflex (Fig. 9-7). Thus, unilateral absence or a right-left latency difference greater than 2.0 ms supports the diagnosis of S1 radiculopathy in a proper clinical context, although it does not, by itself, constitute sufficient evidence of a herniated disk.

Studies of T reflex also revealed absent or delayed response consistent with demyelination in patients with CIDP but not in chronic axonal neuropathies.[258] A number of studies have shown abnormalities of T reflex associated with lumbar and sacral plexopathy[240] and root

Table 9-1 H Reflex*

AMPLITUDE† (mV)	DIFFERENCE BETWEEN THE SIDES (mV)	LATENCY‡ TO RECORDING SITE (ms)	DIFFERENCE BETWEEN THE SIDES (ms)
2.4 ± 1.4	1.2 ± 1.2	29.5 ± 2.4 (35)§	0.6 ± 0.4 (1.4)§

*Mean ± standard deviation (SD) in the same 59 patients shown in Table 6-11.
†Amplitude of the evoked response measured from the baseline to the negative peak.
‡Latency measured to the onset of the evoked response.
§Upper limits of normal calculated as mean + 2 SD.

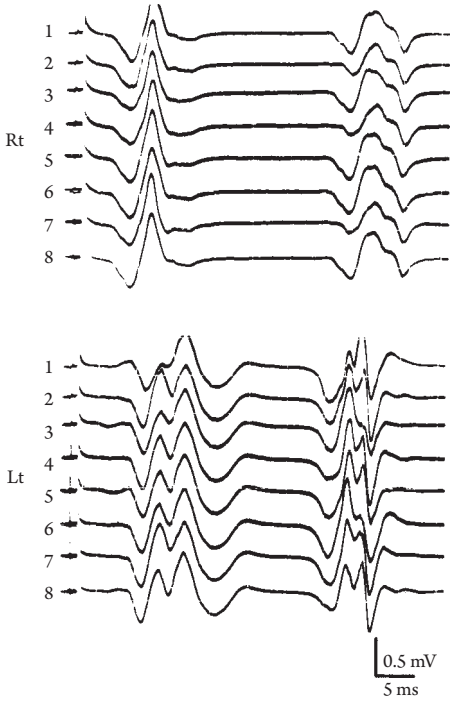

FIGURE 9-7 H reflex in a 77-year-old man with cauda equina syndrome. The recording shown in the same arrangement as for Figure 9-2 indicates a delay by more than 2 ms on the right compared with the left. The central latency as determined by the latency difference between the M response and H reflex corroborates the abnormality.

compression.[217] A diminution of the triceps surae reflex suggests an S1 radiculopathy, like a depression of the ankle stretch reflex in the neurologic examination.[46,65,183,223] In patients with cervical radiculopathy, abnormality of flexor carpi radialis reflex may indicate lesions of the C6 or C7 root or both.[170,171]

The difference between H reflex and distal motor latencies equals the segmental conduction time along the reflex pathway. This latency difference corresponds to the distance between the knee and T11 as a measure of conduction along the afferent and efferent fibers of the tibial nerve. Segmental studies are better suited for latency evaluation of focal lesions like S1 radiculopathy, eliminating the normal portions of the reflex pathway, which tend to dilute the conduction abnormality (see Chapter 11-7). Magnetic or electric stimulation of the S1 nerve root provides a most sensitive latency comparison of the very short proximal segment within the spinal canal.[64,110,155,194,274,276] Some investigators advocate the use of peak latency difference between simultaneously recorded M response and H reflex (H-M interval) elicited by root stimulation. This measures the conduction time across a short segment within the spinal canal, which comprises the proximal afferents, anterior horn cells, and

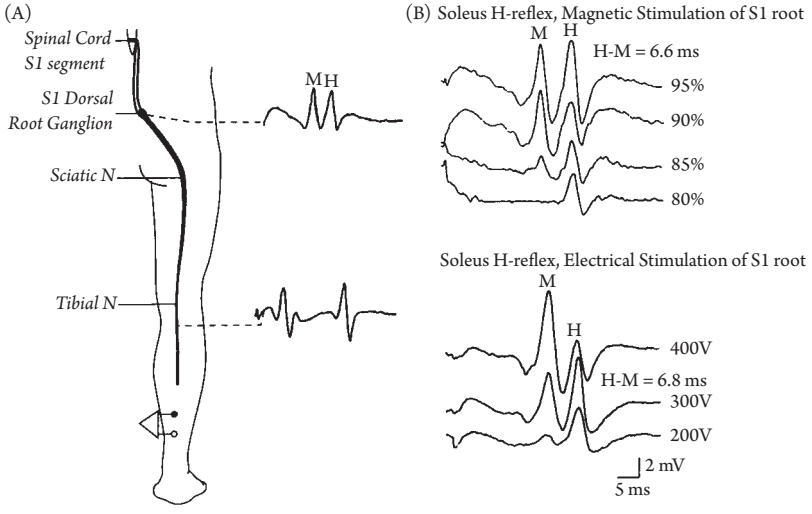

FIGURE 9-8 (***A***) Schematic representation of soleus H reflexes from electrical stimulation at the S1 foramen and of the tibial nerve at the popliteal fossa. (***B***) The response complex of the H reflex and M wave in one of the subjects elicited by magnetic (upper traces) and electrical stimulation (lower traces) at the S1 foramen with stimulus intensity indicated after each trace. (Modified from Zhu, Starr, Haldeman, et al.[274])

ventral roots. In one study of 100 healthy subjects (Fig. 9-8),[274] H-M intervals increased from 2.6 ± 0.7 ms (mean ± SD) when stimulated at T12 or L1 spinal processes to 4.2 ± 0.6 ms at L2 or L3, 5.5 ± 0.3 ms at L4 or L5, and 6.8 ± 0.5 ms at S1.

The recruitment curve of the soleus H reflex may reveal an increased threshold of excitation during transient conduction abnormalities seen, for example, in neurogenic claudication.[58,192] Other conditions associated with a depressed stretch reflex such as neuropathy and Adie's syndrome[175] also show an elevated threshold for excitation of H reflex. Conversely, some patients with the tethered cord syndrome characterized by a lower location of the conus medullaris may show a decreased threshold.[89]

3. THE MASSETER AND PTERYGOID REFLEX

Sudden stretching of the muscle spindles from a sharp tap to the mandible activates the jaw reflex, or masseteric T reflex.[97,137] Electric stimulation of the masseter nerve also elicits, in addition to the direct motor responses, a masseteric H reflex relayed via the midbrain.[43,78,79] The so-called motor root of the trigeminal nerve contains the sensory fibers of the muscle spindle and the motor axons of the extrafusal muscle fibers, the afferent and the efferent arc of the reflex. The cell bodies of the proprioceptive spindle afferents lie in the mesencephalic trigeminal nucleus. The collateral branches from these cells make a monosynaptic connection with the motoneurons of the trigeminal nerve in the pons. The physiology of the jaw reflex differs considerably from that of the spinal monosynaptic reflex. For example, muscle vibration that inhibits the soleus T and H reflexes potentiates the masseteric counterparts.[78,79] Some authors advocate the stretch reflex from the medial pterygoid as an additional electrophysiologic study for the trigeminal nerve.[96,98] Acoustic stimuli can also evoke reflex responses in the masseter muscle, which comprise two components, vestibulo and acoustic masseteric reflexes.[53]

Methods and Normal Values

Table 9-2 (see also Appendix Table 1-7) summarizes normal values in our laboratory.[122]

In eliciting the jaw reflex by a mechanical tap over the mandible, the closure of a microswitch or other pressure-sensitive device attached to the percussion hammer triggers the oscilloscope sweep (Fig. 9-9). During repetitive testing, an increase in the weight supported by the mandible or Jendrassik's maneuver tends to facilitate the masseter reflex. The latency and amplitude vary with successive trials in the same subjects and among individuals. The amplitude ratio between simultaneously recorded right-sided and left-sided responses, however, remains relatively constant.[122] Thus, electrophysiologic evaluation depends on the side-to-side comparison of the reflex responses recorded simultaneously, rather than the absolute values.

Table 9-2 Latency and Amplitude of Masseter Reflex in 20 Normal Subjects

	LATENCY (ms)	LATENCY DIFFERENCE (ms)	AMPLITUDE (mV)	AMPLITUDE RATIO (LARGE OVER SMALL)
Mean right	7.10		0.23	
Mean left	7.06		0.21	
Total	7.08	0.27	0.22	1.44
SD	0.62	0.15	0.24	0.42
Mean + 3 SD	9.0	0.8	Variable	2.7

FIGURE 9-9 Jaw tap for simultaneous recording of mechanically induced masseter reflex from both sides with two pairs of electrodes placed over the belly of the masseter muscle (E1) referenced to the chin (E2). A modified reflex hammer has a built-in microswitch, which, on contact, triggers the sweep.

In one study,[189] using a needle recording electrode, the criteria for abnormality consisted of unilateral absence of the reflex, a difference of more than 0.5 ms between the latencies of the two sides or bilateral absence of the reflex up to the age of 70 years. For the pterygoid reflex, the normal values reported include the latency of 6.9 ± 0.43 ms (mean ± SD) with a side-to-side difference of 0.29 ± 0.21 ms in 23 healthy volunteers.[98]

Clinical Applications

The jaw reflex poses technical problems as a diagnostic test in standardizing the mechanical stimulus and regulating the tonus of the masseter for optimal activation (Fig. 9-10). Masseter reflex abnormalities seen with medullary lesions also restrict its value in localizing the lesion in the pons.[159,244] Nonetheless, an unequivocal unilateral delay or absence usually suggests a lesion of the trigeminal nerve or the brainstem.[122,213] Electromyographic (EMG) study of the masseter muscle may document the presence of denervation, thus localizing the lesion within the motor pathway.[188]

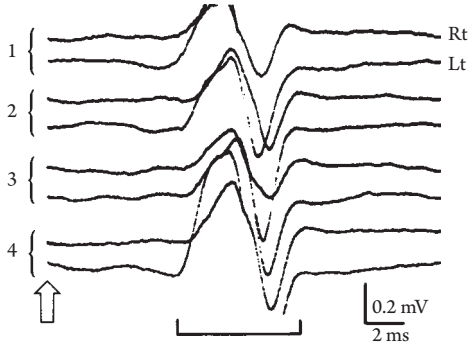

FIGURE 9-10 Jaw reflex recorded simultaneously from right (top tracing of each pair) and left (bottom) masseter after a series of four mechanical taps on the chin (open arrow).

In one study, the use of the jaw reflex as a test of midbrain function revealed absence or increased latency in 12 of an unselected series of 32 patients with multiple sclerosis.[80,271] In another study of 51 patients with internuclear ophthalmoplegia, an abnormality limited to masseter reflex suggested a midbrain lesion in 59%, whereas abnormal R1 of the blink reflex indicated a rostral pontine involvement in 35%.[99] In Friedreich's ataxia characterized by absent or hypoactive stretch reflexes in the upper and lower limbs, the masseter reflex remains unaffected and may paradoxically show hyperactivity.[9,76] This discrepancy probably reflects different location of the afferent nerve cell body, intra-axial mesencephalic nucleus, and extra-axial craniospinal ganglia. If so, a normal masseter reflex in patients with pure sensory symptoms favors a diagnosis of ganglionopathy rather than axonal sensory neuropathy.[11]

Masseteric Silent Period

A jaw reflex elicited during voluntary clenching gives rise to a brief pause in the EMG activity of the masseter muscle (Fig. 9-11). This inactivity, referred to as the masseteric SP, lasts about 30 ms in normal subjects after mechanical tap or electric or magnetic stimulation on the second or third branch of the trigeminal nerve. A similar masseteric silence also follows acoustic or electric stimulation of the tongue, gums, oral mucosa, or belly of the muscle.[78,79,224] A unilateral stimulus suppresses

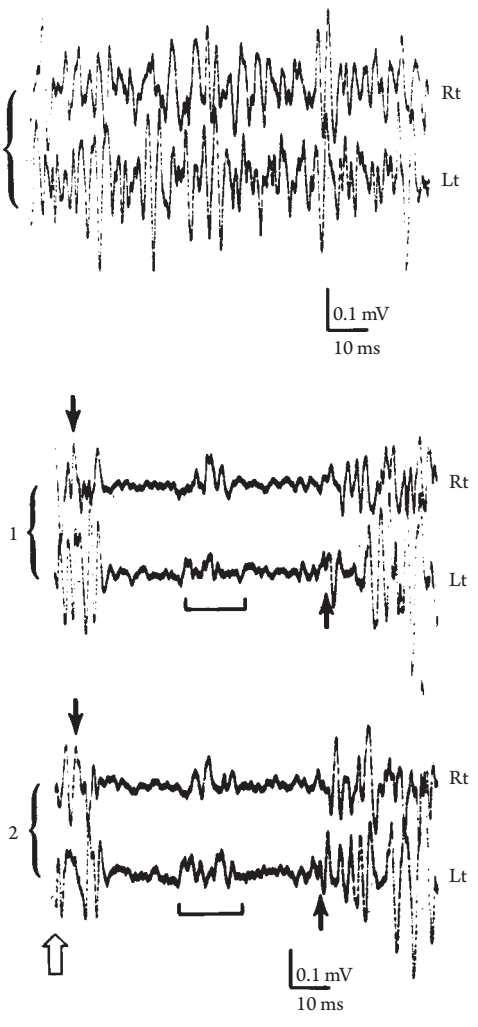

FIGURE 9-11 (***A***) Voluntary contraction of the masseter for simultaneous recording of electromyography from right (top tracing) and left (bottom) side, using two pairs of surface electrodes placed on the belly of the muscle (E1) and under the chin (E2). (***B***) Silent period (SP) of the masseter by a mechanical tap applied to the chin at the beginning of the sweep (open arrow). Electrical activity ceases immediately following the jaw reflex (arrows from top) elicited by the stimulus. Small voluntary potentials (brackets) break through in the midst of the SP before the return of full activity (arrows from bottom) in approximately 80 ms after the tap.

the muscle activity on both sides, indicating the presence of crossed and uncrossed central pathways for this inhibition.[186] The masseteric SP simulates the analogous phenomenon seen in limb muscles after electrical stimulation of the nerve (see Chapter 9-5). Paired shock technique allows assessment of SP recovery cycle yielding a similar time course either with electrical or magnetic stimulation.[75] Masseter muscles also exhibit weak, bilaterally symmetric inhibition following focal transcranial magnetic stimulation of the motor cortex.[107]

In one study assessing the effects of brainstem lesions on the two phases of silence, SP1 and SP2, evoked by stimulation of the mental nerve, abnormalities tended to implicate the pontine tegmentum between the midpons and pontomedullary junction.[187] The afferent impulses for SP1 probably reach the pons via the trigeminal sensory root, enter the ipsilateral trigeminal spinal tract and ascend, via interneurons, to the trigeminal motor nuclei on both sides. The impulses responsible for SP2 follow a similar but independent path descending more caudally to the pontomedullary junction involving the lateral reticular formation. The second and third divisions of the trigeminal nerve constitute the afferent arc of these reflexes. Central activation of inhibitory interneurons in the brainstem results in suppression of the trigeminal motor nuclei, relaxing the jaw-closing muscles.[44] Painless magnetic stimulation also elicits SP1 and SP2, which, therefore, seem to have a nonnociceptive origin.[133]

The force and direction of the tap and the magnitude of jaw clenching substantially influence the mechanically induced SP. In particular, a decrease in voluntary muscle contraction results in a major increase in its duration. Thus, stimulus and subject variables tend to limit its use as a clinical test of the masticatory system.[164] Nonetheless, some patients with tetanus lack the inhibition.[69,201] Conversely, its duration exceeds the normal range in patients with the temporomandibular joint syndrome.[152,156] Wallenberg syndrome accompanies a variety of brainstem reflex abnormalities (see Chapter 8–6), including masseter inhibitory reflex elicited by electrical stimulation.[257] The SP may show a delayed onset latency in various polyneuropathies associated with conduction abnormalities.[10,42]

4. THE TONIC VIBRATION REFLEX

In contrast to the phasic activity of T and H reflexes, the tonic stretch reflex subserves postural

and volitional movements. A vibratory stimulus applied to a tendon or a muscle excites the muscle spindles selectively and produces a sustained contraction of the muscle.[23,24] This tonic vibration reflex in many respects simulates a tonic stretch reflex,[85] although skin mechanoreceptors may also contribute.[1] Hence, the vibration provides a means of testing motoneuron reaction to tonic, rather than phasic, stimuli.[143] Studies of the tonic reflex consist of stimulating the tendon with a small vibrator that oscillates at 150 Hz with an approximate amplitude of 0.5 to 1.5 mm, and recording muscle response with surface electrodes placed over the belly (E1) and tendon (E2). Intervals of at least 10 seconds should separate the stimuli to avoid cumulative depression of the reflex activities evoked segmentally.

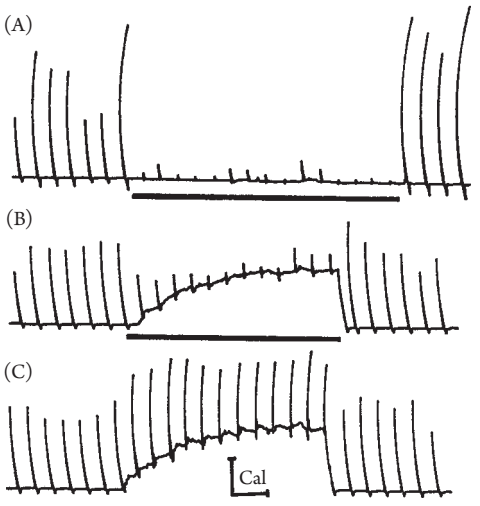

FIGURE 9-12 Effects of continuous quadriceps vibration (black bar) in a normal subject, showing suppression of phasic stretch reflexes elicited every 5 seconds with (***A***) or without (***B***) the generation of the tonic vibration reflex (TVR) and restoration of knee reflexes during voluntary contraction of quadriceps (***C***). Calibration: Vertical, 0.4 kg for ***A***, 0.6 kg for ***B*** and ***C***. Horizontal, 10 seconds. (From De Gail, Lance, and Neilson,[49] with permission.)

Normal and Abnormal Responses

The motor effects of tonic vibration include (1) active and sustained muscle contraction,[2] (2) reciprocal inhibition of motoneurons innervating antagonistic muscles,[83] and (3) suppression of the T and H reflexes (Fig. 9-12).[127] Its generation involves more than a simple spinal neural arc.[92] Studies in cat gastrocnemius muscle before and after lesions at preselected neural sites indicate that (1) the reflex depends on an intact neural axis caudal to the mid colliculus, (2) facilitatory pathways ascend ipsilaterally in the ventral quadrant of the spinal cord, (3) the lateral vestibular nucleus and pontine reticular formation provide essential facilitation, and (4) the medullary reticular formation subserves inhibition.[25] The tonic vibration reflex has helped in assessing reciprocal inhibition,[34] inhibitory effect of acupuncture on the motoneurons,[95] central control of voluntary movements,[112] spasticity,[177,180] and Parkinson's disease.[161]

Clinical Applications

Clinical applications include early detection of incipient weakness, subclinical rigidity, spasticity, and involuntary movements, such as tremors, clonus, choreoathetosis, and dystonia.[112,143] The tonic vibration reflex varies from patient to patient, primarily depending upon the site of spinal cord lesions. Thus, a predictable pattern of abnormality, if clearly elucidated, would localize the responsible lesion. The technique, though not widely used, may help in assessing the patients with spinal cord injuries and dystonia. A large number of papers have also appeared describing the effect of tonic vibration on spasticity or rigidity.[84,94,143] In most reported series, vibration produced beneficial effects, for example, (1) increased voluntary power of a weak muscle, (2) reduced resistance of the spastic antagonist, and (3) increased range of motion. Unfortunately, these positive effects last only for the duration of vibration, which in practice cannot exceed a few minutes because of frictional generation of heat.

5. THE SILENT PERIOD AND LONG-LATENCY REFLEX

Silent Period

Despite continued effort, action potentials of a voluntarily contracting muscle undergo a

transient suppression following electric stimulation of the mixed nerve innervating that muscle or a cutaneous sensory nerve. This period of electrical inactivity, designated either the mixed nerve or cutaneous SP, results from several physiologic mechanisms.[61,70,105,130,224] A number of investigators have studied the SP using electrical[224,253] or purely nociceptive laser stimulation[205] or unloading of the muscle spindles mechanically [234] in normal subjects and in patients with neurologic diso rders.[12,18,88,128,14591,133,150] Electrical stimulation of cutaneous afferents from the face area induces a pause in voluntary firing of facial motoneurons that innervate depressor labii inferioris and levator labii superioris, but not in the other lower facial muscles.[30] Transcranial magnetic stimulation during sustained voluntary muscle contraction also results in the SP (see Chapter 20-3).

Physiologic Mechanisms

The initial segment of muscle inactivity immediately after the M response results from collision in motor axons. Later phases mainly reflect recurrent inhibition by activation of Renshaw inhibitory cells following the passage of an orthodromic or antidromic impulse along the motor axon. Of the two, antidromic invasion produces more effective suppression.[136] During muscle contraction, voluntary orthodromic impulses collide with antidromic impulses in some motor fibers before they reach the central motoneuron pool. A stronger effort to contract the muscle increases the chance of collision in a greater number of axons that carry orthodromic impulses.[118,119] Stimulation of the nerve distally also enhances this probability in proportion to the length of the nerve segment between the stimulus site and the cell body (Fig. 9-13). Thus, the greater the voluntary effort and the weaker and more distal the nerve stimulation, the smaller the antidromic invasion and the weaker the recurrent inhibition of motoneurons (Fig. 9-14).

In addition to the Renshaw effect, other mechanisms such as the unloading of the muscle spindle contribute to the muscle inactivity.[224] Sensory nerve stimulation could also generate a reproducible inhibition with little side-to-side difference,[131] presumably through either Group IB afferent fibers from tendon organs or through

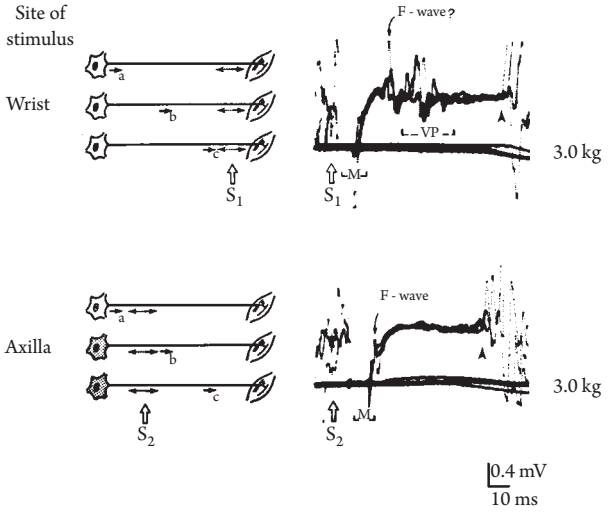

FIGURE 9-13 Muscle force of 3.0 kg (horizontal line in the bottom) and the silent period (SP) from the voluntarily contracting first dorsal interosseous muscle (three trials superimposed). Note a voluntary potential (VP) in the middle of SP with a stimulus at the wrist but not at the axilla, indicating greater inhibition by proximal activation. Distally induced antidromic activity will collide with voluntary impulses, a, b, and c, before reaching the motoneuron pool. Proximally induced antidromic activity, escaping collision, invades recurrent axon collaterals and inhibits the motoneurons (shaded). (Modified from Kimura.[120])

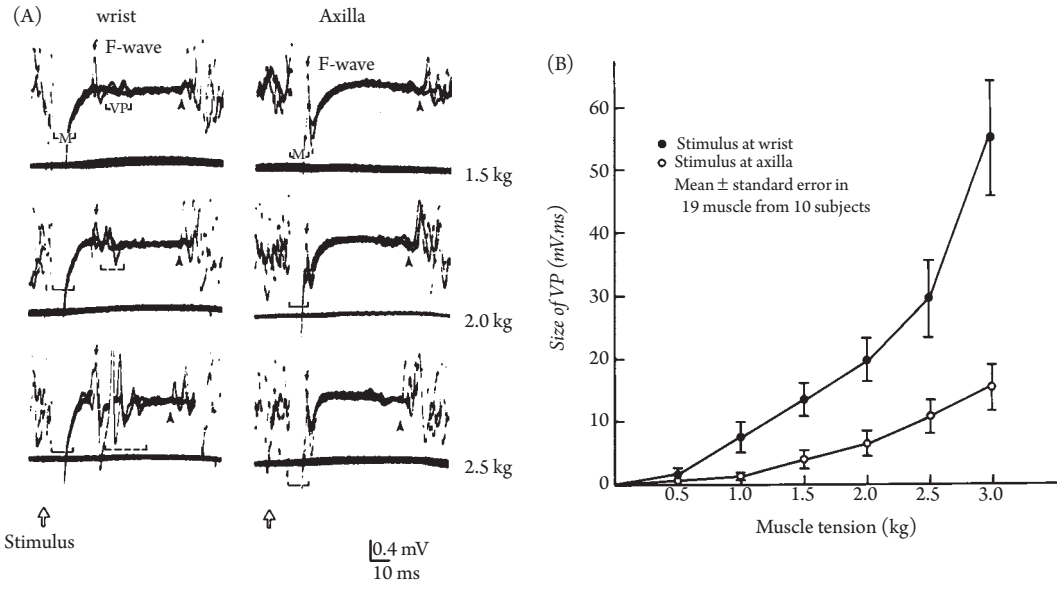

FIGURE 9-14 (***A***) The same arrangement as in Figure 9-13 showing the effect of muscle force ranging from 1.5 to 2.5 kg. With stimulation at the wrist, the voluntary potential (VP) became progressively greater in size at increasingly higher muscle force. With stimulation at the axilla, which induced no VP, the duration of the silent period (SP) shortened with increasing muscle force. (Modified from Kimura.[120]) (***B***) Muscle tension and the size of the VP breaking through the SP. Note larger VP with stimulus at the wrist than at the axilla, indicating a greater inhibition of motoneurons rendered by proximal as opposed to distal nerve activation. This difference became progressively larger with increasing muscle force. (Modified from Kimura.[120])

ascending reflex pathways via low-threshold sensory fibers.[106,146,220,241] Proximal stimulation, which activates a greater number of afferent fibers, would inhibit the motoneurons more effectively. In one study, the intensity of stimulus played a greater role than the degree of muscle contraction on the extent of cutaneous SP.[203] This type of SP may abate in cases of syringomyelia, which interrupts the pathway through the posterior horn.[114] Loss of cutaneous SP and later portion of mixed nerve SP in patients with syringomyelia implies a generator of the spinal level mediated by the same small myelinated Aδ fibers.[232] Consistent with this view, the Type II diabetes mellitus patients with small fiber neuropathy have cutaneous SP characterized by a longer latency, shorter duration, and greater difference between upper and lower limbs.[185] Patients with the carpal tunnel syndrome (CTS) also have an increased SP latency, probably indicating Aδ fiber dysfunction.[135] Cutaneous SP shows little change after administration of an antihistaminic drug, cetirizine.[129]

The physiologic mechanisms generating a cutaneous SP remain elusive.[39,153,182] During this period, F waves show normal or even increased excitability despite reduction in amplitude of the H reflex.[146,149] These findings suggest that cutaneous stimulation causes, in addition to the SP, presynaptic inhibition of Group IA afferents, which would reduce the H reflex but not the F wave. This interpretation may not necessarily hold,[157] however, if the H reflex has a greater sensitivity than the F wave to a change of motoneuron excitability (see Chapter 7–2).[103] Patients with neuropathic pain, showing a reduced amplitude of laser evoked potentials, have a normal cutaneous SP, which therefore does not serve usefully as a measure of nociceptive pathways.[249]

Potentials That Break through the Silent Period

Increasing voluntary muscle contraction can interrupt the SP, which, therefore, must represent

a relative, rather than absolute, suppression. Two separate potentials, V1 and V2, appear,[254] presumably representing H reflex and long-latency reflex generated transcortically.[54,141] If voluntary impulses collide with antidromic activity in most axons at high levels of muscle contraction, the first potential, V1, mainly comprises the H reflex.[163,231] In contrast, if substantial antidromic activity escapes collision at low levels of muscle contraction, then V1 probably represents F waves.[119] The second potential, V2, also designated as the voluntary potential, long-latency reflex, long loop response, or cortical (C) response, interrupts the silence at approximately twice the latency of V1. Despite presumed hypoexcitability of motoneurons, transcranial magnetic stimulation elicits large motor evoked potentials (MEPs) between the V1 and V2.[272] This intuitively paradoxical finding may result from activation of muscle afferents by mixed nerve stimulation, which increases cortical motor excitability.[47,55,134]

The middle portion of the SP at least in part originates from antidromic invasion of the Renshaw loop, which in turn inhibits the motoneurons. Thus, the V2 tends to occur with any maneuver that reduces the recurrent inhibition by axonal volleys arriving at the motoneuron pool.[120] For example, weaker stimuli, which activate fewer motor axons, favor the appearance of V2. Descending volitional inputs play an important role in the generation of V2, normally seen only during muscle contraction strong enough to break the underlying inhibition.[119] A similar activity elicited at rest in patients with posthypoxic cortical myoclonus[273] and several other types of myoclonus,[228] presumably results from segmental polysynaptic inputs to motoneurons through muscle afferent.[252] Alternatively, some investigators equate V2 with the transcortical reflex activity, or C response, elicited by brief stretching of arm muscles.[230]

If V1 occurs segmentally and V2, cortically, the latency difference between them provides a measure of the central conduction along the spinal cord to and from the reflex center of V2. The comparison between the arm and leg then allows calculation of mean spinal conduction time between the C7 and L5 spinous process, as (V2 – V1) leg/2 – (V2 – V1)arm/2.[59] This measure, which varies considerably may serve as an estimate of the mean conduction characteristics in a group of subjects but not as a diagnostic test in individual patients.

Instead of electrical stimulation, sudden tilting of a platform around the axis of the human ankle joint also causes a regular pattern of short- and medium-latency discharges, termed M1 and M2, in the stretched triceps surae muscle, and a long-latency response in its antagonist, the tibialis anterior muscle.[101,214,227] Stretch of the biceps brachii[68] and the quadriceps femoris[17] also produces M1 and M2 responses with a good intraindividual reproducibility. Most authors consider M1 as a segmental response by way of spinal pathway[29,48] and M2 as a "long loop" reflex via transcortical pathways.[90] In agreement with this view, patients with multiple sclerosis, spinal tumor, or cervical stenosis may have normal M1 and a delayed M2, a finding that implies the presence of a supraspinal pathway.[6] The long-latency reflex component also shows a close relationship to the motor preparation and programming.[124]

6. OTHER REFLEXES

The flexor reflex elicited by stimulation of the peripheral nerve consists of two or more components usually demonstrating excitation-inhibition cycles.[56,168] Electrical stimulation of the trigeminal nerve induces reflex responses in the neck muscles, including an early disynaptic and late polysynaptic nociceptive reflex.[218,219] Electrical stimulation of the fingers elicits cutaneous withdrawal reflexes of the upper limb approximately coinciding with an SP in active hand muscles.[71,77,226] Analogous to the Babinski sign, stroking the plantar surface with a blunt probe elicits a flexor reflex recordable from the extensor digitorum longus and extensor hallucis longus. Its latency ranges from 160 to 500 ms depending on the intensity and speed of the mechanical stimulation.[202] Electrical stimulation of the sole also induces withdrawal reflexes.[7]

In standing humans, nociceptive stimulation induces spinal reflex pattern without disturbing the support function of the limb.[8,51] Phrenic nerve stimulation also evokes not only a diaphragmatic CMAP but also a long-latency spinal flexor response from the 7th intercostal space.[206]

In patients with spinal cord injuries, transcutaneous electrical stimulation of the sural nerve tends to suppress flexor reflex.[82] Flexor reflex recording may help quantify the benefit of antispastic therapy such as intrathecal baclofen.[191] Similar to the eye-blink conditioning paradigm, the human flexion reflex can serve as a model in classical conditioning experiments.[132,196,246]

Analogous to flexor reflexes in the limb muscles, stimulation of perianal skin elicits a two-component response in the external anal sphincter.[236] Stimulation of penis or clitoris also evokes reflex responses with a typical latency of 33 ms in the external anal and urethral sphincters.[262] Similarly, stimulation of the dorsal genital nerve activates the external anal sphincter reflexively with the latency of 38.5 ± 5.8 ms (mean ± SD). Patients with fecal incontinence may have absence or delay of this pudendoanal reflex.[259] With the active electrode (E1) over the bulbocavernosus muscle beneath the scrotum and the reference electrode (E2) over the iliac crest, pudendal nerve stimulation applied at a rate of 1.5 Hz elicits, after 30 to 50 averaging, an initially negative biphasic or triphasic reflex response with the onset latency of 35.9 ± 9.0 ms.[86] Unilateral stimulation of the genital nerve also elicits a two-component bulbocavernosus reflex, R1 and R2, bilaterally via crossed and uncrossed spinal cord pathway.[198]

These techniques, though not universally accepted in clinical practice, may prove useful in the evaluation of diabetic neuropathy,[74] impotence secondary to peripheral nerve involvement,[165] and neurogenic bladder.[115] The bulbocavernosus reflex may provide a more sensitive measure of the sacral nervous system than conventional or single fiber EMG of external urethral and anal sphincters.[204,261] Nerve conduction studies of the dorsal nerve of the penis and pudendal somatosensory evoked potentials (SEPs) complement the measurement of the reflex latency in diagnostic evaluation of bowel, bladder, and sexual function (see Fig. 19-15).[270]

Auditory postauricular reflex, generated in the posterior auricular muscle, shows two prominent components at latencies of 12 and 16 ms.[87] Voluntary contraction of the neck extensor or facial muscles enhances the response. A markedly enlarged reflex may help differentiate an upper motoneuron lesion in clinically equivocal cases. Click stimulation evokes a short-latency myogenic potential of vestibular origin in the neck muscle.[35,37] Click intensity and prestimulus tonic contraction of the sternocleidomastoid muscle jointly determine the amplitude of the vestibular click-evoked myogenic potential.[151]

Other less commonly reported studies include head extensor reflex,[144] trigemino-cervical-spinal reflex,[221] spinal reflex during assisted locomotion after complete spinal cord injury,[19] vestibulocollic reflexes in the sternocleidomastoid muscle,[36] primitive reflexes such as snout, glabellar, corneomandibular reflexes,[32] and inhibitory trigemino-facial reflex.[193]

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10

Other Techniques to Assess the Peripheral Nerve

Abbreviations: AIDP—acute inflammatory demyelinating polyneuropathy, ALS—amyotrophic lateral sclerosis, AMAN—acute motor axonal neuropathy, AP—amino pyridine, CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, CTS—carpal tunnel syndrome, ECG—electrocardiogram, E1—active electrode, E2—reference electrode, E/I ratio—expiratory/inspiratory ratio, EIM—electrical impedance myography, EMG—electromyography, gIR—inward rectification, gK_f—fast potassium conductance, gK_s—slow potassium conductance, HSMN—hereditiary sensory motor neuropathy, Hz— hertz, IH—inward rectifier, KHz—kilohertz, LEMS—Lambert-Eaton myasthenic syndrome, mA—milliampere, MG—myasthenia gravis, MMN—multifocal motor neuropathy, MND—motor neuron disease, MUNE—motor unit number estimates, MUNIX—motor unit number index, MUP—motor unit potential, mV—millivolt, Na^+—sodium, NCS—nerve conduction study, QST—quantitative sensory testing, R-R intervals—heart-rate duration between beats, SD—standard deviation, SMA—spinal muscular atrophy, SSR—sympathetic skin response, TEA—tetraethyl ammonium

1. STUDIES OF THE AUTONOMIC NERVOUS SYSTEM

Electrophysiologic evaluations of the sympathetic and parasympathetic pathways help confirm a clinical diagnosis of autonomic neuropathy.[126] Some studies readily performed in a clinical neurophysiology laboratory complement invasive investigations required for precise localization of the site of the lesion. Autonomic functions change with age, requiring appropriately matched control values for comparison.[209]

Noninvasive studies for cardiovascular function include heart-rate (R-R intervals) variation with breathing, spectral analysis of heart rate, valsalva ratio and vagal reactivity tested by blood pressure, and heart-rate response to changes in posture and to eyeball pressure.[91] Evaluation of sudomotor function[208] consists of sympathetic skin response (SSR), thermoregulatory sweat test, quantitative sudomotor axon reflex test,[307] skin and muscle vasomotor reflex,[360] skin conductance response,[200] and sweat imprint.[210] Those routinely used in a clinical neurophysiology laboratory comprise R-R intervals and SSR.[292]

Heart-Rate Variation with Breathing

The heart rate shows a physiologic increase during inspiration and a decrease during expiration as measured by R-R intervals of an electrocardiogram (ECG). To test the degree of this change, the patient breathes deeply in a recumbent position at the rate of 6 breaths per minute for 1 minute after a resting period of 5 minutes. A standard electromyographic (EMG) instrument suffices to record ECGs with a surface electrode placed at the midpoint of the left clavicle and the other electrode over the sternum.[122,313]

Whether tested manually or using automatic methods of analysis, the difference between the shortest and longest R-R intervals during 1 minute serves as the most reliable measure, showing little intraindividual variation.[313] With deep breathing, heart rates should normally change more than 15 beats per minute, although the changes decline with age.[137,211,313] Values of less than 10 beats usually indicate an abnormality. The expiratory/inspiratory ratio (E/I ratio) provides another measure of R-R variation, defined as the mean of the maximum R-R intervals during expiration over the mean of the minimum R-R intervals during inspiration. Subjects under age 40 should have an E/I ratio above 1.2, which then decreases with age.[137]

The respiration-induced variability of the heart rates,[94] determined mainly by vagal activity, reveals parasympathetic function. Atropine but not propranolol blocks its increase during inspiration.[149] Patients with diabetes and other disorders of autonomic pathways show a decrease in breathing-induced heart-rate variation.[204,276] Other conditions associated with abnormalities of heart-rate variability include brain damage after head injury.[320]

Valsalva Ratio

The Valsalva maneuver, or a brief period of forced expiration against a closed glottis or mouthpiece, increases the heart rate by stimulating the intrathoracic stretch receptors such as the carotid sinus and aortic arch baroreceptors. The subject lies in a semirecumbent position with a rubber clip over the nose and breathes forcefully into a mouthpiece for 10–15 seconds, maintaining an expiratory pressure of 40 mm Hg. The Valsalva ratio, calculated by dividing the longest R-R interval after the maneuver with the shortest R-R interval during the maneuver, measures the changes of heart rate resulting from the cardiac vagal efferent and sympathetic vasomotor activity.[195] The highest ratio from three successive attempts, each separated by 2 minutes, normally exceeds 1.4 in subjects under age 40. The Valsalva ratio reflects both parasympathetic and sympathetic function. Blood pressure decline and recovery during Valsalva maneuver also help evaluate the degree of sympathetic failure.[253]

Response to Change in Posture

On standing from the supine position, the heart rate increases usually from 10 to 20 beats per minute. After reaching a maximum at about the 15th heart beat, it declines to a relatively stable rate at about the 30th heart beat. The ratio of

the R-R intervals corresponding to the 30th and 15th heart beats, termed *the 30:15 ratio*, measures parasympathetic function.[88] Young adults should have a ratio of more than 1.04. Atropine blocks the effect, suggesting its dependency on vagal innervation of the heart.[88] Heart-rate responses measured on a tilt-table also normally increase 5 to 30 beats per minute, without the biphasic response seen on standing. This change also declines with age.[137]

Sympathetic Skin Response

Unmyelinated fibers do not contribute to the surface recorded responses measured in the conventional nerve conduction studies (NCS). Recording SSR using a noninvasive technique provides a means to test these axons.[110,293] A surface electrode placed on the palm of the hand (Fig. 10-1) or sole of the foot (Fig. 10-2) serves best as the active electrode (E1) with the reference electrode (E2) on the dorsal surface of the same limb. In contrast, E1, if placed on the axilla, forearm, or dorsal surface of the hand or foot, usually fails to register a response, probably reflecting the paucity of sweat glands. Recording a long-latency response (Fig. 10-3) with low-frequency components requires a very slow sweep down to 0.5 to 1 second per division, a high gain up to 100 μV per division, and a wide band-pass in a range of DC to 2–3 KHz. Any stimuli will suffice if presented as a surprise. These include a loud noise delivered unexpectedly, respiratory stimulation,[167] and a more commonly used electrical shock, 0.1 ms in duration and 10–20 mA in intensity, applied to the ipsilateral or contralateral wrist, ankle, or any digit.[293]

Randomly timed electrical stimuli over the median nerve elicit a biphasic potential with either the initial negativity or positivity over the palmar surface of the hand and the plantar surface of the foot. In one study of 35 healthy subjects,[153] mean latencies increased from the wrist to the middle phalanx but then decreased to the distal phalanx. This finding may reflect density difference of sweat glands, which dictates sympathetic sudomotor nerve activity. A high density of sweat glands also explains a shorter latency of SSR when recorded in the palm as compared to the forearm.[333] In one study of 30 healthy subjects, normal values (mean ± SD) for palmar and plantar responses consisted of the onset latency of 1.5 ± 0.1 sec and 2.1 ± 0.2 sec and amplitude of 479 ± 105 μV and 101 ± 40 μV. Another study[84] showed the normal mean onset latency and amplitude of 1.5 ± 0.1 sec and 3.1 ± 1.8 mV for the hands, and 2.05 ± 0.10 sec and 1.4 ± 0.8 mV for the feet.

Neither the sites[336] nor the type of stimulation[287] alters the onset latency with any consistency. In contrast, the density of spontaneously activatable sweat glands determines the response as a measure of peripheral sympathetic activity. Lower temperatures reduce the amplitude and prolong the latency. In one study,[74] cooling the

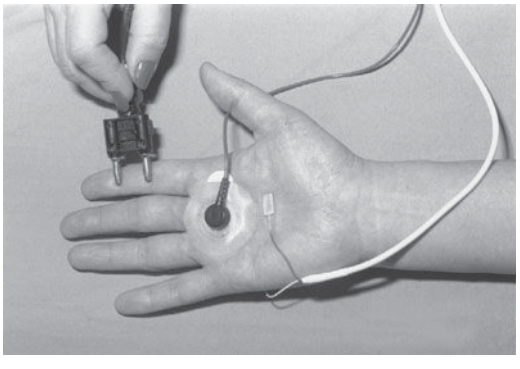

FIGURE 10-1 Electrical stimulation of the index finger and recording of sympathetic skin response over the palm (E1) and the dorsal surface (E2) of the same hand.

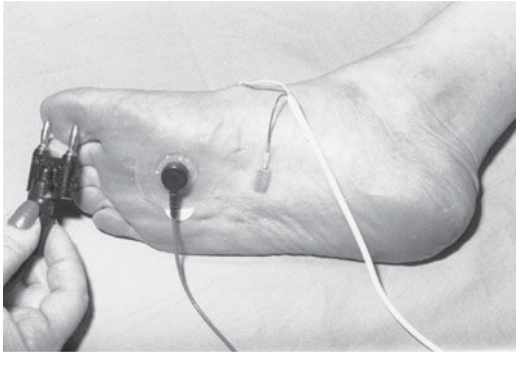

FIGURE 10-2 Electrical stimulation of the big toe and recording of sympathetic skin responses over the sole (E1) and the dorsal surface (E2) of the same foot.

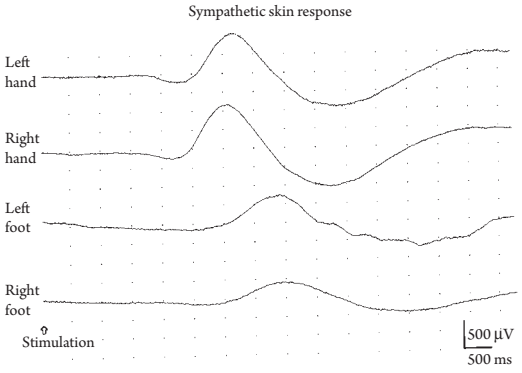

FIGURE 10-3 Sympathetic skin responses recorded simultaneously in four limbs of a normal subject following electrical stimulation of the left wrist. A greater latency for the foot as compared to the hand responses in part reflects different lengths of the descending pathways. Oscilloscope settings consisted of very slow sweep (500 ms/division), high gain (500 μv/division), and a wideband pass (0.16 to 3 KHz).

whole arm as compared to the hand induced a greater effect in latency but not in amplitude. Thus, amplitude change reflects only the neuroglandular junction, whereas latency modulation also involves the postganglionic sympathetic C fibers. In another study,[197] elevating the temperature over the 32°C–34°C range increased the amplitude by 8.5% and decreased the latency by 2.5% per degree.

Magnetic stimulation applied to the neck evokes easily recordable, highly reproducible SSR, reflecting strong afferent sensory inputs proximally. These potentials showed an orderly latency gradient from proximal to distal sites of all limbs.[205,337] Reported onset latencies include 1.0 ± 0.1 sec (mean ± SD) for the arm, 1.2 ± 0.1 sec for the forearm, 1.1 ± 0.1 sec for the thigh, 1.5 ± 0.1 sec for the calf, and 1.7 ± 0.2 sec for the sole.[335] Stimulus intensity may alter the waveform of SSR evoked by magnetic stimulation.[332]

Although SSR can occur in the absence of normal sweat gland function, its abnormalities in general correlate reasonably well with other sweat tests and certain other measures of autonomic function.[292] Its variability and rapid habituation,[57,80] combined with a nonquantitative nature, tend to limit clinical application. Some consider only its absence or major reduction in amplitude as a definite abnormality,[331] whereas others regard a prolonged latency as a sign of neuropathy.[76,80] Iontophoresis of atropine into the skin under the recording site abolishes the response.

Studies showed absent or reduced responses in patients with diabetes,[197,368] scleroderma,[275] familial amyloid polyneuropathy,[300] and history of sympathectomy.[194,207] Ischemic conduction block of the arm abolishes the previously obtainable responses.[336] Other disorders associated with SSR abnormalities include lepromatous leprosy,[47] hereditary motor sensory neuropathy (HMSN),[77] chronic uremia,[356] Meniere disease,[362] epilepsy,[304] palmar hyperhidrosis,[203] peripheral occlusive disease,[12] carpal tunnel syndrome (CTS),[154,240] and cochlear implant with altered auditory thresholds to loud noise.[267] Normal autonomic function characterizes Friedreich's ataxia, which primarily involves large myelinated fibers, sparing smaller fibers.[136]

The SSR also reflects preganglionic sympathetic activity, providing information different from the somatic pathway in evaluating myelopathy[363] and other heterogenous group of system diseases such as multiple sclerosis,[85,204,363] amyotrophic lateral sclerosis (ALS),[78] Parkinson's disease,[95,355] and rheumatoid arthritis.[326] Patients show no detectable asymmetry in the foot as the result of L5 or S1 radiculopathies[8] or after sural nerve biopsy.[263] The enhancement of SSR recovery curve in patients with palmar hyperhidrosis suggests hyperexcitability of the somatosympathetic polysynaptic pathway.[219]

2. MOTOR UNIT NUMBER ESTIMATES

In a neuromuscular disorder characterized by a loss of lower motoneuron function, the muscle strength depends primarily on the number of remaining motor units. Although the amplitude of the compound muscle action potential (CMAP) usually changes in proportion to the number of axons, abnormally large motor unit potentials (MUPs) after reinnervation partially restore the size, thus concealing the loss of axons. Despite the loss of over one-half of its motor innervation, a muscle may maintain its normal amplitude as well as force. Dividing the CMAP by the average size

of an individual MUP would reveal the remaining number of motor axons.

A variety of techniques devised for motor unit number estimate (MUNE)[45,226,314] relies on this principle. All the methods have two assumptions: (1) CMAP represents the sum of all motor unit potentials, and (2) sampling provides a fair estimate of the size of individual elements. In a strict sense, neither holds. In particular, the accuracy of the estimated number depends, among other factors, on the adequacy in sampling the representative population of single unit size, which varies considerably in normal subjects and, to a much greater extent, in patients with neuromuscular diseases. Validation of an incremental MUNE technique in rabbits showed a high degree of reproducibility but poor correlation with histological fiber counts.[72]

Compound Muscle Action Potential

The amplitude of a CMAP does not directly relate to the total number and size of muscle fibers[134] as phase cancellation distorts the pattern of summation.[11,90] Also peripheral nerve stimulation activates not one but all the muscles innervated by that nerve. Thus, the response simply represents a sum of all the activity from multiple sources, each contributing to a greater or lesser extent, depending on their spatial relationship to the recording electrodes. Another technical concern centers on the intensity of stimulation that must activate all the excitable motor axons. During the process of demyelination or regeneration, an ordinarily adequate stimulus may fail for the nerve with an abnormally elevated threshold. The use of submaximal stimulation would underestimate the motor unit number.

Sampling of Single Motor Unit Potential

In general, direct counts provide a reliable, reproducible result up to a maximum of 10 units. With a greater number, an overlap conceals the exact number of all the units, necessitating the selection of a subset for calculation of an average size of a single MUP. Technical limitation in achieving unbiased selection constitutes a major source of error. If all the motor units in the muscle give rise to nearly identical potential, then sampling a subset constitutes a valid approach. Variation among different motor units causes sampling error, especially with a non-Gaussian distribution. Thus, assessing a greater population leads to more reproducible results.[306]

In chronic neurogenic processes with a reduced number of larger potentials, the ease of measuring individual units compensates for the inaccuracy resulting from a pathologically increased variation of unit size. A severe neurogenic process may reduce the number of axons to a level that allows identification of all the existing motor units individually. In patients with defective neuromuscular transmission, both CMAP and MUP may vary in size from one stimulus to the next, necessitating a special interpretation. These include myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), ALS, and neurogenic processes with ongoing reinnervation. With a decrement of CMAP on slow repetitive stimulation, for example, the calculated value falls short of the actual number of motor units, unless MUP size recorded also show the same decline.

Methods for Quantitative Assessments

The methods described for MUNE include (1) all-or-none increments of CMAP; (2) F-wave measurements; (3) spike-triggered averaging, and its variant, decomposition-based quantitative EMG; and (4) statistical estimates. Of these, spike-triggered averaging relies on voluntary recruitment, whereas the remaining three measures use nerve stimulation to record individual elements.[79,226] Different methods place varying technical emphasis on meeting the underlying assumptions mentioned earlier, although basic principles remain the same. All these techniques, when properly executed, yield the same order of estimates.[46,295]

The original incremental method,[225,226] the easiest and most direct approach, counts a single MUP one by one. Based on the all-or-none characteristic of nerve activation, application of finely controlled current in very small steps allows measurement of successively recruited individual

motor units. The maximal muscle action potential divided by the average size of the stepwise increments yields the estimated number of motor units. In incremental methods, a selection bias for more easily activated larger motor units would overestimate the size of individual elements and consequently underestimate the motor unit numbers. This technique may also fail to identify the increments by a very small MUP, such as a nascent unit or those seen in severe myopathies. Several modifications introduced to minimize these errors also tend to favor the low-threshold large motor units with a selection bias against the high-threshold small motor units.[97,341] As a variation, stimulating the nerve at several points with a very low intensity yields only the first recorded single MUP.[5,79,107,339] The average of the MUP obtained with stimulation along its course serves as a unit discharge, which, when divided into the maximal CMAP potential, yields MUNE. The use of the collision technique may alleviate the risk of stimulating the same motor axon at different points along the nerve.[9]

The firing threshold for an individual axon varies in time. Thus, at any given stimulus intensity, different axons may discharge according to their probability of firing. If two motor axons have similar excitability, a threshold stimulus may activate them together or alternately. This possibility, termed *alternation*, constitutes another source of error, recognizing three distinct potentials in the presence of two units, one each or both together. Similarly, in the case of three motor units, alternation could result in an erroneous count of seven instead of the actual number of three. As mentioned later, the stochastic approach[305] avoids such an error by using cluster analysis to sort out the templates of the individual elements from all potentials recorded at a fixed intensity.

The F-wave method relies on the assumption that repeater F waves represent single rather than multiple motor units. If so, dividing the maximal muscle response by their average size yields the number of motor units.[171] Alternation can occur as described earlier. The mistaken inclusion of F waves activated by multiple rather than single motor units inflates the average size of individual elements, lowering the estimated number.[66] Automated use of submaximal stimulation and template matching reduces the risk and improves the accuracy.

Spike-triggered averaging uses a two-channel recorder to isolate voluntarily activated motor units as a measure of single MUP.[68] The technique consists of detecting single units by a needle electrode on the first channel and averaging its size using a pair of surface electrodes on the second channel. An amplitude-trigger window selects the units recorded by single-fiber, bipolar concentric, standard concentric, or fine-wire electrodes. Their average size divided into the maximal CMAP recorded from the same surface electrode yields the number of motor units. Multichannel recording may resolve several methodological limitations of single-channel recording in assessing MUP.[29] As a variant, motor units recruited at three levels of effort and recorded at two locations on the surface provide a broader sampling.[294]

The sources of error unique to this method include recording with a spurious and erroneous trigger[44] and missing some motor units at the surface, unless studying the muscle located superficially.[15] Furthermore, voluntary activation preferentially recruits smaller motor units, without recruiting larger units. Despite these concerns, the method provides the values comparable to those expected from histologic studies and those obtained with other methods of recording. Some authors propose the use of decomposition-based quantitative EMG to aid analyses.[31,69] This technique consists of identifying a minimum of 20 units by needle-detected signal decomposition and uses the corresponding surface signals to divide into the maximal CMAP.

In contrast to all the other methods, the statistical approach makes no attempt to identify individual motor units. Instead, it takes advantage of intermittent firing of individual motor units near threshold that results in variation in the size of a submaximal CMAP.[28,30,70,124,129,231,257] It relies on Poisson statistics to calculate the size of the individual steps based on their known relationship to the variance of multiple measures of step functions. In this type of analysis, the sizes of a series of measurements represent multiples of the size of a single component, and the variance of their distribution provides an estimate of the

average size of the individual components making up each measurement. Obtaining adequate estimates of motor units calls for testing the axons with different thresholds at multiple stimulus intensities.

The statistical method has the advantage of not requiring identification of individual components producing increments too small to isolate at gains used to record a high-amplitude CMAP. It also circumvents the possible miscalculation caused by alternation with activation of the same units in different combinations. The technical problems include the need for a larger sample size, requiring patient cooperation to undergo over 100 low-intensity stimuli. The remaining motor units not tested at the stimulus intensities used for sampling do not contribute for calculation. Thus, this stimulus strength influences the final result excessively.[297] Defective neuromuscular transmission also causes inaccuracies in this measurement resulting from varying sizes of an MUP.[148] A shift from Poisson to normal distributions can produce errors of up to 10%, necessitating a display of the histogram of the individual responses.

Another technique called motor unit number index (MUNIX) yields a measure related to number of motor units, using a mathematical model based on CMAP and the surface EMG interference pattern.[242,247] In one series, patients with ALS with reduced number of motor units showed a higher test-retest reproducibility of MUNIX than control subjects.[3,246]

Normal Values and Clinical Application

Normal values, though they vary among authors using different techniques, range from 200 to 350 for the thenar muscles, 150 to 220 for the extensor digitorum brevis, and 60 to 150 for the tibialis anterior.[70,227] According to histological estimation, the flexor digit minimi has about 130 motor units.[245] This compares to 411 MUNE for the four hypothenar muscles by an automated incremental method.[98] Few studies report on proximal muscles because of the technical difficulty. The number of motor units remains stable for a given muscle except for a mild decrease in the elderly.[45,97] Table 10-1 summarizes normal MUNE obtained by the statistical method tested at different stimulus intensities for distal muscles innervated by median, ulnar, and tibial nerves.[70]

Earlier clinical studies used near-threshold methods.[79,225] This worked well in testing a muscle with a reduced number of motor units, allowing individual recognition of each unit, which in turn, improved reproducibility. The method tends to underestimate the number of motor units in myopathies, which render some of the increments too small to identify. A 20% accuracy gives estimates in the range of 16–24 for 20 motor units and 160–240 for 200. Thus, a larger number of units make a small loss harder to detect. Stimulus currents above 15% of threshold also yield unreliable results even in normal subjects.

The MUNE supplements conventional studies in documenting a loss of motor units, as shown in patients with congenital brachial palsy,[289] tetraplegia,[106] hereditary motor sensory neuropathy (HMSN I),[344] ALS,[2,187,190] and spinal muscular atrophy (SMA).[99] It also serves to quantitate the loss of motor units in follow-up studies of motor neuron disease (MND),[247,302,340] facial paralysis,[361] and other neurogenic processes.[32,118,296,312,365] The technique, however, sheds no light on the functional status of the surviving motor units.[62,64] The method also failed to characterize focal conduction block, presumably because predominant loss of large-diameter motor axons tends to conceal the magnitude of motor unit loss.[147]

3. ASSESSMENT OF REFRACTORY PERIOD AFTER SUPRAMAXIMAL STIMULATION

This section reviews the modulation of axonal excitability following the passage of an action potential,[52,238,319] which still remains elusive even in the study of a single axon. The variously altered excitability of many motor or sensory fibers collectively determines the size of a compound potential. Its analyses will yield even more complex, yet important biophysical information.

Table 10-1 Statistical MUNE in 30 Normal Subjects

STIMULUS LEVEL	MEDIAN THENAR	ULNAR HYPOTHENAR	PERONEAL EDB	TIBIAL ABDUCTOR HALLUCIS
5%–10%	210/90	285/105	154/52	310/195
15%–20%	185/85	223/110	137/45	250/167
40%–50%	153/70	154/70	135/38	195/154
70%–90%	175/85	213/115	105/35	202/115
Multipoint	234/95	256/115	158/58	285/187

Statistical motor unit number estimate (MUNE) in 30 normal subjects tested at different stimulus intensities, showing the mean and lower limit (XX/YY) for each stimulus level for each nerve. Multipoint recordings measured MUNE at 5%–10 %, and at 15%–20% at two distal sites, 1 cm apart along the nerve. (Modified from Daube.[70])

Absolute and Relative Refractory Period

After passage of an impulse, an axon becomes totally inexcitable for a fraction of a millisecond during the absolute refractory period, then gradually recovers to its prestimulus excitability within the ensuing few milliseconds during the relative refractory period. Direct measurement of the nerve action potentials in experimental animals substantiates the results in human studies, mostly tested in the sensory or mixed nerves. When measured by muscle response, the refractory period depends not only on the excitability of the nerve but also the status of the neuromuscular junction, as implied by the term *refractory period of transmission*.[102] Modified paired-shock techniques, however, help delineate the nerve refractory characteristics per se, excluding the influences of other components.[132,166,172,279] Although a considerable amount of data has accumulated in the area of the refractory period, its clinical application remains unclear.[165]

The physiologic mechanism underlying the refractory period centers on inactivation of sodium conductance (see Chapter 2–3). After the passage of an impulse, sodium channels will close to initiate repolarization. Once closed, or inactivated, they cannot open immediately, regardless of the magnitude of depolarization by a subsequent impulse. This constitutes the absolute refractory period, lasting 0.5–1.0 ms. During the subsequent relative refractory period, lasting 3–5 ms, which corresponds to the hyperpolarizing after-potential, only an excessive depolarization, far beyond the ordinary range, can reactivate sodium conductance. Here, the impulse propagates more slowly than usual because it takes longer to reach the elevated critical level required to generate the action potential. The refractory period lengthens with low temperature,[48,54] advanced age,[73] slow conduction velocity, and demyelination.[309,310]

Paired Shock and Collision Technique

A second shock delivered at a varying time interval after the first reveals excitability changes induced by the preceding impulse. In this method, called the paired-shock or conditioning and testing technique, the first shock conditions the nerve and the second impulse tests the effect. The test stimulus, given during the absolute refractory period of the conditioning stimulus, elicits no response. During the relative refractory period that ensues, the test response shows reduced amplitude and increased latency. After extensive investigation in experimental animals, the paired-shock technique has found its way to the study of human sensory potentials[48,318,323] and mixed nerve potentials.[103,214]

In testing the motor fibers with the short interstimulus interval required for the study of the refractory period, the muscle responses elicited by the first and second stimuli overlap. A computerized subtraction technique circumvents this problem by separating the test stimulus from the

conditioning muscle response. The size of the test response measured thereby, however, still depends on the excitability change of not only the motor axons but also the neuromuscular junction and muscle fibers. Therefore, this technique, based on successively evoked muscle responses, fails to measure the nerve refractory period per se. A collision technique originally devised to avoid this difficulty determines the refractory period of antidromic motor impulses by paired distal stimuli followed by an appropriately timed single proximal stimulus, which measures the test volley.[132]

Alternatively, paired proximal stimuli, combined with a single distal stimulus, allow assessment of orthodromic motor impulses, eliminating the effects of the muscle and neuromuscular junction.[164] In this arrangement, the descending impulse generated by the first of the paired axillary shocks, $S(A_1)$, eliminates the antidromic impulse from the distal shock at the wrist, S(W). The impulse of the second axillary stimulus, $S(A_2)$, will propagate distally along the motor fibers cleared of antidromic activity (Fig. 10-4). Its magnitude and speed depend solely on the neural excitability after passage of the conditioning stimulus, $S(A_1)$. The $S(A_1)$-to-S(W) time interval dictates the point of collision and consequently the length of the nerve segment made refractory by $S(A_1)$, before its elimination by the antidromic activity of S(W). Changing the $S(A_1)$-to-$S(A_2)$ time interval defines the range of the absolute refractory periods of the different motor fiber by demonstrating the serial recovery of the test response amplitude (Fig. 10-5A). In contrast, the latency of the test response elucidates the duration of the relative refractory period of the most excitable fibers (Fig. 10-5B). Table 10-2 summarizes the results in 20 ulnar nerves from 10 healthy subjects studied in our laboratory.[166]

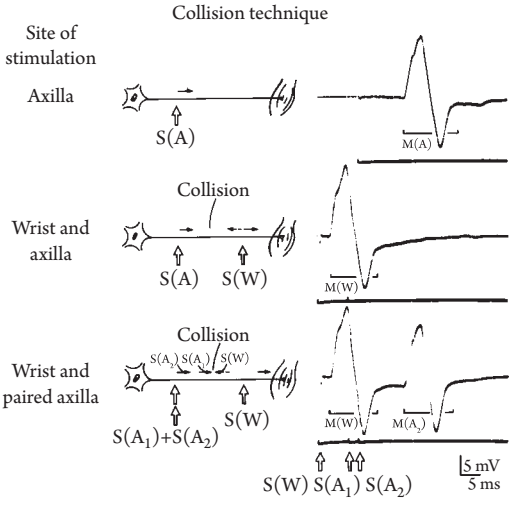

FIGURE 10-4 Compound muscle action potentials recorded by surface electrodes placed over the abductor digiti minimi after stimulation of the ulnar nerve. The diagrams on the left show the collision between orthodromic (solid arrows) and antidromic (dotted arrows) impulses. Axillary stimulation, S(A), given 6.0 ms after the stimulus at the wrist, S(W), triggered sweeps on the oscilloscope. With single stimulation at the axilla and at the wrist (middle tracing), the orthodromic impulse elicited by S(A) collided with the antidromic impulse of S(W) from the wrist. With paired shocks at the axilla (bottom tracing), M(A2) appeared because the first axillary stimulus, S(A1), cleared the path for the second stimulus, S(A2). (Modified from Kimura, Yamada, and Rodnitzky.[166])

Changes in Amplitude versus Latency

The amplitude changes of the test response obtained with shocks of maximal intensity follow a nearly identical course irrespective of the length of the refractory segment (Fig. 10-6). Therefore, reduction in amplitude of the test response must result from failure of nerve activation at the site of stimulation, rather than cessation of propagation along the course of the nerve. The impulse conducts at a slower speed than normal, if transmitted at all, during the relative refractory period, showing the greatest delay near the absolute refractory period (Fig. 10-7). Thereafter, the conduction progressively recovers to normal as the interstimulus interval between the conditioning and test stimuli increases. The length of the refractory segment, which hardly influences the recovery of the amplitude, substantially alters the time course of the latency. The longer the refractory segment, the greater the change in latency of the test response. The delay, however, does not increase linearly in proportion to the length of the refractory segment; in fact, a change in latency per

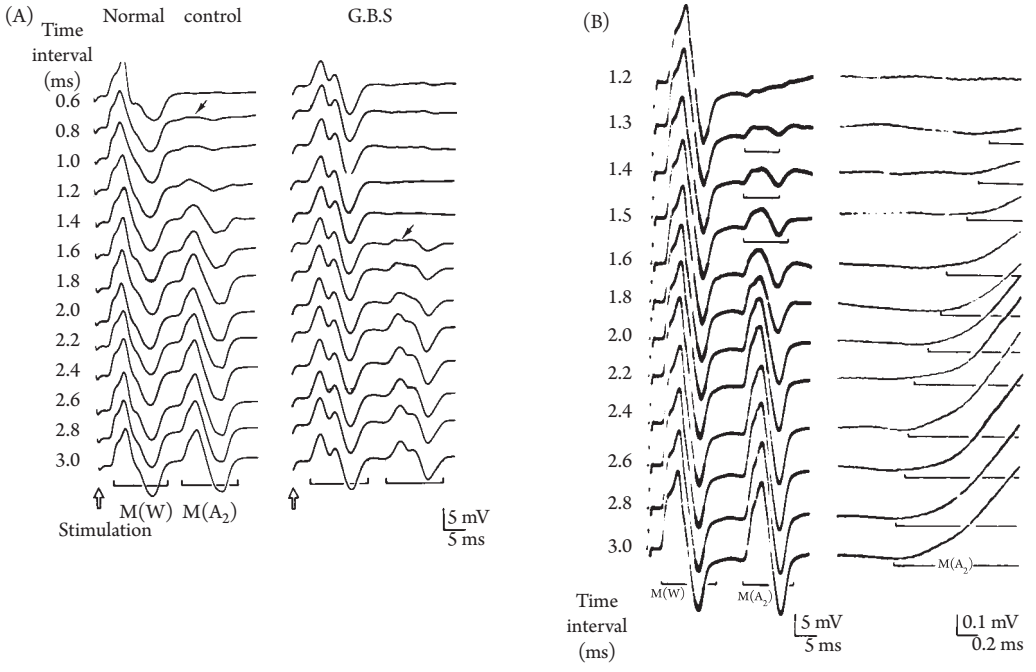

FIGURE 10-5 (***A***) Paired axillary shocks, S(A1) and S(A2), of just maximal intensity combined with a single shock at the wrist, S(W). Interstimulus intervals between S(A1) and S(A2) ranged from 0.6 to 3.0 ms. S(A2) always occurred 5.0 ms after S(W), which triggered sweeps on the oscilloscope. In the normal subject, M(A2) first appeared (small arrows) at an interstimulus interval of 0.8 ms and recovered completely by 3.0 ms. The patient with Guillain-Barré syndrome showed delayed and incomplete recovery. (Modified from Kimura.[163,164]) (***B***) Paired axillary shocks, S(A1) and S(A2), of just maximal intensity combined with a single shock at the wrist, S(W) (cf. bottom tracing in ***A***). Delivering S(A1) 6.0 ms after S(W) allowed collision to occur 1.5 ms after S(A1). The interstimulus intervals between S(A1) and S(A2) ranged from 1.2 to 3.0 ms in increments of 0.2 ms. The figures on the left show amplitude measurements with a slow sweep triggered by S(W). The figures on the right illustrate latency determination with a fast sweep triggered by S(A2) and displayed after a predetermined delay of 11.0 ms. (Modified from Kimura, Yamada, and Rodnitzky.[166])

unit length decreases for a longer conduction distance. Therefore, the average conduction velocity improves as the refractory segment increases in length (Fig. 10-8).

These findings confirm the results of an animal study[330] that indicate the following: (1) a delay of the test impulse during the refractory period allows an increasing interval between conditioning and test impulses as they travel further distally, and (2) an increasingly longer interval between the two impulses, in turn, leads to progressive recovery of the test impulse conduction velocity. Because of this regressive process, the test impulse conducts at a relatively normal speed by the time it reaches the end of the refractory segment, especially for a longer nerve.[164] Electrophysiologic studies of human sensory fibers[48] as well as computer simulation have shown the same relationship between the refractory period and the length of the nerve segment.[358] The absolute and relative refractory periods affect motor fibers,[166] sensory fibers, and mixed fibers[103] alike. For example, full recovery in the amplitude of the test response precedes full recovery of the conduction velocity, regardless of the type of the nerve fibers tested.[48,103,131,166]

Human studies of the refractory period suffer from technical limitation in precisely measuring the amplitude and latency of the test response. Specific problems include small signals, unstable baseline, gradual onset of the evoked response, and partial overlap of the test response with the preceding events, despite the use of a collision technique. A computerized cross-correlation

Table 10-2 Interstimulus Intervals of the Paired Shocks and Conduction Velocity of the Test Response (Mean ± SD)

LENGTH OF REFRACTORY SEGMENT	INITIAL RECOVERY IN AMPLITUDE (TEST RESPONSE >5% OF UNCONDITIONED RESPONSE)		FULL RECOVERY IN AMPLITUDE (TEST RESPONSE >95% OF UNCONDITIONED RESPONSE)		FULL RECOVERY IN VELOCITY (>95%)
	INTERSTIMULUS INTERVAL BETWEEN PAIRED SHOCKS (ms)	CONDUCTION VELOCITY OF TEST IMPULSE (% OF NORMAL)	INTERSTIMULUS INTERVAL BETWEEN PAIRED SHOCKS (ms)	CONDUCTION VELOCITY OF TEST IMPULSE (% OF NORMAL)	INTERSTIMULUS INTERVAL BETWEEN PAIRED SHOCKS (ms)
A distance normally covered in 0.5 ms	1.16 ± 0.18	55.3 ± 19.2	2.11 ± 0.50	81.2 ± 17.4	2.65 ± 0.65
A distance normally covered in 1.5 ms	1.18 ± 0.16	70.3 ± 13.5	2.16 ± 0.52	87.3 ± 14.2	2.36 ± 0.45

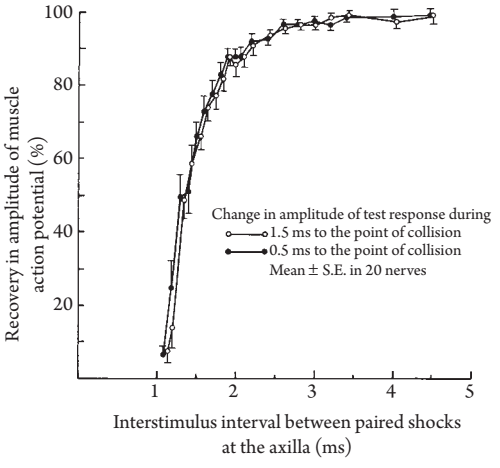

FIGURE 10-6 The pattern of recovery in amplitude of M(A2) during the refractory period in 10 healthy subjects. The return of M(A2) followed the identical time course with the passage of impulse along the shorter (0.5 ms) or longer refractory segment (1.5 ms). The gradual increase of M(A2) indicates the range of the absolute refractory periods of different motor fibers. (Modified from Kimura, Yamada, and Rodnitzky.[166])

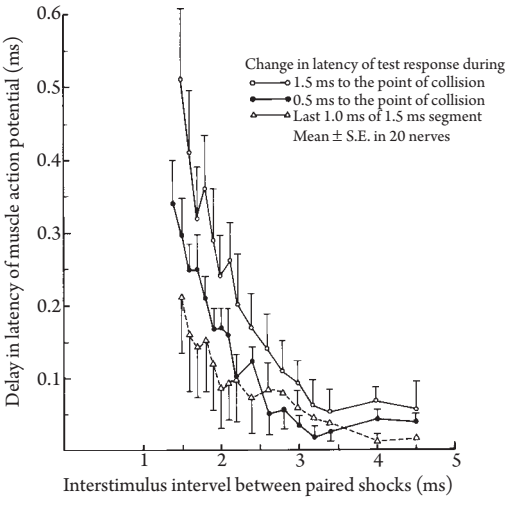

FIGURE 10-7 The pattern of recovery in latency of M(A2) in the same subjects as shown in Figure 10-6. The curve shows the latency difference between the response to a single axillary shock, M(A), and the response to the second axillary shock, M(A2). The passage of impulse across the longer refractory segment (1.5 ms) showed significantly slower recovery as compared with the shorter refractory segment (0.5 ms). The bottom curve (triangles) plots the difference in delay of latency between 1.5 ms and 0.5 ms segments. The values so calculated represent the delay attributable to the last 1.0 ms of the 1.5 ms segment. (Modified from Kimura, Yamada, and Rodnitzky,[166] with permission.)

analysis helps improve numeric quantification of a CMAP in shape and latency.[89] In this method, the height of the peak in the correlation curve gives a shape-weighted measure of the size of the test response, and the time lag of the peak indicates the delay of the test response as compared with an averaged unconditioned muscle response. Another technique, called the double-collision method, alleviates the transient changes in nerve and muscle fiber conduction that can distort test muscle responses.[10,33,139,140]

A number of studies have shown prolongation of the refractory period of sensory and mixed nerve fibers in diseases of the peripheral nerve.[214,324] Patients with alcoholic neuropathy had an increased refractory period of the median sensory fibers.[6] In patients with chronic renal failure, the initially abnormal relative refractory period reverted to normal after hemodialysis.[213] An increased refractory period of median nerve sensory fibers in patients with multiple sclerosis suggested the possible involvement of peripheral nerve fibers in this disorder.[130] Conversely, hypokalemia of various origins shortened the relative refractory period.[224] Hyperglycemia alters refractory periods in human diabetic neuropathy.[234,327] In one series, acute motor axonal neuropathy (AMAN) patients had an increased relative refractory period with abrupt threshold increase at short interstimulus intervals indicating distal conduction failure.[189] In contrast, acute inflammatory demyelinating polyneuropathy (AIDP) patients had normal refractoriness.

Compared to recording from single motor units, studies of the whole nerve lack precision because fibers with different conduction characteristics contribute to the absolute and relative refractory period. Furthermore, in contrast to amplitude, which follows a predictable time course, small, often variable changes in latency provide limited value in clinical assessment. In

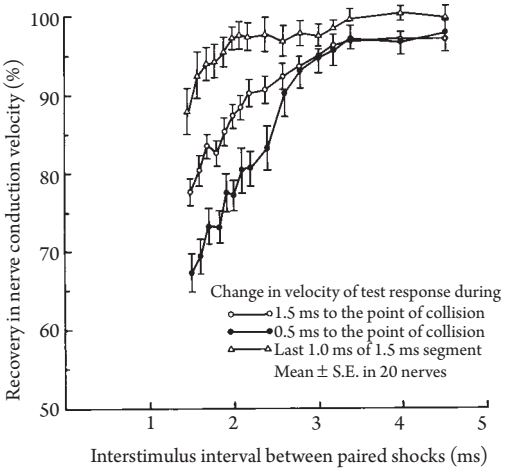

FIGURE 10-8 The time course of recovery in conduction velocity of M(A2) in the same subjects shown in Figures 10-6 and 10-7, calculated based on the delay of M(A2) in the segment proximal to the point of collision. In contrast to the pattern of recovery in latency (cf. Fig. 10-7), the conduction velocity returned significantly faster for the passage of impulse across the longer (1.5 ms) than the shorter (0.5 ms) refractory segment. The top curve (triangles) shows the estimated velocity of M(A2) over the last 1.0 ms of the 1.5 ms segment. (Modified from Kimura, Yamada, and Rodnitzky.[166])

general, the measurement of the refractory period has shown disappointing results in diagnosing diseases of the motor fibers and in elucidating their pathophysiology.

Super and Subexcitable Phases

Studies of the myelinated axons reveal early superexcitable and late subexcitable phases of threshold changes (see Chapter 4-3) after absolute and relative refractory periods.[319] Superexcitability reflects negative, or depolarizing, after-potential from long-lasting depolarization of the internodal axon.[16] Activation of fast potassium channels terminates this phase by regulating the conductance of the internodal axon membrane. Thus, blocking these channels by 4-amino pyridine (AP), breaks down the normal relationship between superexcitability and membrane potential.[14] The late subexcitability results from positive, or hyperpolarizing, after-potential that reflects two very different mechanisms: opening of slow potassium channels[319] and activation of an electrogenic sodium potassium pump triggered by intracellular sodium accumulation.[38,162] The confusing terms *negative and positive after-potentials* denote changes of membrane potential as viewed from outside the cell membrane, corresponding to the opposite, positive and negative shifts occurring intracellularly. Following a single supramaximal conditioning stimulus, the median nerve showed a greater threshold increase than the sural nerve during the late subnormal period.[201] This difference, consistent with lesser expression of slow potassium conductance, may explain a greater susceptibility to depolarizing stresses seen in the sural as compared to the median cutaneous afferents.

Compared to the conventional recovery cycle with a single conditioning stimuli, the use of paired conditioning pulse provides a greater threshold change for late subexcitability and a possibly clearer identification of a peak threshold change.[299] The hyperpolarizing effects intensify after the passage of a train of impulses, probably contributing to the rate-dependent conduction failure in demyelinating neuropathies. Long, high-frequency trains, however, lead to an opposite, hyperexcitatory state, causing posttetanic repetitive activity and ectopic discharges.[24] These paradoxical hyperexcitability and spontaneous discharges may account for neuropathic sensory disturbance and neuromyotonia (Bergmans, 1982).[25] Threshold tracking study of a single motor axon during posttetanic hyperexcitability[38] revealed a buildup of extracellular potassium ions. Rat axons show similar phenomena after injection of potassium ions into or under a myelin sheath.[71,155] A reversal of the electrochemical gradient causes the influx of potassium ions across the internodal axolemma into the axon. Resulting depolarization and further opening of potassium channels accelerate inward potassium current.

4. THRESHOLD TRACKING AFTER SUBTHRESHOLD STIMULATION

Classical Strength-Duration Curve

The threshold intensity just capable of exciting the axons varies according to the duration of the

current; the shorter the duration, the greater the intensity to achieve the same depolarization. The strength-duration curve plots this relationship with a motor point stimulation that elicits a constant muscle response (Fig. 10-9A,B). A long-duration shock excites both nerve and muscle, whereas a short-duration stimulus activates the nerve more effectively than the muscle. The excitability characteristics expressed by this curve, therefore, can differentiate a normally innervated muscle from a partially or totally denervated one. Numerical indices of excitability include (1) rheobase, or the minimal current strength below which no response occurs even if the current lasts infinitely or at least 300 ms, and (2) chronaxie, or the minimal duration of a current required to excite the cell at twice the rheobase strength. Although of historical interest, neither rheobase nor chronaxie has proven satisfactory as a test in clinical practice.[206] The strength-duration curve itself has fallen into disrepute because of the excessive time required for its determination and the complexity of its interpretation, but the test of nerve excitability remains an area of considerable theoretical and possibly clinical interest.

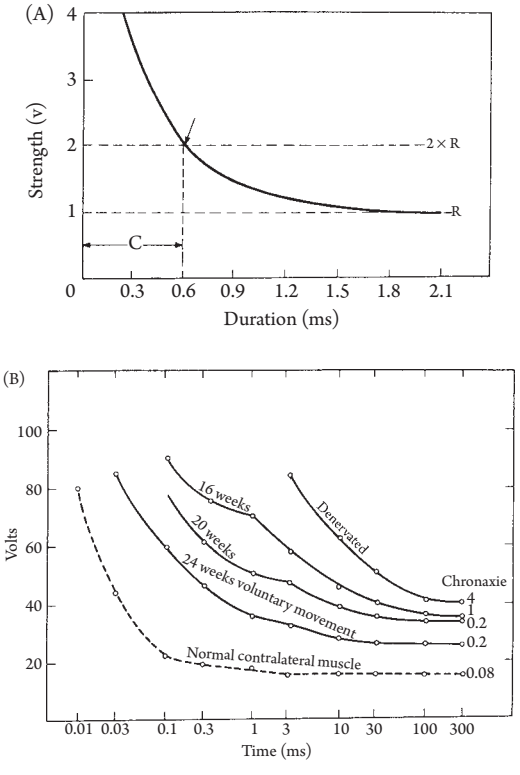

FIGURE 10-9 (***A***) The strength-duration curve showing the intensity (ordinate) required for each duration of stimulus (abscissa). In this example, the stimulus intensity required remains the same after the stimulus duration reaches 1.8 ms. This strength, or the rheobase (R), determines chronaxie (C) (arrow) defined as the duration along the strength-duration curve at a strength twice the rheobase (2 x R). (Modified from Ochs,[256]) (***B***) The normal strength-duration curve from a motor point of the abductor pollicis brevis compared to the dashed line plotting curves from the denervated muscle of the other hand. Determinations at different times during reinnervation showed the return of the strength-duration curve toward normal. (Modified from Ochs.[256])

Threshold Measurement

Axonal excitability also undergoes profound changes after subthreshold stimulation. Threshold tracking techniques test this type of nerve excitability to assess the membrane potential, properties of ion channels and electrogenic ion pumps.[40,158] Changing the environment may alter the threshold, for example, by inducing ischemia or applying preceding currents. As described in the previous section, a single shock or a train of supramaximal shocks, given as a conditioning stimulus, test refractoriness and superexcitability that follow the passage of an action potential (Fig. 10-10). In contrast, a brief or prolonged subthreshold current assesses subliminal excitability changes, which latent addition and threshold electrotonus measures. The threshold measurements all test the membrane properties of the nerve at a point of stimulation, thus complementing the conventional studies that measure the conduction characteristics of the axon along its length. The technique, therefore, is better suited for studying diffuse axonal properties, as in metabolic or toxic neuropathies, than focal abnormalities, as in segmental demyelination. Excitability studies using palm stimulation provide information in the terminal segment, which a variety of clinical conditions tend to affect preferentially.[354] Although these methods elucidate important insights into physiology and pathophysiology of

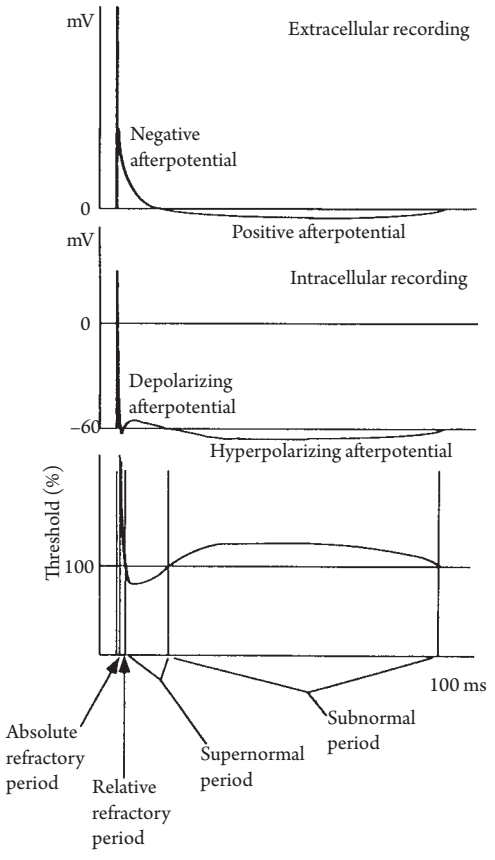

FIGURE 10-10 Nerve excitability changes following an action potential. (Modified from Ochs,[256] with permission.)

neuronal properties, their clinical utility awaits confirmation.

Strength-Duration Time Constant

In the simplest type of threshold tracking, only test stimuli delivered alone determine the nerve excitability change brought about by ischemia, hyperventilation, anesthetic agents, or other drugs.[359] Baseline studies consist of the application of a series of stimuli, stepped up and down, at regular intervals to determine the intensity required to activate a standard fraction (e.g., 40%) of the maximum muscle response. A repeated procedure then evaluates the new threshold compared to the control value after altering the environment. The changes detected by these means, if expressed in percentages, apply equally to both single-fiber and multifiber preparations.

As shown in the strength-duration curve, increased duration reduces the current strength needed to excite the same fraction of a CMAP. Threshold tracking tests this relationship in human peripheral nerve.[239] The old term, *chronaxie*, corresponds to the strength-duration time constant defined from the thresholds for just two pulses of different duration.[235] The sensory fibers with more prominent, persistent sodium conductance[41] have longer strength-duration time constants than the motor fibers.[235] Abnormalities may result from changes in resting membrane potential, sodium conductance, or myelination. Its increase by depolarization and decrease by hyperpolarization[38,41] reflect the voltage-dependent behavior of sodium conductance.

When the nodes under the stimulating electrode have a very high value in threshold, inadvertent excitation of the intact nodes further away may show a normal value in strength duration time constant. Therefore, studies may remain normal in carpal tunnel syndrome (CTS), despite abnormally high rheobase.[236] This limitation applies to all threshold-tracking techniques, making them unsuitable for studying focal neuropathies, especially if a pathologic segment shows hypoexcitability. In contrast, the method yields better in assessing a condition of peripheral nerve hyperexcitability. For example, patients with acquired neuromyotonia show an increased strength-duration time constant of motor but not sensory axons.[217] This finding suggests relative axonal depolarization, greater persistent sodium conductance, or enlarged nodal area as a result of paranodal demyelination.

Effect of Subthreshold Conditioning

Very brief subthreshold conditioning pulses produce a membrane potential, called "local response," confined to the node of Ranvier, and shows a decay regulated by the membrane time constant. It simply adds to the changes induced by a subsequent test stimulus, if given within a certain time, as implied by the term *latent addition*.[329] In contrast, currents longer than a few milliseconds affect not only the nodes but also the

myelin sheath, altering the potential difference across the internodal axon membrane. Activation of a variety of nodal and internodal ion channels regulates this type of change of membrane potential, termed *electrotonus*. The threshold to the subsequent stimulation also changes in association with electrotonus, as implied by the term *threshold electrotonus*.[6,14,35,36]

Latent Addition with Brief Conditioning

A brief subthreshold depolarizing current enhances the nerve excitability or lowers the threshold by making the membrane potential that much closer to the critical level of activation. In other words, a second stimulus generates an action potential more easily if applied to an already depolarized membrane. A brief hyperpolarizing currents show the opposite effect on the membrane excitability, elevating its threshold on the test stimulus (Fig. 10-11). One study of latent addition with depolarizing conditioning stimuli estimated the sensory fibers to have about three times larger average time constants of a local response than motor fibers.[262] This difference dropped to about one and a half with hyperpolarizing conditioning stimuli.[261] Another study,[41] using automatic threshold tracking, found a slower recovery from hyperpolarizing pulses than from depolarizing pulses in sensory fibers, although both motor and sensory fibers had a similar membrane time constant of about 45 μs. These findings suggest greater resting activation or persistent sodium conductance in the sensory fibers, which adds a slow component to the recovery of threshold from hyperpolarizing pulses and increases the strength-duration time constant.[41,161] Latent addition allows in vivo study of persistent sodium conductance, which may explain the mechanism underlying some forms of axonal hyperexcitability.[325] Patients with neuropathic pain have

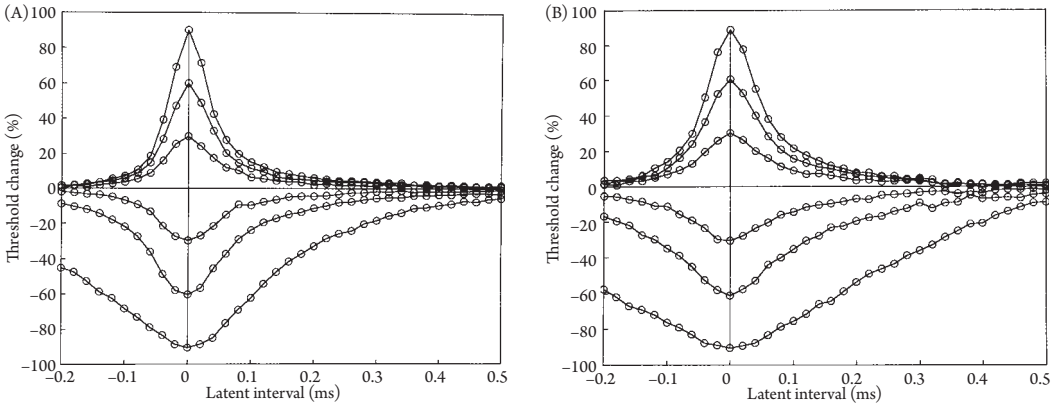

FIGURE 10-11 (***A***, *top*). Latent addition for the motor axons of a human ulnar nerve, plotting percentage threshold changes (ordinate) against time delay (abscissa). From top to bottom, the traces show time course of recovery after three sets each of hyperpolarizing and depolarizing conditioning stimuli of 60 μs duration. The intensities used equal to −90%, −60%, −30% (upper half) and 30%, 60%, and 90% (lower half) of the control stimulus established by threshold tracking to maintain a 30% amplitude of maximal hypothenar compound muscle action potential. Changing membrane excitability measured by test stimuli of 60 μs duration delivered every 20 μs indicated a slower recovery of excitability following depolarizing (lower half) than hyperpolarizing (upper half) conditioning pulses. (Courtesy of Shouchan Lin, MD, Department of Neurology, Cheng-Kung University Hospital, Tainan, Taiwan). (***B***, *bottom*) Latent addition for the sensory axons of a human ulnar nerve, using the same arrangements as for the motor axons (***A***), except for the use of the target threshold to maintain 30% amplitude of maximal fifth digit compound sensory potential. Compared with motor fibers, sensory fibers show a slower time course of recovery after a hyperpolarizing conditioning stimulus (*top half*) and to a lesser extent, a depolarizing conditioning stimulus (*bottom half*). (Courtesy of Shouchan Lin, MD, Department of Neurology, Cheng-Kun University Hospital, Tainan, Taiwan.)

abnormally increased nodal persistent sodium currents, which mexiletine, a sodium channel blocker, used as an analgesia, can suppress.[142]

Accommodation with Prolonged Conditioning

A prolonged subthreshold current may not increase the excitability as much as expected because the voltage-dependent channels tend to oppose depolarization in the process known as accommodation. Similarly, opposing action of voltage-dependent ion channels tends to modify the effect induced by hyperpolarizing current, or negative accommodations. Testing the change of membrane excitability in this context, therefore, can uncover function and dysfunction of the ion channels regarding their rectifying properties. In particular, this method holds promise in assessing the role of potassium channels, which probably play a key role in the accommodative process under ordinary circumstances.[216]

Capacitative and resistive membrane properties[16] determine the internodal potential changes in the axons induced either by a nerve impulse or by externally applied currents. Various rectifying channels in the nodal and internodal axon membranes alter electrotonic potentials recorded from the axon. A slow and fast potassium conductance, gK_s and gK_f, activated by prolonged subthreshold depolarization, relates to the currents induced by the specific channel types identified in voltage-clamp and patch-clamp studies: gK_s to K_s currents via S channels, and gK_f to K_{f1} currents via I channels. Subthreshold electrotonus probably does not involve K_{f2} currents related to F channels, which respond to a greater depolarization compared to I channels. Subthreshold hyperpolarization activates inward rectification, gIR. The channel blockers used to test conductance include tetraethyl ammonium (TEA) for gK_s, 4-amino pyridine (4-AP) for gK_f, and Cs_+ for gIR.[14]

Electrotonus and Threshold Electrotonus

A study of threshold electrotonus determines the time course of membrane excitability change induced by a rectangular subthreshold current pulse based on the intensity of the test shock necessary to evoke a defined fraction of the maximal response.[40] Multiunit recording enables direct comparisons between the changes in threshold determined by this method and the changes in membrane potential measured by extracellular recordings.[13] According to these studies, the change in threshold normally follows the electrotonic changes in membrane potential caused by the subthreshold polarizing currents.[36] The channel blockers seem to affect these two measures in the same way, confirming the close causal correspondence between electrotonic and threshold changes.[36]

The threshold measurements usually parallel electrotonic potentials: thus, the term *threshold electrotonus*[14] defines the threshold changes corresponding to electrotonic changes. This technique, measuring the threshold noninvasively, estimates changes of membrane excitability after subthreshold polarization. Threshold electrotonus, like electrotonus, evaluates the effect of depolarizing as well as hyperpolarizing current pulses. A family of accommodation curves, thus generated, will provide information about the subthreshold electrical properties of the axon or the nerve. The slow changes in threshold in response to depolarizing currents occur mainly in the direction of accommodation or less excitability than expected. Hyperpolarizing currents induce the response mainly in the opposite direction or less suppression than expected, as implied by the term *negative accommodation*.[13]

A normally very close relationship between membrane potential and threshold, and therefore between electrotonus and threshold electrotonus, breaks down in a few situations, where a fast component of accommodation not reflected in the membrane potential causes threshold electrotonus to deviate from electrotonus. Such separations occur with DC depolarizing currents, raised extracellular potassium concentrations, or ischemia. Inactivation of closed, unactivated sodium channels probably underlies the most important accommodative process that manifests without altering the membrane potential per se, as reported in isolated toad fibers.[338] Mammalian fibers show this type of rapid accommodation

with depolarization by only 15–20 mV.[40] The insensitivity to potassium channel blockers of this fast accommodation supports the hypothesis that sodium channel inactivation plays a role.[13]

Techniques to Measure Threshold Electrotonus

Threshold electrotonus[36,51] tests the effect of standardized subthreshold depolarizing or hyperpolarizing currents on "threshold," defined as the current required to just excite a standard, submaximal response. Subthreshold depolarizing currents lasting 100 ms adequately activate the slow potassium channels responsible for Ks currents inducing accommodation. Hyperpolarizing current pulses, usually 100 to 300 ms in duration, activate IH, an inwardly rectifying current causing negative accommodation. A test shock applied to measure thresholds ordinarily has a 1 ms duration: the value chosen as being longer than the time constants of the nodes of Ranvier but shorter than the time constants of the internodal axon and slowly activating ion channels. Normalizing both the polarizing currents and threshold measurements as percentages of the unconditioned threshold current minimizes the effect of tissue impedance.

Under computer control, 1 ms test pulses, delivered alone at 1 Hz, determine the "threshold" current just sufficient to maintain a constant response in amplitude of a predetermined size. The value usually chosen equals 40% of the maximal response established by a supramaximal shock prior to the study. Depolarizing and hyperpolarizing conditioning current pulses of 100 ms duration usually have ±20% and ±40% of "threshold" current. The procedure consists of alternating test pulses on their own and test pulses superimposed on 100 ms depolarizing and hyperpolarizing conditioning pulses. The slowly advancing interval between the start of the test and conditioning shocks ranges from +2 ms to –98 ms, over a period of 10 minutes. The increase in excitability produced by a depolarizing current, expressed upward as percentage reductions in threshold, cannot exceed the line at the top for 100% threshold reduction (Fig. 10-12).

The start of the current pulse immediately depolarizes the node, resulting in a step increase in excitability. Subsequent depolarization of the node, as well as of the internodal part of the axon, causes a further increase in excitability, but more slowly, for about 20 ms. Accommodation follows,[35] with a partial repolarization of the nodal membrane, mainly caused by the activation of slow potassium channels present in the nodal and internodal axon membrane.[36] Hyperpolarization gives rise to two phases of response, the fast

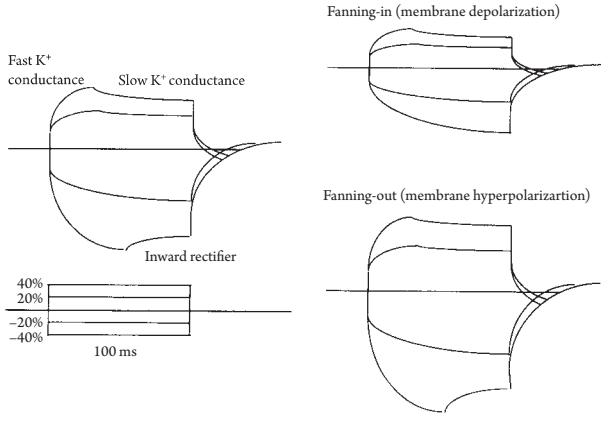

FIGURE 10-12 Membrane potential and threshold electrotonus showing increased excitability followed by accommodation to depolarizing subthreshold currents (*top half*) and decreased excitability followed by negative accommodation to hyperpolarizing currents (*bottom half*). Prior membrane depolarization or hyperpolarization shifted the response curves toward the baseline (fanning-in) or away from the baseline (fanning-out). (Modified from Kaji.[150])

component with changes in the nodal potential and prominent slow changes affecting both the node and the internode together. Longer and stronger hyperpolarizing currents lead to a late depolarization or negative accommodation by inward rectification, a phenomenon more prominent in the sensory than motor fibers.[39]

A computer model of a node and an internode gives a reasonable account of the time course of threshold electronus, taking into consideration one type of sodium and three types of potassium channels.[40] For example, increased activation of potassium channels would decrease the axonal membrane resistance, resulting in "fanning in" or flattening of the excitability curve. The opposite abnormalities would result in "fanning out" of the threshold electrotonus. In tests of these changes, threshold tracking of a constant fraction of the CMAP shows results similar to those obtained from tracking of a single fiber.[37]

Applications of Threshold Measurements

The two threshold-tracking techniques, latent addition and threshold electrotonus, test human nerve excitability in vivo providing better understanding of any channel abnormalities. According to the experimental data on latent addition,[41] the axonal responses to brief current pulses depend, for the most part, on a small, persistent sodium conductance. Thus, any models of human nerve excitability should incorporate persistent as well as transient nodal sodium channels, in addition to fast and slow potassium channels and inward rectification, which may vary among different nerves.[181] The classical theory based on nodal currents suffices to analyze the normal waveform of action potential. Modern approaches emphasize internodal mechanisms to account for pathologic nerve activity, as seen in Barrett and Barrett's equivalent circuit,[16] derived from the electrical interaction between nodes and internodes.[281]

This model can explain many conditions in which threshold electrotonus closely parallels electrotonus,[315] for example, pathophysiology of postischemic ectopic discharges.[37] Motor and sensory axons show very similar responses to depolarization, but not to hyperpolarization, which activates the axonal inward rectifier, IH, an excitatory channel with permeability to sodium as well as potassium ions. A difference in expression of the inward rectifier in this model helps to explain the characteristic behaviors of the motor and sensory axons on release of experimentally induced ischemia[39,50] and on the cessation of prolonged tetanization.[162] The model, if modified, can also reproduce abnormal features when threshold electrotonus deviates from electrotonus in such conditions as ALS[42] or prolonged depolarized state.[13]

Applying a pneumatic tourniquet to a limb induces substantial ischemia, which inhibits the electrogenic sodium-potassium pump (see Chapter 2–2), inducing membrane depolarization and extracellular accumulation of potassium ions, which also reduces membrane potential. On release of the cuff, rebound hyperactivity of the electrogenic sodium pump rapidly hyperpolarizes the axons. Thus, ischemia, like depolarization, initially causes a "fanning in" of the threshold electrotonus, reflecting increased activation of fast and slow potassium channels. The pattern reverses after release of ischemia, showing a "fanning out" mimicking the trend seen during hyperpolarization. These findings indicate that the ischemic fall in threshold primarily reflects depolarization; the postischemic rise, hyperpolarization.[114] This close relationship breaks down, however, if the axons become so depolarized that sodium channel inactivation becomes a major determinant of excitability.[13] This occurs during prolonged ischemia and in some patients with ALS.

During ischemia, motor latency increases despite depolarization, reflecting inactivation of sodium channels.[236] Post ischemia, latency stays prolonged, reflecting the hyperpolarization of axons with a threshold increase exceeding 200%. Studies of sensory fibers have shown similar observations.[39,230] The greater changes in threshold in extensor digitorum brevis than tibialis anterior suggests increased susceptibility of more distal axons to ischemia.[176] Threshold tracking studies have also elucidated the mechanism of postischemic ectopic discharges in motor axons,[37] as well as postischemic paresthesias originating from cutaneous afferents.[39] Patients with diabetic neuropathy show resistance to ischemia,[317] as

indicated by deviation of threshold changes from the normal pattern within 5 minutes of arterial occlusion[359] and an even greater dissociation during postischemic hyperpolarization.[317] A similar study in patients with ALS failed to confirm previous reports of ischemic resistance.[237]

Clinical Assessments

Noninvasive nerve excitability testing may provide clinically useful information by measuring the membrane polarization and ion channel function of peripheral nerves in healthy subjects and various neuromuscular disorders.[251] Regional differences in ulnar nerve excitability with relative depolarization at the elbow may predispose to the development of entrapment neuropathy.[177] Intranerve differences in excitability properties also include site-dependent changes, for example, motor axons innervating flexor carpi radialis and abductor pollicis brevis.[144,179] Early studies of ALS showed varied results from normal to changes indicative of widespread dysfunction in ion channel conduction.[42,133,169] An increase in persistent sodium conduction[269] and reduction in potassium current may predispose axons to generation of fasciculations and cramps.[349] Compared to normal subjects, ALS patients show greater changes to depolarizing conditioning currents at the motor point and wrist than at the elbow.[241] This finding supports the notion that fasciculations mostly arise from the nerve terminal.[192] In addition to motor fibers, cutaneous sensory axons may show excitability change in patients with ALS.[53]

In one study of diabetic polyneuropathy, testing the motor and sensory axons at the wrist, only a minority of responses lay outside the normal range.[133] The group means, however, showed a highly significant difference when compared to the normal control subjects or patients with ALS. The abnormalities, seen only in response to hyperpolarization, implied a deficit in inward rectification involving both motor and sensory nerves.[133,270] The inward rectification depends on the level of intracellular cyclic adenosine monophosphate,[4,141] a substance reportedly lacking in diabetic nerves.[143] Interestingly, threshold electrotonus applied to biopsied human sural nerve in vitro has shown the most prominent inward rectification in C fibers,[108] often most severely affected in diabetic neuropathy. This method has also demonstrated the reversal of the pathologic resistance to ischemia[271] and restoration of transaxonal sodium gradient[168] after glycemic control. Diabetic nerves also show altered axonal potassium conductance[232] and altered strength-duration properties.[233]

Threshold electrotonus showed a marked symmetrical "fanning in"[116,291] in rapidly developing, predominantly large-fiber sensory neuropathy induced by combination chemotherapy of taxol and cisplatin.[63] These findings, seen before any clinical or neurologic signs of neuropathy,[291] indicate disturbances in membrane excitability caused by depolarization or increased conductance of the internodal axon membrane. Taxol also depolarized human sural nerves in vitro.[272] Patients with the carpal tunnel syndrome (CTS) show no abnormalities probably because stimulation at the point of involved sites preferentially excites adjacent normal nodes or other more normal fibers.[236] During focal nerve compression, however, reduction in SNAP amplitude and superexcitability developed more rapidly for CTS patients compared with controls, suggesting axonal depolarization.[115] The other conditions tested by threshold electrotonus include multifocal motor neuropathy (MMN) with conduction block, showing hyperpolarization[159] restricted to the site of the lesion,[56,150] monomeric amyotrophy with spinal hemiatrophy,[170] chronic inflammatory demyelinating polyneuropathy (CIDP) with high thresholds to hyperpolarizing currents,[322] kidney disease,[178,350] and end-stage liver disease.[248]

Related studies of interest include fluctuation of serum potassium level,[185] sodium-potassium pump function in kidney disease,[174,178] tetrodotoxin blockade of sodium channels with puffer fish poisoning,[160] activity-dependent changes in myotonic dystrophy,[173] properties at the motor point,[180] length-dependent gradient in lower-limb motor axons,[175] regenerating motor axons,[288] age-related changes,[145] effect of anesthetic agent,[186] internerve variability,[202] axonal hyperpolarization associated with acute hypokalemia,[184] difference in accomodative properties of the median and peroneal nerves,[182] effect of voluntary contraction,[183] plasticity of lower-limb motor axons after cervical cord injury,[34] and experimental focal compression on human motor axons.[135]

In summary, a single suprathreshold stimulus or a train of such stimuli cause refractoriness and superexcitability, which threshold tracking can delineate. In contrast, brief and prolonged subthreshold currents induce more complex excitability changes that require latent addition and threshold electrotonus to elucidate. This technique, initially described to study nerve function, also applies in excitability testing of the muscle.[367] The membrane excitability established by these methods under most circumstances closely corresponds to the changes in membrane potentials. These measures provide important insights into membrane properties in normal and various neuromuscular disorders. In contrast, this approach, despite theoretical interest, has so far found little use in practice in the clinical context because of its inherent limitations. Their usefulness as a diagnostic test, therefore, remains uncertain. The method tests the excitability of only a small population of axons with thresholds close to the level chosen for tracking, disregarding the remaining, more or less excitable fibers.[298] Abnormalities also go undetected for degenerated axons or for demyelinated fibers with conduction block that lie between the stimulation site and the recording site. Furthermore, the technique relates only to the point of stimulation, making it less applicable for focal lesions, which escapes if the stimuli activate the more excitable neighboring segments.

5. ADDITIONAL EVALUATION OF NERVE FUNCTION

Microneurography

The conventional nerve conduction studies provide accurate measurement of the fastest conduction velocities as well as an approximate number of volleys based on the size and waveform of the evoked response. The technique usually relies on the application of an artificially synchronized electrical stimulus that the nervous system never experiences in the natural environment. Thus, despite the established diagnostic applications, such studies rarely help elucidate the exact physiologic mechanisms underlying the clinical signs and symptoms that concern the patients most. For example, the evaluation of pain and paresthesia falls outside the conventional stimulation methods, which only detect deficits in nerve function. Similarly, the conduction studies help assesses the involvement of small fibers only indirectly by localizing focal abnormalities of large axons, which may have little to do with the patient's symptoms. Thus, the lack of clinical correlation becomes particularly evident when the patient has positive rather than negative signs and small rather than large fiber dysfunction. These and other concerns necessitate a different approach to explore the areas not easily accessible by the ordinary means of conduction assessments.

Microneurography allows recordings of impulse activity in single nerve fibers within skin or muscle nerve fascicles through tungsten microelectrodes inserted percutaneously.[112] Recording of this type in an alert human subject provides a great deal of physiologic information about various types of fiber population.[49,111] Most human studies have centered on postganglionic sympathetic fibers innervating autonomic effector organs.[222,321,352] Other areas of possible interests include cutaneous afferents from mechano, thermo, and nociceptors[254] as well as muscle afferents from spindles and Golgi tendon organs. Surface stimulation of the receptive field gives rise to evoked sensory action potentials.[188]

Studies of normal subjects have substantiated the association between complex high-frequency burst and sensation of paresthesia induced by nerve compression, hyperventilation, or prolonged tetanic stimulation of cutaneous afferents.[138] The findings suggest that the abnormal sensation results from ectopic discharges of hyperexcitable cutaneous afferent. Combined with intraneural microstimulation,[255] the method also helps establish the direct link between impulse propagation along various primary afferents and subjective somatosensory experiences. In fact, careful stimulation of single efferent axons gives rise to distinctive perception correlated with the type of cutaneous receptor in question.[255] Microstimulation of individual muscle afferents fails to evoke a coherent sensation, but stimulation of joint afferents evokes a sense of pressure or movement in 50% of cases.[49]

In addition to physiologic studies conducted in healthy subjects, this technique can explore

the pathophysiologic mechanisms underlying various abnormalities of somatosensory, motor, and autonomic systems. Spontaneous activity identified by this method in cutaneous afferent fibers shows a good correlation to paresthesia experienced in neuropathies, neuromas, entrapment syndromes, radiculopathies, thoracic outlet syndromes, and Lhermitte's signs.[55] High-frequency discharges also originate at the site of nerve damage spontaneously or during and after ischemia.[38,162] A previous impalement of a nerve by a microelectrode gives rise to similar abnormalities from discharges generated ectopically at the site of injury. These recordings typically consist of brief bursts of 2 to 5 spikes occurring at a frequency of 7–10 Hz with peak frequencies usually exceeding 300 Hz.[215]

In the clinical context, microneurographic techniques allow recordings of neural activity in single C fibers,[254] and autonomic fibers.[81,199,220,221,353] Despite theoretical interest in correlating cutaneous pain with neural discharges[357] and vasoconstriction with sympathetic activity, the technique has only limited value for electrodiagnostic purposes primarily because the nature of recording requires the expertise not generally available in an ordinary EMG laboratory.

Quantitative Sensory Testing

The cutaneous sensory tests usually include warm and cold thermal perception, vibration, touch-pressure sensation, and current threshold study.[212,290,334] Tactile testers measure threshold values for light touch, high-frequency vibration, pinprick, warming, two-point discrimination,[120] and bump detection threshold.[157] Compared to thermal discrimination thresholds, vibratory perception tests in general show a better reproducibility.[75]

Thermal thresholds tests use either the method of limits or a forced-choice technique.[17] A large-scale survey in patients with diabetes[196] indicates that either approach suffices as a simple, noninvasive tool to evaluate small-fiber neuropathy. Technical factors of potential importance include thermode application pressure[264] and intrinsic noise generated by a thermotesting.[265] Weighted needle pinprick using inexpensive apparatus may give comparable information on small-fiber dysfunction that compares with thermal threshold determination.[61] In one experiment measuring reaction times to stimuli at two sites on the lower limb,[92] the estimated conduction velocity (mean ± SD) for cooling (2.1 ± 0.8 m/s) exceeded that for warming (0.5 ± 0.2 m/s). These figures confirm the transmission of warming sensation via the unmyelinated peripheral nerve fibers and cooling via small myelinated peripheral nerve fibers.

As expected, thermal and vibratory threshold increases in proportion to the severity of neuropathy.[146] In addition to thermal hypoesthesia, the test may reveal hyperalgesia, or the perception of temperature-induced pain preceding cold or warmth sensation, as a characteristic finding of small-fiber damage.[117,343] In one study on diabetes,[244] thermal and sweating tests correlated significantly with the scores of abnormal temperature and pinprick sensation obtained by physical examination but not with the duration of the illness. Thermal sensitivity but not sweat gland number predicted the degree of motor and sensory nerve conduction abnormalities. Quantitative assessment of thermal sensitivity may detect small-fiber dysfunction, even if conventional electrophysiologic studies reveal no abnormalities.[218,303] Thus, some advocate that vibratory and thermal testing should constitute the primary screening test for diabetic neuropathy.[345] Nerve conduction studies, however, provide better diagnostic value than quantitative sensory testing.[277]

Current perception threshold testing uses constant current sine wave stimulator usually at three different frequencies of 5, 250, and 2000 Hz, which may selectively activate three subsets of nerve fibers.[280] Some studies have shown good correlation of high-frequency stimulation with large-fiber, and low-frequency stimulation with small-fiber function [223] but its clinical usefulness remains uncertain.[1,282] Measurement of alternating current perception thresholds may improve the quantitative assessment as shown in grading the severity of diabetic sensory neuropathy[280] and the degree of sensory function recovery after nerve transplant.[67]

Determination of the thresholds for heat pain in the foot may help evaluate disturbances of

C-fiber-mediated sensibility in lumbosacral disc disease.[316] The test may also provide a quantitative means to confirm elevated heat pain thresholds, or heat hypoalgesia, seen in advanced stages of small-fiber neuropathy[156,243] and the effect of capsaicin treatment.[273] For this test, thermal stimulation must exceed 43°C, bearing some risk of burn injury, especially in patients with sensory loss.[125]

This quantitative sensory testing (QST) has found a limited but useful role in the characterization and quantitation of cutaneous sensory function.[26,2765,83,228,266,268] As a noninvasive, nonaversive method, the test yields reliable results even in children as young as 4 years old.[127] Like any psychophysiological tests, however, QST cannot differentiate simulated sensory loss from sensory neuropathy.[93] The findings also vary among different control groups, for example, between paid volunteers and laboratory personnel familiar with the procedure,[278] although subjects' mood has no influence on vibrotactile perception thresholds.[286] Such quantitative measurements also help detect minor sensory signs of central origin in patients with multiple sclerosis.[123] These tests may allow documentation of abnormalities in a higher percentage of patients than do more traditional clinical evaluations, but QST cannot resolve medicolegal matters because of its psychophysical nature.[301]

Thermography

Despite the initial enthusiasm and favorable reports concerning thermography in many neurological disorders, later studies conclude that it offers little value as a test of neural function in the clinical context. For example, a well-controlled study of CMT[229] documented thermographic alterations in 0 of 9 hands with mild nerve conduction changes and 7 of 14 hands with marked abnormalities. Similarly, the thermography provides nonspecific findings of uncertain diagnostic or prognostic relevance in the evaluation of lumbosacral radiculopathy.[121,3113]

Other Techniques

Over the last two decades, imaging techniques have developed into useful technology for evaluation of disease of nerve and muscle.[21,113,351] These comprise magnetic resonance imaging [43,100,250,348] and ultrasonography used, for example, in the assessment of carpal tunnel syndrome,[19,128,258] ulnar neuropathy [22,249] at the elbow[18,20,308,364] and at Guyon's canal.[104] Other conditions shown to have ultrasound abnormalities include nerve transection,[59] nerve enlargement,[198] intraneural ganglia,[347] tumors and cyst,[259] HMSN,[58] nerve regeneration,[342] and polyneuropathy,[366] showing increased nerve cross-sectional area against established normal values.[60] Some authors advocate the use of ultrasonography to guide a nerve biopsy using a probe-induced tinel sign,[64] to place a needle for recording a sural SNAP[151] and injecting steroid to treat mild ulnar neuropathy [274] and to locate superficial radial nerve,[346] median nerve following nerve repair,[86] intrapatellar branch of the saphenous nerve,[193] sciatic nerve after lower-limb amputation,[105] and sural nerve to assess anatomic variant.[369]

Electrical impedance myography (EIM) measures how the tissue in its resting state affects the low-intensity, high-frequency alternating current applied to a limb through a pair of electrodes. Consequent surface voltage over a selected muscle recorded by a second set of electrodes reveals a pattern characteristic of neuromuscular disease.[87,283,284] Although this technique may help assess disease severity in a variety of conditions, such as ALS,[285] inflammatory myopathy,[328] and radiculopathy,[284] its diagnostic value remains uncertain, especially in the absence of disease specificity.

Sural nerve biopsy, though invasive, plays an important role in selected patients (see Chapter 6–5). In a consecutive series of 50 cases, its finding altered the diagnosis in 14%, and modified management in 60%, although it caused persistent localized pain at the biopsy site in 13%.[96] In a visual assessment of myelinated fiber density and sizes, quantitative studies improve the reliability and accuracy.[260] Some advocate skin biopsies to assess pilomotor nerve fiber density as a tool to study cutaneous autonomic nerves.[252] Other techniques generally recommended include distal leg skin biopsy with quantification of intraepidermal nerve fiber density to assess the diagnosis of small-fiber neuropathy[7,191] and skin biopsies to quantificate pseudomotor innervation.[101]

Other techniques reported include ambulatory foot temperature measurement,[152] manual

muscle testing with isokinetic dynametry,[82,119] laser Doppler imager flare technique and acetylcholine iontophoresis to assess C-fiber function,[109] and interpolated twitch technique to determine voluntary muscle activation.[23]

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11

Facts, Fallacies, and Fancies of Nerve Conduction Studies

Abbreviations: CMAP—compound muscle action potential, CPT—cold perception threshold, CTS—carpal tunnel syndrome, E1—active electrode, E2—reference electrodes, EMG—electromyography, ICC—intracrass correlation co-efficiency, MUNE—motor unit number estimate, MUP—motor unit potential, NCS—nerve conduction study, RIV—relative intertrial variation, QST—quantitative sensory testing, SNAP—sensory nerve action potential, VPT—vibratory perception threshold

1. INTRODUCTION

Nerve conduction studies, as an extension of clinical assessment, help delineate the extent and distribution of the neural lesion and distinguish two major categories of peripheral nerve disease: demyelination and axonal degeneration. With steady improvement and standardization of methods, they have become a reliable test not only for precise localization of a lesion but also for accurate characterization of peripheral nerve function.[71] This chapter will review the fundamental principles and changing concepts of nerve stimulation techniques and their proper

application in the differential diagnosis of peripheral nerve disorders. These considerations generally discourage the use of automated handheld nerve conduction devices as a replacement of the standard studies.[33,131]

Despite the simple principles in theory, pitfalls abound in practice.[67,69,70] Commonly encountered, yet often overlooked, sources of error include intermittent failure in the stimulating or recording system, excessive spread of stimulation current, anomalous innervation, temporal dispersion, and inaccuracy of surface measurement. Stationary far-field peaks, often associated with a referential montage, may also appear in a bipolar derivation intended to record near-field potentials for nerve conduction studies (see Chapters 2-4 and 19-3). Lack of awareness of this possibility can lead to an erroneous interpretation. Because of these factors, conduction studies show lower than expected reproducibility despite the effort to maintain a good quality control.[26,79,163]

Careful attention to the waveform of evoked potentials improves the accuracy of interpretation in any electrophysiologic studies. If the responses elicited by distal and proximal stimuli have dissimilar shapes, their onset latencies probably represent fibers of different conduction characteristics. This type of discrepancy results, for example, from the use of unbalanced stimuli, submaximal at one point and a supramaximal at a second site. Even with adequate shock intensity, diseased nerves may fail to propagate a proximal impulse in some fibers because of conduction block. In addition, regenerating or severely demyelinated axons may effectively prevent the excitation of the nerve segment despite application of high-intensity stimuli. Spread of stimulation may inadvertently excite the neighboring nerve. A properly placed stimulation may activate an anomalously innervated muscle. Any of these circumstances preclude the accurate calculation of conduction velocity.

Conventional studies primarily deal with evaluation of the fastest conducting fibers based on the latency measured to the onset of the evoked potential. In some clinical entities, special techniques may add in evaluating other aspects such as conduction velocity of the slower fibers and the time course of the absolute and relative refractory periods. The collision techniques help assess these features of nerve conduction.[51,63,64,74] Here, a second stimulus delivered distally to the nerve blocks the unwanted impulses not under study. Other areas of interest include studies of autonomic nervous system, motor unit number estimate (MUNE), and threshold electrotonus (see Chapter 10). Although these methods supplement the conventional technique in evaluating physiology and pathophysiology, their clinical application for routine diagnostic practice awaits further clarification.

2. COMMON TECHNICAL PROBLEMS

Technical problems often account for unexpected observations during routine nerve conduction studies. The failure to appreciate this possibility will lead to an incorrect diagnosis, especially if the findings mimic abnormalities expected in the disease under consideration. Commonly unidentified yet easily correctable problems include malfunction of the stimulating and recording system.

Stimulating System

Absent or unusually small responses result from an inappropriately low shock intensity or misdirected stimulus despite adequate current strength. This possibility calls for relocation of the stimulating electrodes pressing them firmly closer to the nerve and, if necessary, increasing the shock intensity or duration. The use of monopolar or concentric needle may help achieve sufficient shock intensities, especially in obese patients. Profuse perspiration or excessive amount of cream over the skin surface may shunt the cathode and anode, rendering an otherwise sufficient stimulating current ineffective. The anode, if placed between the cathode and the recording electrode, could, in theory, block the propagating impulse. In the usual clinical setup of separating the cathode and anode by 2–3 cm, however, induced hyperpolarization abates before the impulse reaches the anodal position, thus rendering no detectable effects. Conversely, locating the cathode distant from the nerve may shift effective stimulus site to the anode placed on the nerve, the phenomenon

sometimes referred to as floating cathode, shortening the onset latency (see Chapter 6-3). More important, inadvertent reversal of the cathodal and anodal position would invalidate the relationship between the measured distance and latency (see Chapter 7-3). In motor or antidromic sensory conduction studies, submaximal activation of the nerve proximally would erroneously suggest a conduction block, especially if a distal stimulus elicits a full response. For example, in some neuropathic states with abnormally elevated threshold, an ordinarily sufficient intensity may fail to excite the nerve at the site of pathology. In this case, more proximal stimulation applied to the unaffected nerve segment elicits a larger response, confirming the propagation of an impulse across the site of lesion (see Chapter 11-5).

Recording System

As a quick check of the recording system, ask the patient to contract the muscle with the electrode in position and the amplifiers turned on. Deficiencies at any step of the recording circuit would preclude a normal display of muscle action potentials on the oscilloscope. Even optimal stimulation elicits a small response if a faulty connection hampers the recording system. Common problems include inappropriate placement of the pickup electrodes; breaks in the electrode wires; use of a disconnected preamplifier; loss of power supply; and incorrect oscilloscope settings for sensitivity, sweep speed, or filters. A broken wire of the recording electrode may escape visual inspection, especially if the insulating sheath remains intact. Stimulus-induced muscle twitches may cause movement-related potentials from partially damaged wire, sometimes with surprising consistency, which can then mimic a compound muscle action potential (CMAP).

An initial positivity preceding the major negative peak of a CMAP usually results from incorrect positioning of the recording electrode away from the endplate region. Alternatively, it may represent a volume conducted potential from distant muscles, activated by anomalous innervation or by spread of stimulation to other nerves. Any deviation from the standard placement of the active (E1) and reference (E2) electrodes on the belly and tendon of the target muscle distorts the CMAP waveform. Switching the position between E1 and E2 reverses the polarity of the recorded response.

3. SPREAD OF STIMULATION CURRENT

With a very high shock intensity, stimulating current can spread to a neighboring nerve not under study. Failure to recognize this possibility may result in fallacious determination of latencies to the onset of a volume-conducted potential generated by distant muscles. Under these circumstances visual inspection of the contracting muscle, rather than the waveform on the oscilloscope, identifies the generator source. In some of these cases, the collision technique can, in effect, activate the intended nerve selectively by blocking the unwanted nerve.[63] The use of needle also helps a selective pickup from a small target area uncontaminated by nearby activities. This type of recording, well suited for studying the innervation of individual motor branches, also helps assess function of atrophic muscles, which may escape surface detection, but fails to elucidate the important CMAP size.

In bipolar stimulation of a nerve, the anode can theoretically hyperpolarize the nerve, thus blocking the propagation of impulse. Placing the cathode closer to the pickup electrode avoids this effect. In motor nerve or antidromic sensory nerve conduction studies, therefore, the convention calls for cathode distal stimulation. For the same reason, cathode proximal stimulation, in theory, serves better for F waves and orthodromic sensory recording. Contrary to common belief, however, anodal hyperpolarization, if any, does not seem to affect impulse propagation in clinical practice. Conversely, with the use of high-intensity shocks, anodal stimulation may activate the nerve, shortening distal motor latency in anode distal arrangement.[164] Similarly, anodal activation may give rise to double peak orthodromic sensory response at submaximal stimulation in anode proximal arrangement.[6] In these cases, anodal pulse may comprise initial positivity followed by a smaller negativity, especially if the stimulator has an interposed transformer. With

sufficient stimulus intensity, this negativity may depolarize the nerve beyond the threshold at the anodal point.

Stimulation of the Facial Nerve

The facial nerve becomes accessible to surface or needle stimulation as it exits from the stylomastoid foramen (see Chapter 8-2; see Figs. 8-1 and 8-2). The distal segment, tested by stimulating the nerve here and recording CMAP from various facial muscles, remains normal for a few days even after complete separation of the nerve at a proximal site. The loss of distal excitability by the end of the first week coincides with the onset of nerve degeneration, which generally implies poor prognosis. With shocks of very high intensity, stimulating current may activate the motor point of the masseter muscle because of its proximity to the cathode. A volume-conducted potential then erroneously suggests a favorable prognosis, when in fact the facial nerve has already degenerated (Fig. 11-1). As stated before, visual inspection would verify the stimulus-induced contraction of the masseter, rather than twitches of the facial muscles. Surface stimulation of the facial nerve may also activate cutaneous fibers of the trigeminal nerve, causing reflexive contraction of the orbicularis oculi (see Chapter 8-3). The reflex response may mimic a late component of the CMAP or F wave induced by antidromic activation of the motoneurons.

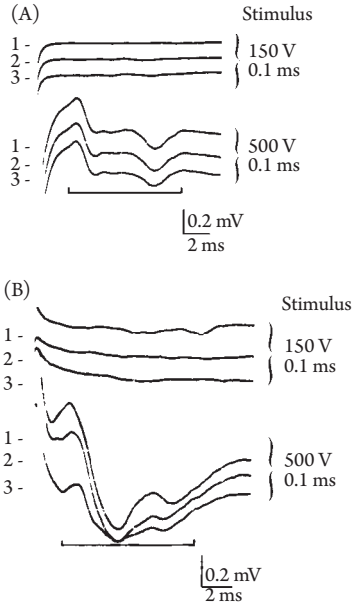

FIGURE 11-1 Compound muscle action potential recorded from E1 and E2 placed on the lower portion of the right (***A***) and left (***B***) orbicularis oculi after stimulation of the facial nerve in a patient with traumatic facial diplegia. Shocks of ordinary intensity (top three tracings) elicited no response, but with a much higher intensity, a definite muscle response appeared (bottom three tracings). Close observation of the face revealed contraction of the masseter rather than the orbicularis oculi.

Axillary Stimulation and Collision Technique

Shocks of an ordinary intensity activate the median or ulnar nerve selectively at the wrist or elbow but not necessarily at the axilla, where the two nerves lie in close proximity.[62] In studying the median nerve in a patient with carpal tunnel syndrome (CTS), for example, spreads of current to the ulnar nerve activate adductor pollicis with normal latency (Fig. 11-2A). In the same case, a stimulus at the elbow activates only the median nerve, revealing a prolonged latency. The calculated conduction time between the axilla and elbow would then suggest an erroneously fast conduction velocity. In extreme cases, the latency of the median response after stimulation at the elbow exceeds that of the ulnar component elicited with shocks at the axilla.

The reverse discrepancy may occur in a case of tardy ulnar palsy with spread of axillary stimulation to the median nerve. In this case, the surface electrodes on the hypothenar eminence register the volume conducted response from the thenar muscles or lumbricals as a small positive potential of 1 to 5 mV in amplitude and 10 to 20 ms in duration. This positivity, though usually buried in a simultaneously evoked much larger ulnar response, becomes visible if the ulnar nerve conducts slower than the median nerve (Fig. 11-2B). The earlier median component showing a normal latency then obscures the delayed onset of the ulnar response. A stimulus at the elbow in the same case activates only the ulnar nerve with a prolonged latency, leading to a miscalculation of

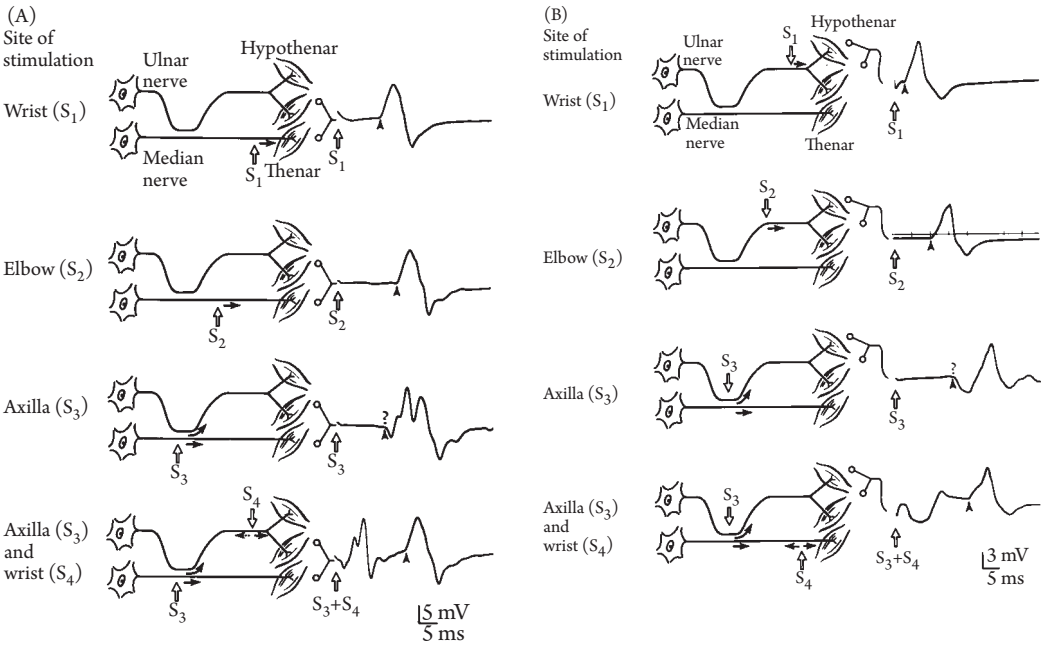

FIGURE 11-2 (***A***) A 39-year-old man with carpal tunnel syndrome. The stimulation of the median nerve at the wrist (S1) or elbow (S2) elicited a muscle action potential with increased latency in the thenar eminence. Spread of axillary stimulation (S3) to the ulnar nerve (third tracing from top) activated ulnar-innervated thenar muscles with shorter latency. Another stimulus (S4) applied to the ulnar nerve at the wrist (bottom tracing) blocked the proximal impulses by collision, unmasking the median response from the axilla. The distal ulnar response elicited by S4 occurred much earlier. The diagram on the left shows collision between the orthodromic (solid arrows) and antidromic (dotted arrows) impulses. (Modified from Kimura.[63]) (***B***) A 29-year-old man with tardy ulnar palsy. Stimulation at the wrist (S1) or elbow (S2) selectively activated the ulnar nerve, the latter giving rise to an abnormally delayed muscle action potential over the hypothenar eminence. Spread of axillary stimulation (S3) to the median nerve (third tracing from top) elicited an additional short-latency median response with initial positivity. This potential, registered through volume conduction, obscured the onset (arrow head) of the ulnar response under study. Another stimulus (S4) applied to the median nerve at the wrist (bottom tracing) blocked the proximal impulses by collision, unmasking the ulnar response from the axilla. The positive median potential elicited by S4 clearly preceded the ulnar component under study. (Modified from Kimura.[63])

an erroneously fast conduction velocity for the segment from the axilla to elbow.

A physiologic nerve block based on collision allows selective recording of the median or ulnar component despite coactivation of both nerves proximally (Kimura, 1976a). In studying the median nerve, for example, a distal stimulus delivered to the ulnar nerve at the wrist generates the antidromic impulse, which collides with the orthodromic ulnar impulse from the axilla. Thus, only the median impulse reaches the muscle (Fig. 11-2A). The ulnar response induced by the distal stimulus precedes the median response under study usually without an overlap. If necessary, delivering the distal stimulus a few milliseconds before the proximal stimulation accomplishes a greater separation between the distally and proximally elicited ulnar and median components. This time interval should not exceed the conduction time between the distal and proximal points of stimulation, lest the antidromic impulse from the wrist passes the stimulus site at the axilla without collision. The same principles apply for the use of a distal stimulus to block the median nerve in selective recording of the ulnar response after coactivation of both nerves at the axilla (Fig. 11-2B).

The collision technique can clarify otherwise confusing results in patients with the CTS or

tardy ulnar palsy. In each of the illustrated cases (Figs. 11-2 A and B) spread of stimulus caused obvious distortion in waveform of the proximally evoked potential. Less apparent discrepancies escape detection unless the collision methods block unwanted nerve impulses, uncovering the true response from the intended muscle. The collision technique provides a simpler, noninvasive means than a procaine nerve block sometimes employed to identify the origin of the recorded muscle potentials or high-frequency electrical conduction block used experimentally.[7] Optimal studies of motor nerve conduction depend on either selective activation of the nerve in question or isolated recording from the target muscle. The collision method improves latency and waveform determination even under the circumstance that disallows selective stimulation of the nerve at a proximal point. As an alternative method, the use of needle recording renders reliable latency measurement even after coactivation of more than one nerve, but it has a major deficit of not studying the CMAP size.

Palmar Stimulation of the Median and Ulnar Nerves

Palmar stimulation (see Chapter 6-3) uniquely contributes in the evaluation of the median nerve distally, although motor conduction studies in this region pose some technical problems.[17,25,65,111,122,161] For accurate calculation of motor latency over the wrist-to-palm segment, palmar stimulation must activate the median nerve precisely at the origin of the thenar nerve as intended. With the ordinary placement of the cathode distal to the anode, spreading negativity, acting as floating cathode, may activate the thenar nerve even when the cathode lies clearly distal to the origin of the nerve. A surface distance measured to the cathodal point would then overestimate the nerve length, thereby making the calculated conduction velocity erroneously fast.

To circumvent this problem, we prefer to proceed from the distal palm toward the wrist with reversal of the electrode position, placing the cathode proximally to the anode. In this approach, palmar stimulation applied distal to the deep palmar branch of the ulnar nerve fails to produce any muscle twitch. Stimulation given slightly more proximally causes thumb adduction, indicating activation of the deep palmar branch of the ulnar nerve. Another shock, applied about 1 cm further proximally, induces thumb abduction, signaling the arrival of the cathode just over the origin of the thenar nerve, or the recurrent branch of the median nerve. In most subjects, this point lies 3 to 4 cm distally from the distal crease of the wrist, near the edge of the transverse carpal ligament.[65]

The pattern of muscle twitch, rather than recorded waveforms, confirms a selective activation of the intended nerve: thumb abduction and opposition with stimulation of the recurrent thenar branch of the median nerve, and thumb adduction with stimulation of the deep palmar branch of the ulnar nerve. Thus, in nerve stimulation technique, visual confirmation of the muscle twitch identifies the nerve being activated. This practice bears particular importance when attempting selective stimulation of the target nerve in the proximity of other neural elements as in the palm. In our own experience, careful inspection allows reasonable segregation between the median and ulnar nerves in about 85% of unselected population. In doubtful cases, monitoring ulnar response from another set of electrodes placed over the first dorsal interosseus helps assess the validity of the recorded response. The use of needle, allowing more precise stimulation with less shock intensity, may facilitate the process, especially when testing the palm with thick callous skin surface.

With coactivation of two nerves proximally (Fig. 11-3), a second shock delivered distally can block unintended nerve to achieve a selective recording of the desired response. One cannot exploit this technique, however, if distally placed stimulation excites two nerves as seen with a palmar activation of the median and ulnar nerves. As an alternate means, one can block the unintended coactivation of the ulnar nerve by initially inducing the refractory period through its prior activation at the wrist (S1). Application of a properly timed palmar stimulation (S2) then selectively activates the recurrent thenar branch while the ulnar nerve remains inexcitable. The median thenar response thus elicited by S2 appears superimposed on the preceding ulnar response evoked by

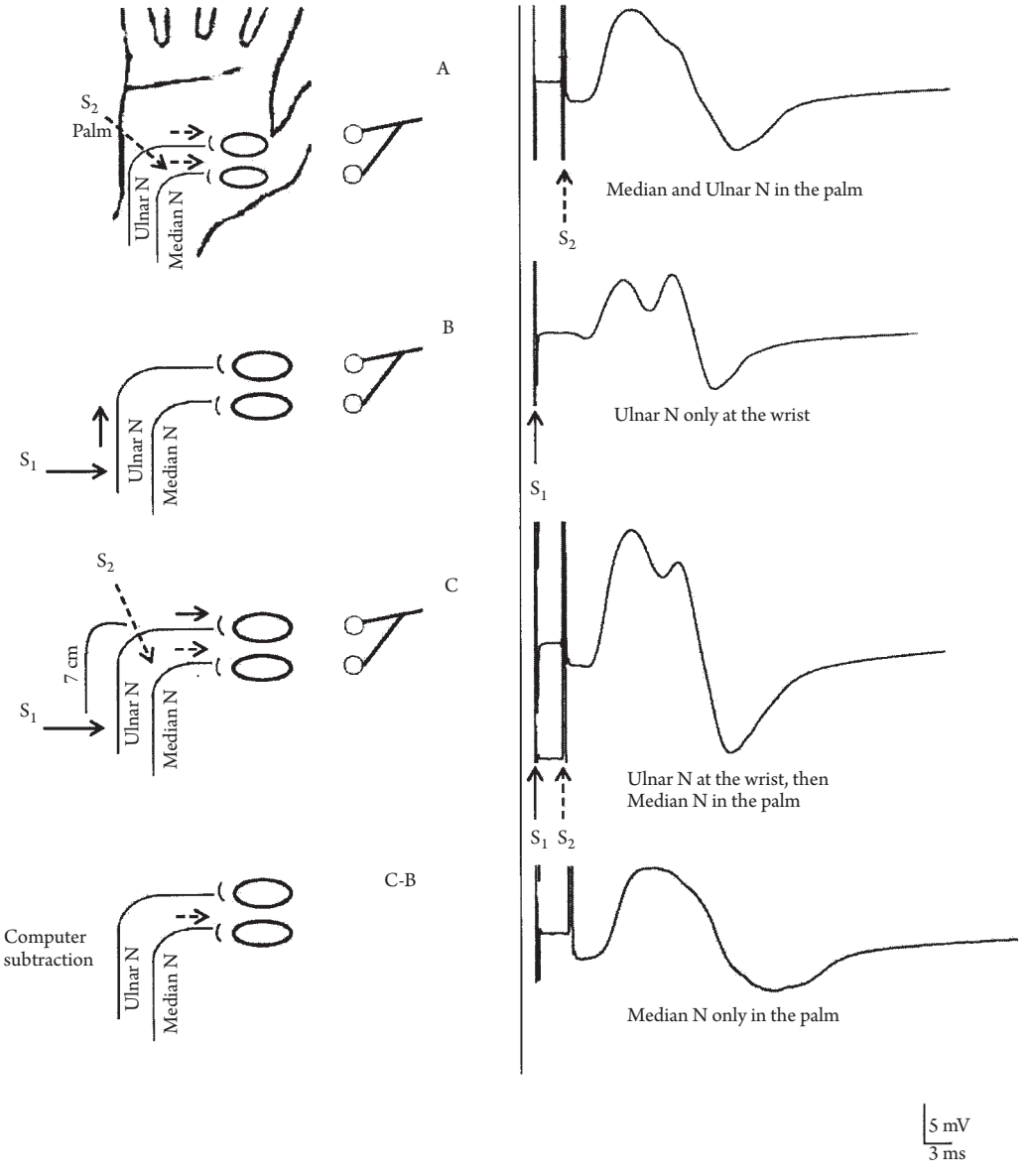

FIGURE 11-3 (***A***) Stimulation (S2) intended for the recurrent branch of the median nerve may inadvertently coactivate the deep palmar branch of the ulnar nerve. (***B***) Assuming a normal conduction velocity of 50 m/s, or 1 cm/0.2 ms, an impulse generated by ulnar nerve stimulation (S1) at the wrist will pass the site of palm stimulation located 7 cm distally in approximately 1.4 ms. (***C***) With a combined stimulation delivering S1 at the wrist 2.0 ms before S2 at the palm, S2 will fall in the absolute refractory period of the ulnar nerve. This arrangement will thus achieve a selective activation of the recurrent branch of the median nerve even with a shock intensity that would otherwise coactivate both the median and ulnar nerves. (***C-B***) Digital subtraction of the ulnar nerve component elicited by S1 at the wrist from the composite yields the median nerve response activated by S2 applied in the palm.

S1. Digital subtraction of the latter from the composite yields the intended median component evoked by S2, representing selective stimulation of the median nerve in the palm.[72]

With serial stimulation in 1-cm increments from palm to wrist, the sensory latency increases linearly (see Fig. 6-8B in Chapter 6). The motor study, recording from the thenar eminence, sometimes shows unexpected latency changes if successive stimuli fail to follow the recurrent course of the motor fibers precisely. For example, a stimulus intended for the branching point of the thenar nerve in the palm could accidentally activate a more distal portion near the motor point. If another stimulus, delivered 1 cm proximally, excites only the median nerve trunk, the latency difference between the two points of stimulation becomes unreasonably large, erroneously suggesting a focal slowing (Fig. 11-4A). To avoid this type of misinterpretation, serial stimulation must show a linear latency increase in the proximal and distal segments flanking the disproportionate latency change across a localized lesion (Fig. 11-4B). Placing the pickup leads over the second lumbricalis,[1,115] in lieu of the abductor pollicis brevis (see Chapter 6–3), facilitates inching studies of motor fibers that takes a relatively straight passage to the target muscle (Fig. 11-5A,B). As an additional advantage, the same pair of electrodes works well for registering a CMAP from the first volar interosseus for inching studies of the ulnar nerve along the course of the palmar branch across the wrist (Fig. 11-5C,D).

4. ANOMALIES AS SOURCES OF ERROR

Martin-Gruber Anastomosis

Anatomic studies of Martin[93] and Gruber[43] demonstrated frequent communication from the median to the ulnar nerve at the level of the forearm a few centimeters distal to the medial humeral epicondyle.[154] This anastomosis, often originating from the anterior interosseous nerve, predominantly consists of motor axons with rare sensory contribution, which may follow different distribution.[21,137,156] The communicating branch usually, though not always,[85] supplies ordinarily ulnar-innervated intrinsic hand muscles, most notably the first dorsal interosseous, adductor pollicis, and abductor digiti minimi.[140,162] The number of axons taking the anomalous course varies widely. A properly adjusted electrical stimulus delivered at the elbow may activate the anomalous fibers maximally and selectively without exciting the median nerve proper or vice versa (Fig. 11-6).[74] This observation suggests a grouping of the nerve fibers forming the anastomosis in a separate bundle, rather than being scattered within the median nerve. The anomaly occurs, often bilaterally, in 15% to 46% of subjects in an unselected population.[4,74] A higher incidence reported among congenitally abnormal fetuses, in general, and those with trisomy 21, in particular, indicates its phylogenetic origin.[140] The communicating fibers rarely cross from the ulnar to the median nerve in the forearm,[41,104] occasionally involving only the sensory axons.[50] Other anomalies associated with Martin-Gruber anastomosis include (see Chapter 6-3) innervation of the ulnar aspect of the dorsum of the hand by the superficial radial sensory nerve.[86,94]

Careful analysis of the CMAP readily reveals the presence of a Martin-Gruber anomaly during routine nerve conduction studies. For the most part, this anastomosis, in effect, represents a small bundle of the ulnar nerve, which accompanies the median nerve as it descends from the axilla to the elbow before separating from it in the forearm to join the ulnar nerve proper above the wrist. Thus, stimulation of the median nerve at the elbow simultaneously excites the small bundle of the ulnar nerve activating not only the median-innervated thenar muscle but also anomalously innervated first dorsal interosseus and thenar and hypothenar muscles. In contrast, stimulation of the median nerve at the wrist evokes a smaller response lacking the ulnar component. In general, this type of disparity, showing a greater response with proximal as compared to distal stimulation, implies the presence of an anomaly, provided, of course, in the absence of technical problems such as the use of an insufficient intensity distally. Reverse anomalies showing a larger response distally than proximally may erroneously suggest a conduction block.[78] For example, stimulation

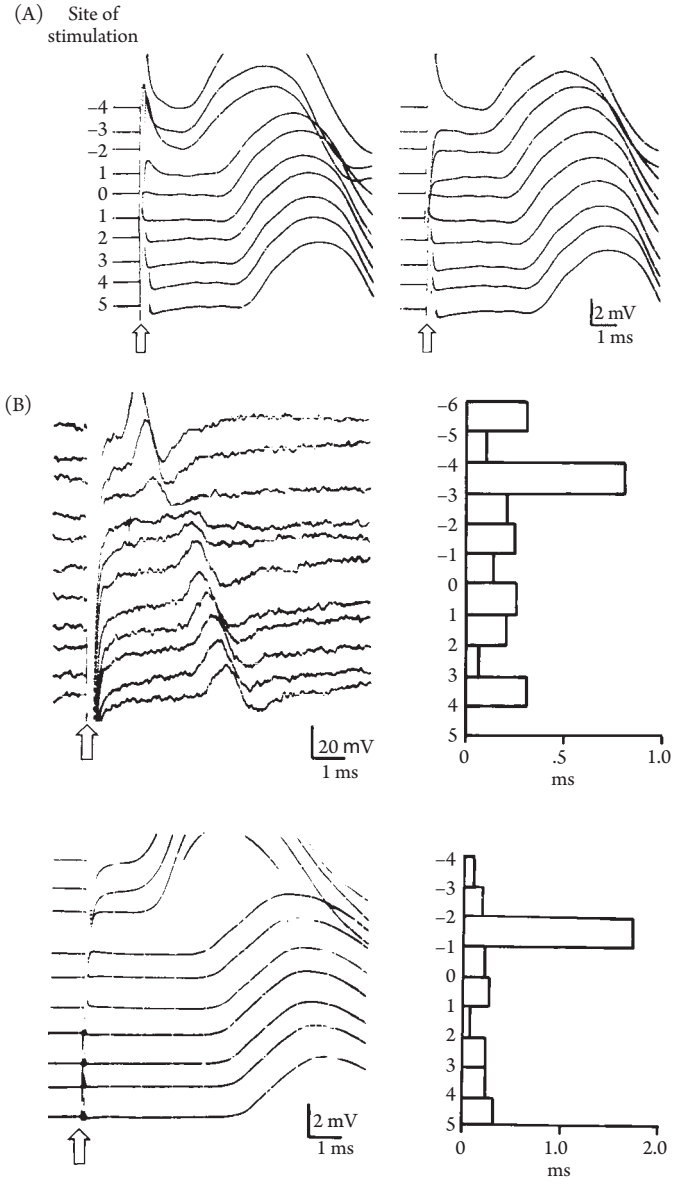

FIGURE 11-4 (***A***) Compound muscle action potentials in a normal subject recorded after stimulation of the median nerve at multiple points across the wrist. On the initial trial (*left*), the latency decreased with the cathode inching proximally from –4 to –2, indicating inadvertent spread of stimulating current to a distal portion of the thenar nerve. An apparent steep latency change from –2 to –1 gave an erroneous impression of a focal slowing at this level. A more careful placement of the cathode (*right*) eliminated unintended activation of the thenar nerve. The 0 level at the distal crease of the wrist corresponds to the origin of the transverse ligament (cf. Fig. 6-3). (***B***) Sensory nerve (*top*) and muscle action potentials (*bottom*) in a symptomatic hand with the carpal tunnel syndrome. Serial stimulation showed a linear motor latency increase from –4 to –2 and from –1 to 5 with a localized slowing between –2 and –1. A temporally dispersed, double-peaked sensory nerve potential indicates the point of localized conduction delay from –4 to –3 (cf. Fig. 6-8). (Modified from Kimura.[65])

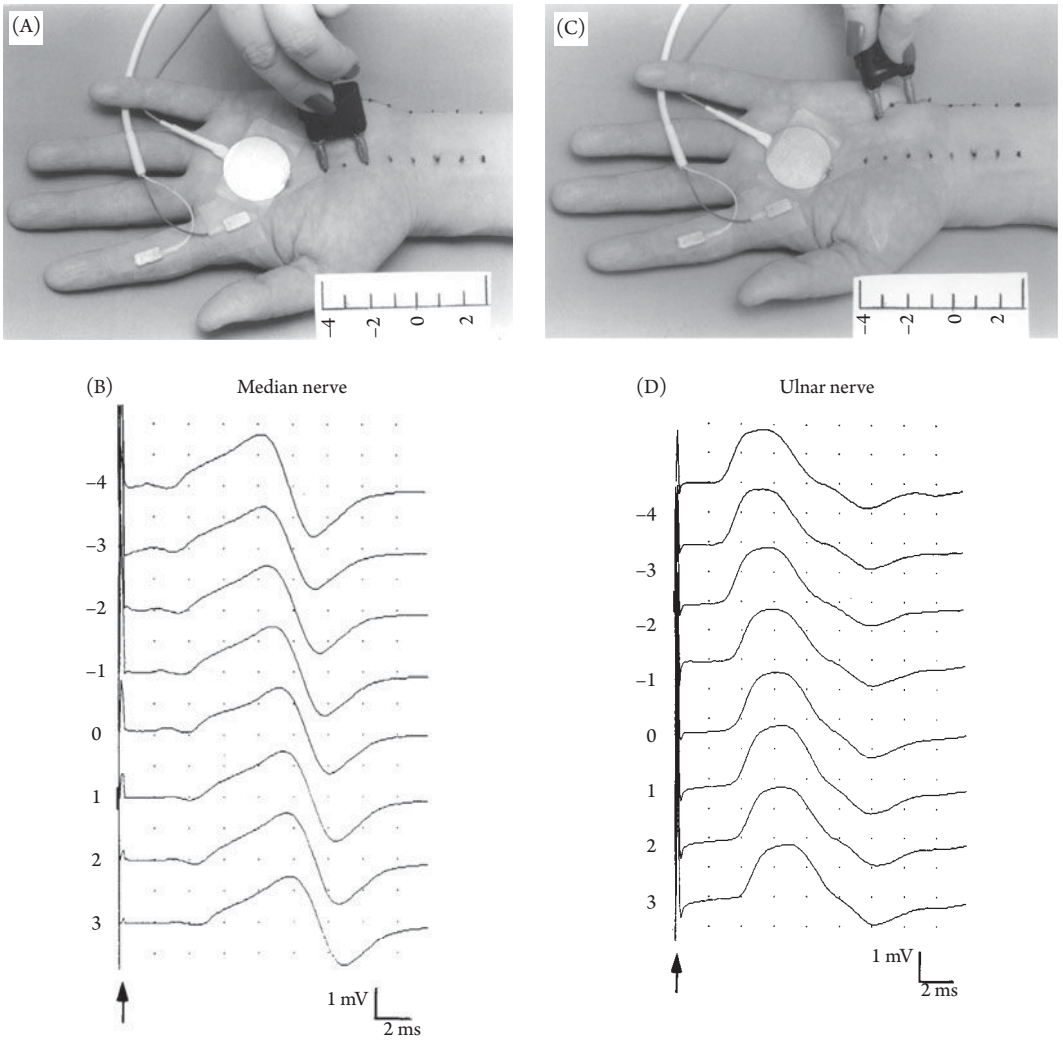

FIGURE 11-5 An inching study of median (***A*** and ***B***) and ulnar nerve (***C*** and ***D***) across the wrist in 1-cm increments at eight sites of stimulation along the course of the nerve. The zero level at the distal crease of the wrist corresponds to the origin of the transverse carpal ligament and Guyon's canal. The photograph shows a recording arrangement for muscle action potentials from the second lumbricalis after stimulation of the median nerve (***A***) and the first volar interosseous after stimulation of the ulnar nerve (***C***). The latency increased linearly with stepwise shifts of stimulus site proximally in 1-cm increments for both median (***C***) and ulnar study (***D***).

of the ulnar nerve at the elbow spares the communicating branch still attached to the median nerve, whereas stimulation at the wrist activates the additional anomalous fibers, giving rise to a full response. A smaller response with proximal stimulation mimics an ulnar neuropathy at the elbow.[92]

In assessing the possibility of anastomosis, stimulating the median nerve and recording from the ulnar innervated muscles do not necessarily prove the point because volume-conducted potentials confuse the issue. The use of a needle electrode localizes the origin of the response better, although distant activities may still contaminate the recording. A careful comparison between distal and proximal stimulation usually clarifies the ambiguity.[11,63] In questionable cases, the collision technique[63,129] helps selectively record the anomalous response transmitted via the communicating fibers as follows (Fig. 11-7).

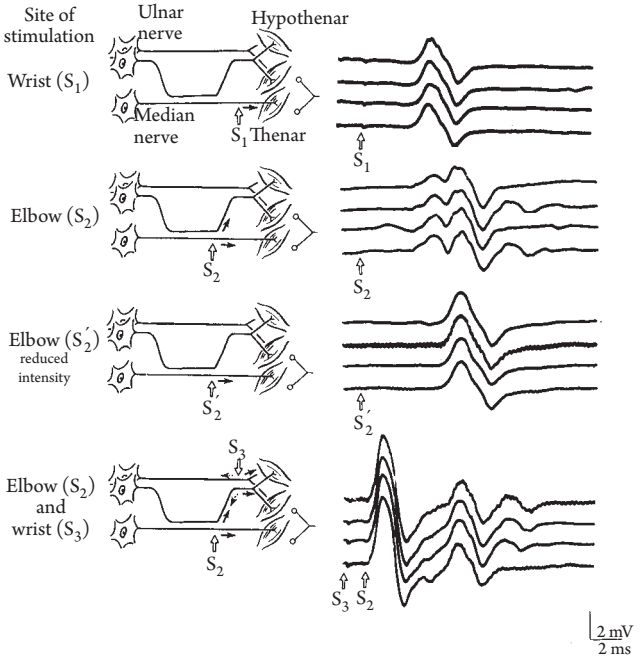

FIGURE 11-6 A 46-year-old woman with the carpal tunnel syndrome and the Martin Gruber anomaly. Stimulation at the elbow (S2) activated not only the median nerve but also communicating fibers, giving rise to a complex compound muscle action potential. With proper adjustment of electrode position and shock intensity, another stimulus at the elbow (S2) excited the median nerve selectively without activating the anastomosis. Another stimulus (S3) applied to the ulnar nerve at the wrist (bottom tracing) achieved the same effect by blocking the unwanted impulse transmitted through the communicating fibers. (Modified from Kimura.[68])

Normally, antidromically directed impulses from the distal stimulation will completely block the orthodromic impulses from the proximal stimulation in the median nerve. The orthodromic impulse through an anastomotic branch to the ulnar nerve, however, would, bypassing the antidromic impulses, escape collision.[63] This technique can identify and characterize the anomalous response, although a thenar, as opposed to hypothenar, response elicited via anastomosis tends to overlap with a large median potential elicited by stimulation applied distally (Fig. 11-8). Delaying the proximal stimulation by a few milliseconds usually achieves satisfactory separation of distally and proximally elicited responses. To ensure the intended collision, the time interval must not exceed the latency difference between the two stimulus sites.

If patients with this anastomosis develop a CTS, stimulation of the median nerve at the elbow evokes two temporally separate potentials: a normal ulnar component and a delayed median component. The anomalously innervated ulnar muscles usually lie at some distance from the recording electrodes placed on the thenar eminence. Thus, the ulnar component commonly, though not always, displays an initial positive deflection.[44] The latency of the initial ulnar response erroneously suggests the presence of normally conducting median fibers. In contrast, stimulation of the median nerve at the wrist evokes a delayed response without an ulnar component.[55,63,82] The comparison between proximal and distal stimulation would lead to an unreasonably fast conduction velocity from the elbow to the wrist.[11,63,82] The collision technique can block the impulses in the anomalous ulnar nerve fibers without affecting those transmitted along the median nerve proper (Fig. 11-9).

Severance or substantial injury of the ulnar nerve at the elbow ordinarily results in wallerian degeneration and inexcitability of the distal

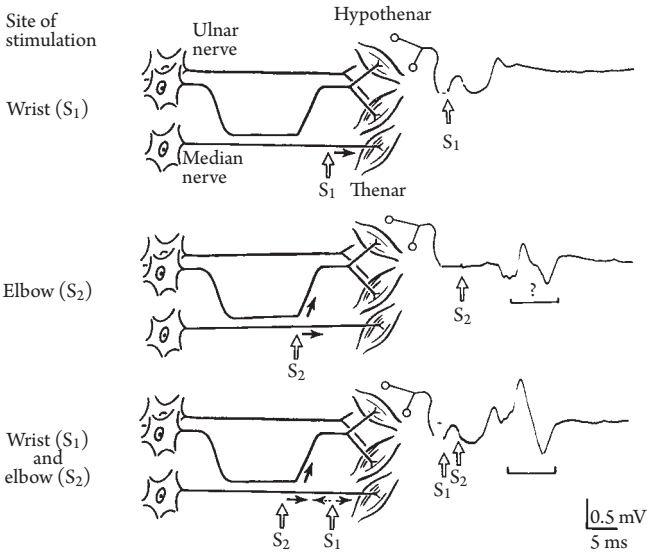

FIGURE 11-7 Muscle action potentials recorded from the hypothenar eminence after stimulation of the median nerve at the wrist (Sl) or elbow (S2) in a patient with the Martin Gruber anomaly. The top tracing shows a volume-conducted potential from thenar muscles (U-shaped wave of positive polarity). The middle tracing reveals a small negative potential superimposed upon the thenar component. In the bottom tracing, collision technique clearly separated the anomalous response (bracket), with Sl preceding S2 by 4 ms. (Modified from Kimura, Murphy, and Varda.[74])

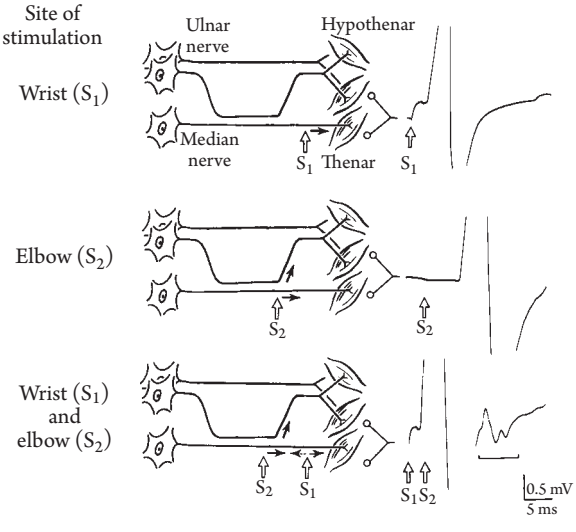

FIGURE 11-8 Muscle action potentials recorded from the thenar eminence after stimulation of the median nerve at the wrist (Sl) or elbow (S2) in the same patient shown in Figure 11-7. In the middle tracing, a large compound action potential buried a small anomalous response mediated by the anastomosis. In the bottom tracing, a collision technique separated the anomalous response (bracket) with Sl preceding S2 by 4 ms. (Modified from Kimura, Murphy, and Varda.[74])

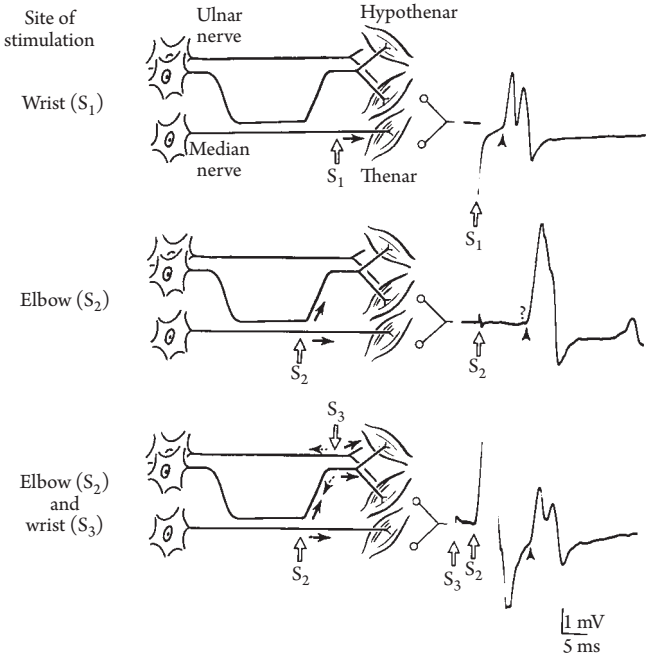

FIGURE 11-9 A 55-year-old man with the carpal tunnel syndrome and the Martin Gruber anastomosis. Stimulation at the elbow (S2) spread to the ulnar nerve through the anomalous communication (middle tracing). Another stimulus (S3) applied to the ulnar nerve at the wrist (bottom tracing) blocked the impulses transmitted through the communicating fibers. In the bottom tracing, S3 preceded S2 by 4 ms to avoid the overlap of the muscle responses elicited by S3 and S2. (Modified from Kimura.[68])

segment. In the presence of this anomaly, stimulation at the wrist will excite the communicating fibers that bypass the lesion to evoke a small but otherwise normal muscle action potential. In a rare condition, called all-median hand, all intrinsic hand muscles ordinarily supplied by the ulnar nerve receive innervation via the communicating fibers. In this case, a major injury at the elbow, which would normally sever the ulnar nerve, may not appreciably affect the intrinsic hand muscles because all or nearly all ulnar fibers, attached to the median nerve, escape injury. Electromyography (EMG) may reveal normal motor unit potentials in the ulnar-innervated muscles, despite severe damage at the elbow. Conversely, an injury to the median nerve at the elbow could lead to the appearance of spontaneous discharges in the ulnar-innervated intrinsic hand muscles. Hence, an anomaly of this type, if undetected, gives rise to considerable confusion in the interpretation of electrophysiologic findings.[45]

Anomalies of the Hand

Common anomalies of the peripheral nerves include variations in innervation of the intrinsic hand muscles.[134] Although not as widely recognized as the median-to-ulnar anastomosis, they too constitute sources of error in the evaluation of nerve conduction study (NCS) and EMG. Electrophysiologic techniques often hint at the presence of such anomaly, although its precise characterization calls for anatomic studies.[142] The recurrent branch of the median nerve may take an anomalous course bypassing the carpal tunnel.[42] Various communications may also link this branch and the deep branch of the ulnar nerve in the lateral portion of the hand[14,90,119,124] with an inherited trait.[8] Any of the intrinsic hand muscles, the flexor pollicis brevis in particular, may receive median, ulnar, or dual innervation.[133] In a small percentage of cases, thenar muscles, including the adductor pollicis, may derive their supply

exclusively from the median or ulnar nerve.[38,127] In addition to neural anastomoses, skeletal anomalies of the upper limb may cause confusing clinical pictures. The congenital absence of thenar muscles, for example, may suggest a false diagnosis of CTS.[16] The posterior interosseous nerve may innervate accessory hand muscles consistent with extensor digitorum brevis manus.[96] The deep branch of the ulnar nerve may form a motor neural loop, causing an atypical clinical presentation after penetrating injuries or compression neuropathy at the wrist.[120]

Accessory Deep Peroneal Nerve

The most frequent anomaly of the lower limb involves the innervation of the extensor digitorum brevis, the muscle commonly used in conduction studies of the peroneal nerve. This muscle usually derives its supply from the deep peroneal nerve, a major branch of the common peroneal nerve. In 20% to 28% of an unselected population the superficial peroneal nerve also contributes via a communicating fiber. This branch, the accessory deep peroneal nerve (Fig. 11-10), descends on

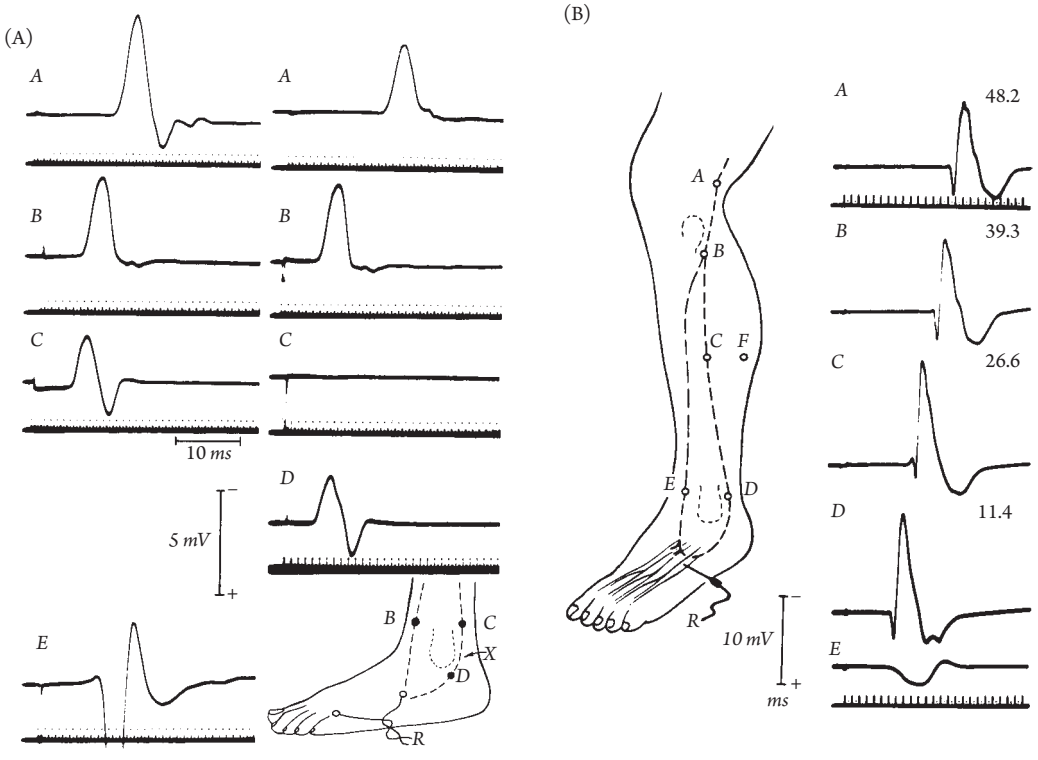

FIGURE 11-10 (***A***) Compound muscle action potentials recorded from surface electrodes over the extensor digitorum brevis after a maximal stimulus to the common peroneal nerve at the knee (A), deep peroneal nerve on the dorsum of the ankle (B), accessory deep peroneal nerve below the head of fibula (C) and posterior to the lateral malleolus (D), and tibial nerve posterior to the medial malleolus (E) at the ankle. Left and right panels show responses before and after block of the accessory deep peroneal nerve with 2% lidocaine posterior to the lateral malleolus. Diagram of the foot indicates the site of block (x) and the points of stimulation (B, C, and D) and recording (R). (***B***) Course of the accessory deep peroneal nerve and action potentials recorded with coaxial needle electrode (R) in the lateral belly of the extensor digitorum brevis muscle following stimulation of the common peroneal nerve at the knee (A), just below the head of fibula (B), superficial peroneal nerve (C), accessory deep peroneal nerve posterior to the lateral malleolus (D) and deep peroneal nerve on the dorsum of the ankle (E). The volume-conducted positive potential from the medial bellies of the extensor digitorum brevis (E) reduced amplitude of negative response recorded from the lateral belly with stimulation of the common peroneal nerve at A or B. (From Lambert,[83] with permission.)

the lateral aspect of the leg after arising from the superficial peroneal nerve, then passes behind the lateral malleolus and proceeds anteriorly to innervate the lateral portion of the extensor digitorum brevis.[83] Occasionally, the extensor digitorum brevis may receive its exclusive supply from this communication.[100] The anomaly, when inherited, shows a dominant trait.[24]

In patients with this anastomosis, stimulation of the deep peroneal nerve at the ankle elicits a smaller CMAP than stimulation of the common peroneal nerve at the knee. Stimulation of the accessory deep peroneal nerve behind the lateral malleolus activates the anomalously innervated lateral portion of the muscle. Injury to the deep peroneal nerve ordinarily causes weakness of the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and extensor digitorum brevis. In the presence of the anastomosis, however, such a lesion would spare the lateral portion of the extensor digitorum brevis, which therefore shows no evidence of denervation. Overlooking this possibility would lead to an erroneous interpretation.[29] The collision technique[63] may help identify isolated abnormalities of the accessory deep peroneal nerve.[130]

Other Anomalies of the Lower Limb

The sural nerve, ordinarily a sensory branch of the tibial nerve, may arise from the common peroneal nerve, which in turn receives anastomosis from the tibial nerve.[112] Although the nerve usually consists purely of sensory fibers, its anomalous motor branch may innervate the abductor digiti quinti of the foot.[88] Rare motor anastomosis between the peroneal and tibial nerves, if undetected, may give rise to confusing patterns of waveform similar to those seen in Martin-Gruber anomaly.[139] In rare cases, the tibial nerve may supply all the intrinsic foot muscles.[89] Documenting this and other anomalous innervation patterns has proven difficult in the presence of volume-conducted responses.[3,91] In fact, a pair of surface electrodes placed anywhere in the foot register a muscle action potential after stimulation of peroneal or tibial nerve. Needle studies may also fall short of establishing conclusive evidence because this type of recording, though restricted, does not eliminate the contribution from other intrinsic foot muscles. In questionable cases, a collision technique[63] or nerve block may establish selective activation of the target nerve by removing the unwanted impulses.

5. CONDUCTION BLOCK VERSUS PHASE CANCELLATION

Physiologic Temporal Dispersion

In addition to the maximal motor or sensory conduction velocities based on the onset latencies, waveform changes of compound muscle and sensory nerve action potentials help estimate the range of the functional units.[67,109] This aspect of analysis plays a greater role when studying a peripheral neuropathy with a focal lesion affecting some axons and sparing others.[40,87,99] In clinical tests of motor and sensory conduction, the size of the recorded response approximately parallels the number of excitable fibers (see Chapter 10-2). The responses elicited by proximal and distal shocks may vary as the result of physiologic or pathologic desynchronization among the individual potentials.

Under normal condition, the impulses of physiologically slow-conducting fibers lag increasingly behind those of fast-conducting fibers over a long conduction path. With increasing distance between stimulating and pickup electrodes, the recorded potentials become smaller in amplitude and longer in duration; and, contrary to the common belief, the area under the waveform also diminishes. Thus, proximal stimulation in the axilla or Erb's point normally gives rise to a very small digital potential compared to a much larger response elicited by distal stimulation at the wrist or palm. This discrepancy may lead to a false diagnosis of a conduction block between the proximal and the distal sites of stimulation.[66,108]

A phase cancellation results when two waveforms contain negative and positive phases of comparable size, which superimpose. With short-duration diphasic sensory spikes, a slight physiologic latency difference could line up the positive peaks of the fast fibers with the negative peaks of the slow fibers, canceling both (Figs. 11-11 and 11-12A). This phenomenon

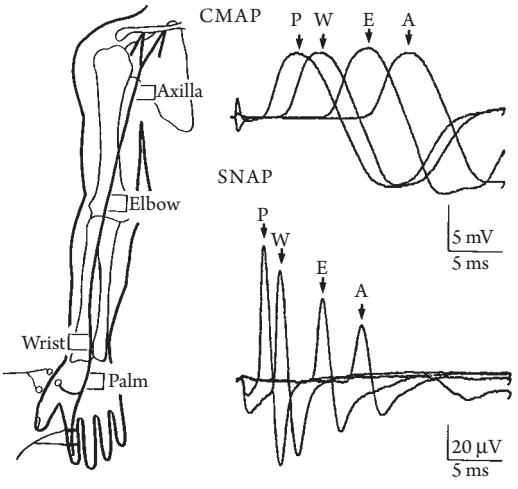

FIGURE 11-11 Simultaneous recordings of compound muscle action potentials from the thenar eminence and sensory nerve action potentials from the index finger after stimulation of the median nerve at palm, wrist, elbow, and axilla. A series of stimuli elicited nearly the same muscle response but progressively smaller sensory response from the wrist to the axilla. Note a linear change of sensory amplitudes, which usually indicate physiologic temporal dispersion and phase cancellation (cf. Fig. 11-12). (Modified from Kimura, Machida, Ishida et al.[73])

alone can reduce the normal sensory nerve action potential to below 50% in amplitude as well as in area, a conservative figure derived from computation of a small number of nerve fibers.[75,118,157] Thus, a major reduction in size of the compound sensory action potential can result solely from physiologic phase cancellation. In a triphasic orthodromic sensory potential, as compared with biphasic antidromic digital potentials, the initial positivity provides an additional probability for phase cancellation. In contrast, motor unit potentials, having a longer duration, superimpose nearly in phase rather than out of phase for the same latency shift (Fig. 11-12B). This accounts for a limited reduction in size of CMAP by the same temporal dispersion.[107] As expected from the term *duration-dependent phase cancellation*,[73] a physiological temporal dispersion may substantially reduce the amplitude of a short duration CMAP such as those recorded from intrinsic foot muscles.[132] Considering linear changes of amplitude and duration, the area will follow a second-order polynormal function of conduction distance provided the area equals amplitude times duration and a constant.[56]

The degree of overlap between peaks of opposite polarity depends on the separation between E1 and E2, which dictates the duration and waveform of unit discharges.[10] Changes in temperature also affect the temporal dispersion influencing the fast- and slow-conducting fibers more or less equally in percentage, and therefore differently in absolute terms.[126] Consequently, a set of criteria for normal range of reduction established in one study does not hold universally unless the methodology used matches exactly in every detail. Difficulty in adhering to the technical specificity makes the most commonly used percentage criteria untenable for clinical assessments. To circumvent this difficulty, segmental stimulation at more than two sites compares successively elicited responses intraindividually, eliminating the need to refer to the established norms. The size of sensory potentials normally changes linearly with the length of the nerve segment based on physiologic phase cancellation.[73,77] A nonlinear drop in size, therefore, signals an abnormality.

Pathologic Temporal Dispersion

If the latency difference between normal and demyelinating motor fibers reaches approximately one-half the duration of a motor unit potential (MUP), as expected in some neuropathy, the CMAP also diminishes dramatically based solely on phase cancellation as predicted by our model.[75] This type of pathological phase cancellation reduces the amplitude of muscle response well beyond the usual physiologic limits. This finding commonly seen in acquired and, to a lesser extent, in hereditary demyelinating neuropathy[22,141] may give rise to a false impression of motor conduction block.[75,99,118] This phenomenon explains an occasionally encountered discrepancy between severe reduction in amplitude of the CMAP despite relatively normal recruitment of the motor units and preserved strength. Pathologic temporal dispersion may also abolish a sensory nerve action potential (SNAP) with proximal stimulation, mimicking

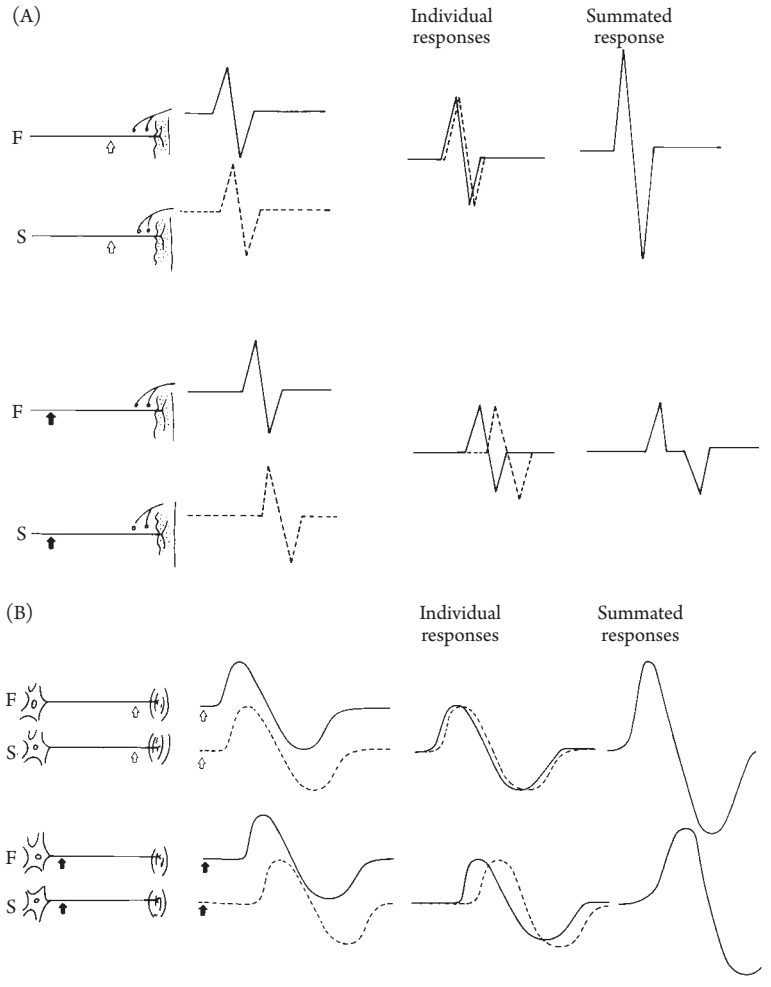

FIGURE 11-12 A model for duration-dependent phase cancellation between fast (F) and slow (S) conducting sensory (***A***) and motor (***B***) fibers. With distal stimulation, two unit discharges summate in phase to produce a potential twice as large for both sensory and motor responses. With proximal stimulation, a slight delay of the slow fiber causes phase cancellation for short-duration sensory potentials as the negative peak of the slow fiber (dotted line) superimposes on positive peak of the fast fiber (solid line), resulting in a 50% reduction in size of the summated response (***A***). In contrast, despite the same latency shift as sensory potential between fast- and slow-conducting fibers, long-duration motor unit potentials still superimpose nearly in phase (***B***). Thus, a physiologic temporal dispersion usually alters the size of the muscle action potential only minimally. This does not hold true with short-duration muscle responses such as those recorded from intrinsic foot muscle, which may show substantial reduction of amplitude by physiologic phase cancellation. (Modified from Kimura, Machida, Ishida, et al.[73])

a conduction block, if distal stimulation elicits a relatively normal response.

Model for Phase Cancellation

A simple model provides an excellent means to test the effects of desynchronized inputs.[75] A shock applied to the median (S1) or ulnar (S2) nerve at the wrist evokes a SNAP of the ring finger and a CMAP over the thenar eminence. Hence, a concomitant application of S1 and S2 with varying interstimulus intervals simulates the effect of desynchronized inputs (Fig. 11-13). In 10 hands, an interstimulus interval on the order

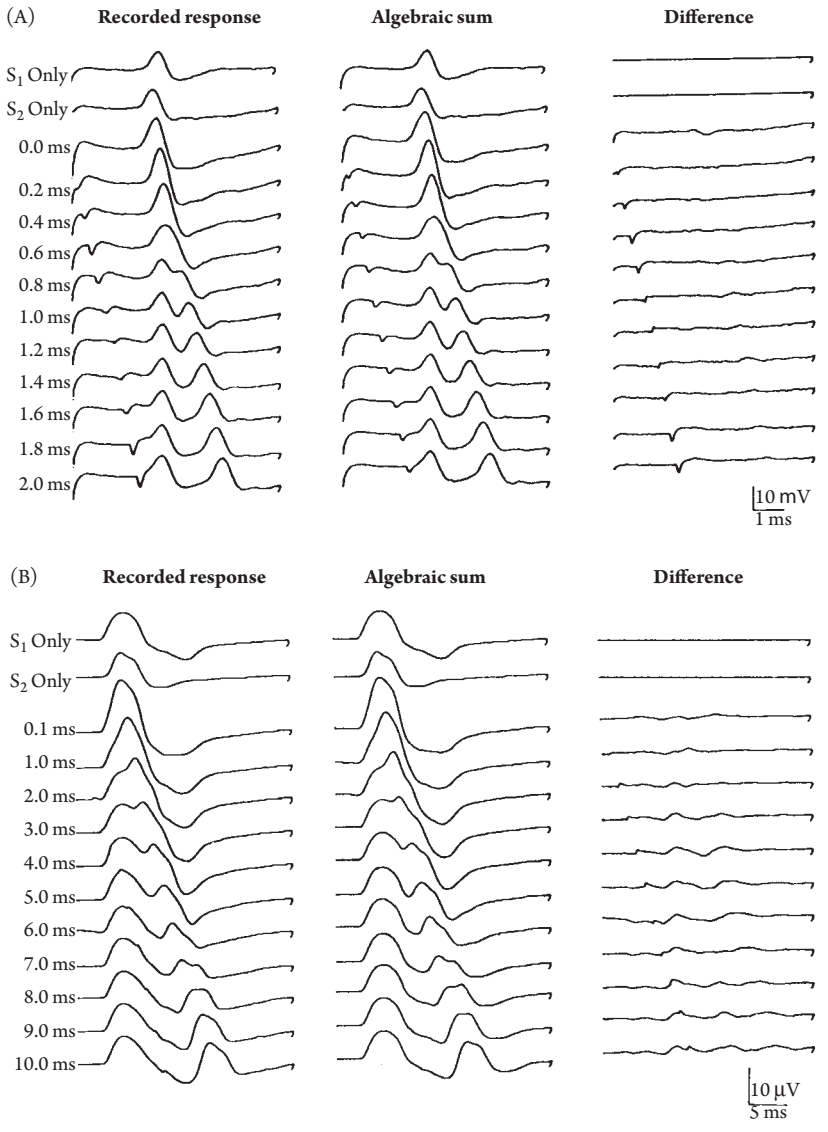

FIGURE 11-13 (***A***) Antidromic sensory potentials of the ring finger elicited by stimulation of the median (Sl) or ulnar (S2) nerve (top two tracings), and by both Sl and S2 at interstimulus intervals ranging from 0 to 2.0 ms (*left*). Algebraic sums of the two top tracings (*middle*) closely matched the actual recording at each interval as evidenced by small difference shown in computer subtraction (*right*). The area under the negative peak reached a minimal value at 0.8 ms in actual recordings as well as in calculated waveforms (Modified from Kimura, Sakimura, Machida, et al.[75]) (***B***) Compound muscle action potentials from the thenar eminence elicited by stimulation of the median (Sl) or ulnar (S2) nerve (top two tracings) and by both Sl and S2 at interstimulus intervals ranging from 0 to l0 ms (*left*). Algebraic sums of the top two tracings almost, but not exactly, equaled the actual recordings as shown by computer subtraction at each interstimulus interval (*right*). The area under the negative peak reached a minimal value at 5 ms in actual recordings as well as in calculated waveform (Modified from Kimura, Sakimura, Machida, et al.[75])

of 1 ms between S1 and S2 caused a major reduction in sensory potential by as much as 50% but little change in muscle action potential. With further separation of S1 and S2, the muscle response began to decrease in amplitude and area, reaching a minimal size at interstimulus intervals of 5 to 6 ms. The duration also increased in proportion to the latency shift, although a gradual return of the response to the baseline obscured this aspect of change in waveform. A latency difference slightly less than one-half the total duration of unit discharge maximized the phase cancellation between the two components and consequently the loss of area under the waveform. Further increase in latency difference results in complete separation of the two potentials, precluding phase cancellation. As an inference, pathological temporal dispersion, ordinarily associated with reduction of compound action potentials, may cause a paradoxical increase in size if excessive desynchronization counters the physiologic phase cancellation (see Fig. 6-8B in Chapter 6).

Comparison between two responses elicited distally and proximally often fails to differentiate pathologic, as opposed to physiologic temporal dispersion because many variables make the commonly held percentage criteria untenable except in entirely standardized studies.[84] A simpler, more practical approach relies on a linear relationship seen in physiologic phase cancellation between the latency and the size of the recorded responses (Fig. 11-11).[70] This approach has a distinct advantage of not requiring adaptation of any specific recording variables such as interelectrode spacing, although it calls for segmental stimulation at more than two sites to test the linearity of observed changes (Figs. 11-14 and 11-15). Superimposing consecutive traces often reveals subtle abnormalities that may otherwise escape detection (Fig. 11-16). A nonlinear reduction in amplitude or area, often associated with waveform changes, indicates either a pathologic temporal dispersion or conduction block. The distinction between the two possibilities must in part depend on clinical and EMG findings. Conduction block, but not pathologic temporal dispersion, causes muscle weakness and decreased recruitment of motor units with voluntary contraction.

Alleviating the possibility of phase cancellation would simplify waveform analyses in nerve conduction studies. For example, referential derivation of a monophasic waveform in a "killed-end" arrangement, if technically feasible, would conserve the area irrespective of stimulus sites. This type of approach, however, would necessitate blocking the impulse propagation across the site of recording. Alternatively, area difference between negative and positive peaks in each unit discharge provides a unique measure, which sums without phase cancellation irrespective of

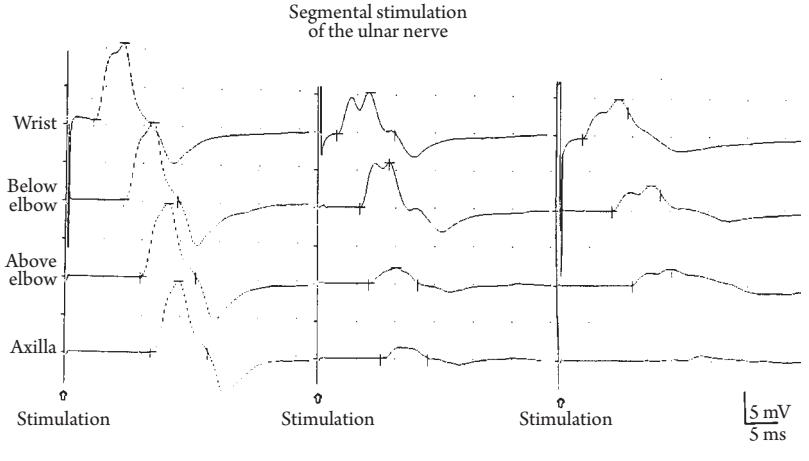

FIGURE 11-14 Ulnar nerve conduction study with segmental stimulation at the wrist, below elbow, above elbow, and axilla. Traces show a nearly complete conduction block in a 42-year-old patient (*right*), a partial conduction block in a 40-year-old patient (*center*), and a normal study (*left*) for comparison.

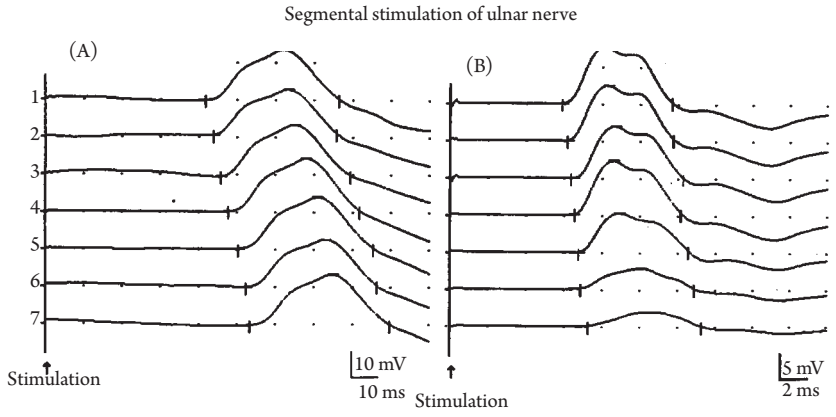

FIGURE 11-15 Segmental study of the ulnar nerve in 1 cm increments from below elbow (1) to above elbow (7). (***A***) A 41-year-old man (*left*) with distal ulnar neuropathy had prolonged terminal latency (3.7 ms) with a normal conduction across the elbow. (***B***) A 52-year-old woman (*right*) with a tardy ulnar palsy showed a normal distal latency with an abrupt drop in amplitude above the elbow (5 to 6 and 6 to 7), indicating a partial conduction block as the cause of weakness.

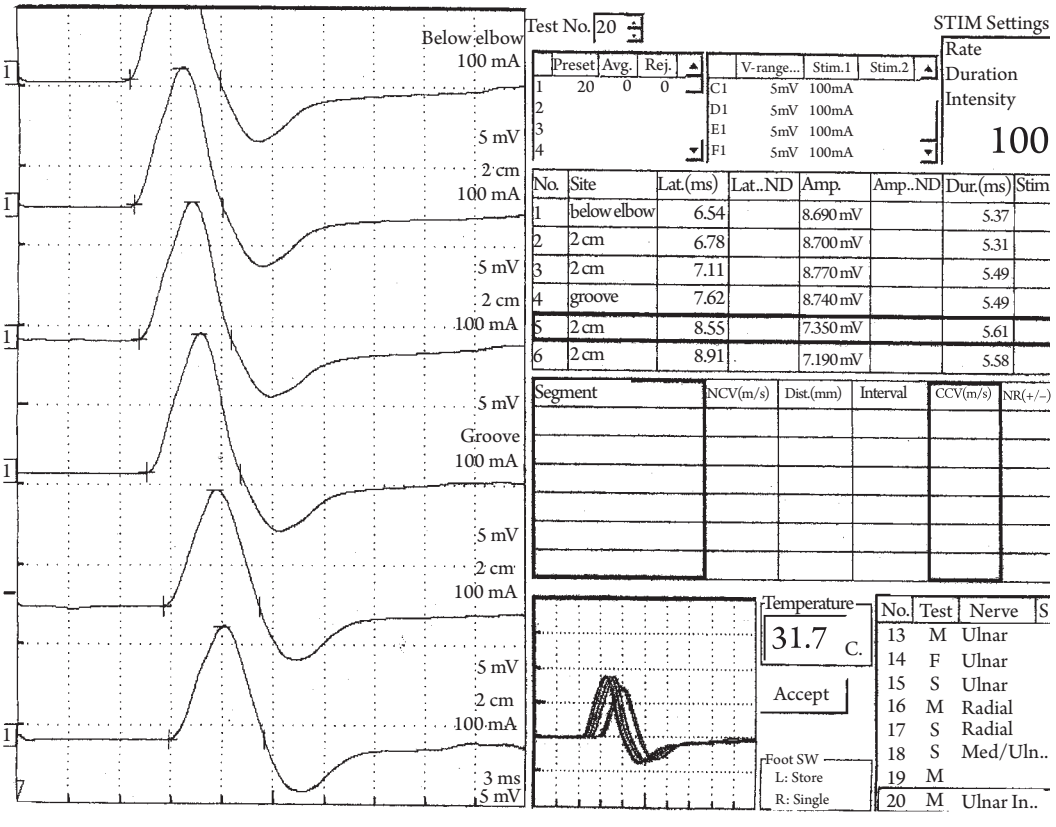

FIGURE 11-16 A patient with mild ulnar neuropathy at the elbow: Note nonlinear latency and amplitude shift clearly detected on superimposing consecutive traces as depicted in the smaller display shown on the right lower corner (cf. Fig. 5-7 in Chapter 5).

desynchronization among different units. In practice, however, muscle and nerve action potentials tend to have negative and positive peaks of similar size, and consequently a small area difference between the two makes precise determination difficult. Also, baseline shift or other electrical interference poses a major technical problem for reliable measure of area for this purpose.

Detection of Conduction Block

In motor or antidromic NCS, a nonlinear reduction in amplitude of the proximally elicited response usually suggests a conduction block, although it may also result from pathologic temporal dispersion.[23,151] Either finding usually implies the presence of focal demyelination,[141] although other conditions such as ischemia can cause similar reversible changes.[49] Except for occasional cases of secondary axonal degeneration associated with damage of the myelin sheath, EMG reveals little or no evidence of denervation. In the presence of partial conduction block, the MUPs, normal in amplitude and waveform, show poor recruitment from loss of functional fibers accompanied by a compensatory, rapid firing of the remaining axons.

Activity-dependent hyperpolarization of the motor axons induced by high-frequency nerve stimulation or voluntary contraction activity may produce conduction block (see Figs. 4-10 and 4-11).[15,48,57,58,103,160,161] A reduction in amplitude of CMAP elicited after 60-second maximal voluntary contraction documents a rate-dependent failure of nerve transmission. The refractory period of transmission tested by paired stimuli at intervals of 1–5 ms may also reveal loss of the safety factor and transmission failure in the distal segment.[80]

The usual criteria for conduction block in motor fibers evolve around the comparison of CMAP amplitude or area elicited by proximal versus distal stimulation.[2,117] This ratio remains normal in axonal neuronopathy, which reduces distal and proximal responses equally. A 20% to 50% reduction of proximally elicited CMAP with less than 15% increase in duration tends to suggest a conduction block. These percentage criteria, however, do not necessarily apply in all studies because the effects of temporal dispersion vary depending on the electrode placement and other factors. A nonlinear drop in amplitude or area serves as a better measure of abnormalities as discussed earlier. A triple stimulation method with double collisions (see Chapter 20-5) allows identification of motor conduction block even in the presence of desynchronization.[123] The technique fails for a lesion located proximal to the stimulus site or any pathology compromising nerve excitability, which may preclude supramaximal stimulation.

Combination of clinical and electrophysiologic findings helps document motor conduction block more definitely than the criteria based purely on waveform analysis.[69] In the case of conduction block, a shock applied distally to the nerve lesion in question elicits a vigorous twitch and a large CMAP despite disproportionately severe clinical weakness[68] as evidenced by paucity of voluntarily activated motor unit potentials.[19] The same finding also characterizes the weakness during the first few days of nerve transection while the distal stump of the nerve remains viable.[95] In this situation, subsequent studies performed 5 to 10 days after nerve severance show a progressive decrease in CMAP amplitude elicited by stimulation distal to the site of the lesion as the wallerian degeneration evolves (see Fig. 8-3 in Chapter 8).

Increased ranges of conduction velocities result in pathologic temporal dispersion broadening and diminishing the evoked action potential by phase cancellation in the absence of conduction block. Inability to distinguish pathologic temporal dispersion from conduction block poses some diagnostic problem, although either finding usually suggests demyelination. The absence of F waves complements conventional nerve conduction studies to document conduction block in the proximal segment[34,62] provided the excitability of the anterior horn cells remains normal.[36,106,147,148] Desynchronization of the nerve volley may also result from repetitive discharges at the site of axonal injury after the passage of a single impulse.

Several other factors may confuse clinical assessment of conduction block. The use of insufficient stimulus intensities at the proximal site erroneously reduces the proximally elicited

amplitude. Likewise, increased threshold for excitation of a regenerated or chronically demyelinated nerve segment may account for a reduced proximal response.[97] In some cases of multifocal motor neuropathy, failure to maximally excite the involved segment sometimes calls for near nerve stimulation using a needle electrode. Alternatively, stimulation of more proximal, unaffected nerve segment may give rise to a normal response, indicating the passage of impulse across the lesion site despite its abnormally elevated threshold for local excitation (Fig. 11-17). Unexpected contribution from anomalous branches such as Martin-Gruber anastomosis may lead to a confusing discrepancy in amplitude, as does inadvertant current spread to a neighboring nerve.[63] Temperature variation has profound effects on myelinated nerve fiber function. Heat can induce conduction block, and focal cooling can reverse it as shown in peroneal neuropathy at the fibular head.[125]

Nerve conduction studies primarily assess large-diameter myelinated fibers. Thus, lesions selectively affecting smaller myelinated fibers may result in no major loss of the proximal-to-distal

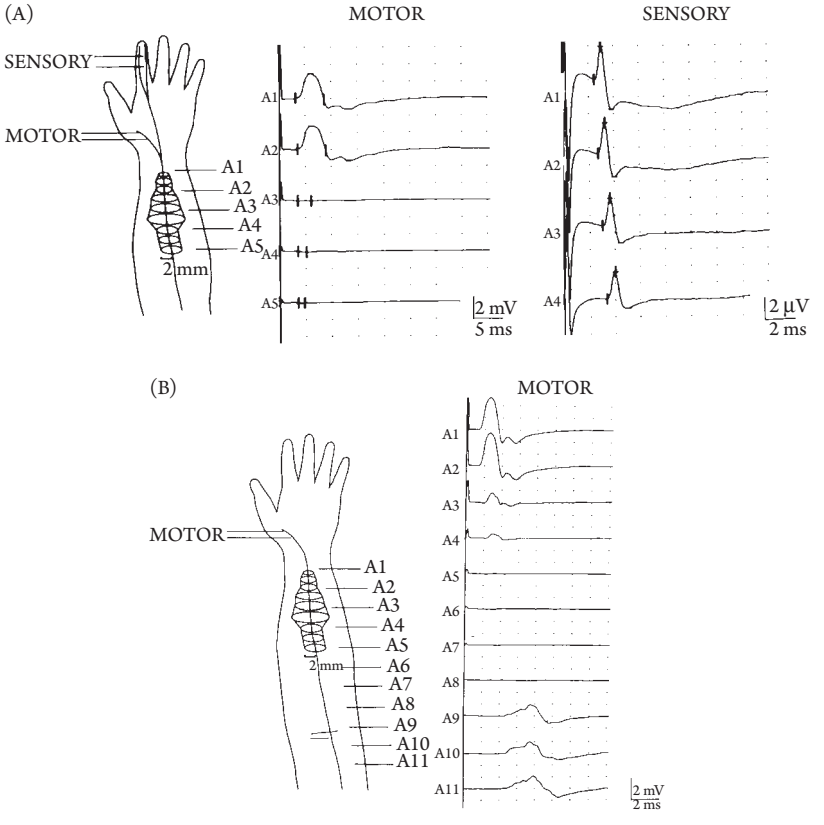

FIGURE 11-17 (***A***) Motor and sensory conduction studies of the left median nerve in a patient with multifocal motor neuropathy. The left diagram illustrates the consecutive slices of magnetic resonance images in relation to the sites of stimulation at the wrist crease (A1) and at 2-cm increments more proximally. One horizontal division equals 5 ms (motor) or 2 ms (sensory). Note a complete and selective motor conduction block across the segment between A2 and A3, corresponding to the site of maximal nerve enlargement. (From Kaji, Oka, Tsuji, et al.,[59] with permission.) (***B***) A repeat study in the same patient as shown in (*A*) after return of strength of the median-innervated intrinsic hand muscles. High-intensity stimulation failed to excite the nerve along the affected segments, A5–A8, mimicking a conduction block. More proximal stimulation at the elbow applied to the presumably normal nerve segments, A9–A11, however, induced a series of temporally dispersed muscle response associated with thumb abduction, indicating recovery of conduction. (Modified from Kimura.[69])

ratio. In antiserum-mediated experimental demyelination,[81] smaller fibers underwent conduction block first. Contrary to the common belief, experimental studies in human sensory nerve conduction also suggest that a focal compression initially affects the slow-conducting, small-diameter fibers.[143] Sequential study of quantitative sensory testing (QST) documents the same order of modality-specific vulnerability of sensory nerve fibers to mild compression.[152] Thus, testing cold perception threshold (CPT), rather than vibratory perception threshold (VPT), provides a better QST to delineate rapidly reversible symptoms induced by acute compression seen in neurogenic claudication and entrapment syndrome. If this holds in the acute phase of neuropathies, normal conduction studies do not necessarily rule out the presence of conduction block if it involves small-diameter fibers selectively.

In contrast to motor studies that rely heavily on clinical assessment of weakness to define conduction block, sensory studies usually depends solely on waveform analysis of antidromic response elicited by segmental or short incremental stimulation (see Chapter 6-3). Surface stimulation applied at multiple sites may not necessarily activate the exact point of nerve as intended. An alternate method to circumvent this uncertainty consists of stimulating the digital nerve and recording the orthodromic sensory potentials at multiple points with a series of electrodes mounted 1 cm apart on a specially constructed flexible strap.[52,67] Though applicable to any superficially located sensory or mixed nerve (see Fig. 19-2 in Chapter 19), the method suffers from a major deficiency. Using surface recording, the depth of the nerve from the skin surface greatly influences the amplitude of the evoked potential. Thus, a small potential, if derived from a deeply located portion of the nerve segment, does not necessarily imply pathologic amplitude reduction.

Conduction block also constitutes a feature of intraoperative spinal cord monitoring usually conducted by stimulating the spinal cord distally at one caudal level and recording the ascending sensory potentials at multiple rostral points with a series of electrodes. Unlike peripheral study, spinal segmental recording registers comparable evoked potential because recording electrodes lie nearly equidistant to the spinal cord, if placed in the subdural or epidural space, the ligamentum flavum, or the intervertebral disc.[105,146] Figure 11-18 shows unipolar recording from the ligamentum flavum at multiple levels after epidural stimulation of the cauda equina in a patient with cervical spondylotic myelopathy. The combination of an abrupt loss of the negative peak at one level, augmentation of the negative peaks in the leads closely caudal to that level, and monophasic positive waves at more rostral levels constitutes a typical pattern for a complete focal conduction block.

Paradoxically enhanced negative peak caudal to the lesion site results from resynchronization of physiologically desynchronized signals because the leading impulses stop traveling when they reach the site of involvement, whereas the trailing impulses continue to propagate until they arrive at the same point. In addition, the fast-conducting fibers lose their terminal-positive phases, which would have reduced the negative phases of the slower fibers by physiologic phase cancellation. Even when only some of the fibers sustain a conduction block, the identical mechanism enhances the negative peak at the points immediately preceding an incomplete lesion. Thus, the response consists of positive-negative diphasic waves with enhanced negativity at points immediately preceding the block, a diphasic wave with reduced negativity at the point of the block, and initial-positive waves alone or abolition of any wave at points beyond the block.[70,144,145]

6. COLLISION TECHNIQUE AND WAVEFORM ANLAYSIS

Distribution of Conduction Velocities

In contrast to the onset latency, which measures only the fastest conducting fibers, the waveform of the elicited response reveals the functional status of the remaining slower conducting fibers. The range between the fastest and slowest nerve fibers determines the degree of temporal dispersion and the duration of the evoked potential. With a loss of axons, a smaller range of conduction velocity among the remaining nerve fibers reduces the duration of the CMAP or SNAP. Selective slowing

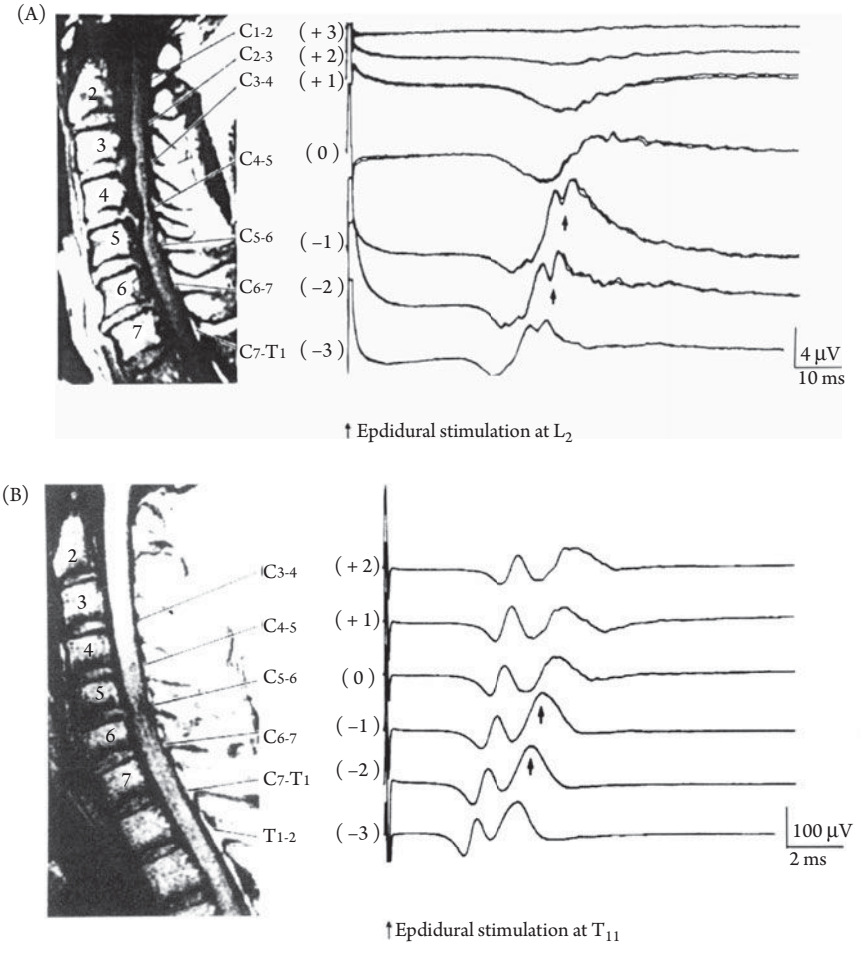

FIGURE 11-18 (***A***) T1-weighted magnetic resonance image (TR 400 ms; TE 13 ms) (*left*) and a recording of spinal somatosensory evoked potentials (*right*) obtained from a 65-year-old patient with cervical myelopathy. Epidural stimulation at L2 spinous process elicited a series of potentials recorded unipolarly from the ligamentum flavum of C7-T1 through C1–2 intervertebral space. Note the progressive increase in size of the negative component (arrows pointing up) from C7-T1 (–3) through C5-C6 (–1) with the abrupt reduction at C4-C5 (0) followed by a monophasic positive wave at C3-C4 (+1). The negative wave doubled in amplitude and quadrupled in area at "–1" compared to "–3." The "0" corresponded to the level of the spinal cord showing the most prominent compression on the magnetic resonance image. (Modified from Tani, Ushida, Yamamoto, et al.[144]) (***B***) A T1-weighted magnetic resonance image (TR 600 ms; TE 90 ms) (*left*) and a recording of spinal somatosensory evoked potentials (*right*) obtained from a 36-year-old patient with cervical spondylotic myelopathy. Epidural stimulation at T-11 spinous process elicited a series of potentials recorded unipolarly from the ligamentum flavum of T1–2 through C3–4 intervertebral space. Note the progressive increase in size of the second negative component (arrows pointing up) from T1–2 (-3) through C6–7 (-1) with the abrupt reduction at C5–6 (0). The "0" corresponded to the level of the spinal cord showing a moderate compression on the magnetic resonance image. (Modified from Tani, Ushida, Yamamoto, et al.[144])

of faster conducting fibers also shows the same tendency. Conversely, selective slowing of slower conducting fibers will result in a greater temporal dispersion.[73] Near nerve recordings may serve as a sensitive measure of peripheral nerve pathology uncovering late components from slow sensory fibers, not detectable by surface electrodes.[136]

The use of a needle electrode allows selective recording from different motor units within a given muscle. A wide range of motor fibers with

different conduction characteristics sampled by this means show a close correlation to the twitch tension and recruitment threshold.[28] The technique has limited clinical application because patients tolerate multiple needle insertions poorly. The length of the motor axons, rather than the conduction characteristics, may also dictate the latencies of individual MUP. If so, unlike in sensory studies, onset latencies do not necessarily represent the fastest conducting motor fibers. Similarly, peak and terminal latencies do not always reflect slower conducting elements, as shown by velocity calculations from proximal and distal stimulation based on these values. This finding also supports the notion that the range of muscle fiber conduction velocity, in addition to the motor axon characteristics, dictates the CMAP waveform.

Mathematical models[153,158] based on decomposition of compound action potentials have provided some interesting, though unconfirmed, estimates of conduction velocity distribution. For example, nerve conduction velocities of the large myelinated axons varied by as much as 25 m/s between fast and slow sensory fibers but over a much narrower range of 11 m/s for motor fibers.[31] This observation, although not universally accepted,[30] would in part explain the different effect of temporal dispersion on sensory and motor fibers for a given nerve segment.[108] Decomposition techniques, in general, suffer from inherent difficulty of identifying individual elements no longer retained in the CMAP or SNAP because of phase cancellation. Any sophistication in technology cannot retrieve the information, if already lost. Furthermore, some of the assumptions derived from normal distributions may not hold in various types of neuropathies.[27,149] To improve clinical utility, some advocate frequency attenuation method, which, based on Fourier therory, elucidates dissimilarities of distally and proximally elicited CMAP waveform.[12]

Collision Block of Fast or Slow Fibers

The duration of the compound action potentials, although useful as an indirect estimate, falls short of providing a precise measure of slow fibers. Different methods devised for a more quantitative assessment commonly employ the principle of collision. A distal stimulus of submaximal intensity initially excites the large-diameter, fast fibers with low thresholds. A shock of supramaximal intensity given simultaneously at a proximal site, then, allows selective passage of impulses in the slower fibers, because antidromic activity from the distal stimulation blocks the fast fibers. This assumption, however, may fail if the order of activation with threshold stimulation depends on the spatial relationship between the stimulating electrode and the different fascicles rather than their excitability.

An alternative method utilizes paired shocks of supramaximal intensity.[46,53,54,101,126] This technique, in essence, consists of incremental delay of proximal shock after distal stimulation without varying stimulus intensity. Shocks applied simultaneously cause collision to occur in all fibers. With increasing intervals between the two stimuli, the fastest fibers escape collision before the slow fibers. Measurement of the minimal interstimulus interval sufficient to produce a full CMAP yields an indirect assessment of the slowest conduction (Table 11-1).

Direct latency determination of the slowest fibers requires blocking of the fast-conducting fibers, leaving the activity in the slower fibers unaffected. The use of two sets of stimulating electrodes, one placed at the axilla and the other at the wrist, allows delivering two stimuli, S(A1) and S(A2), through the proximal electrodes and another shock, S(W), through the distal electrodes. The antidromic impulse of S(W) blocks the orthodromic impulse of S(A1) provided the distal shock precedes the arrival of the proximal impulse. With an appropriate adjustment of the interstimulus interval between S(A1) and S(W), the collision takes place only in the slow fibers, sparing the antidromic activity from S(W) in the fast fibers. Thus, the impulse of the subsequent proximal stimuli, S(A2), collides with the antidromic activity only in the fast fibers. In this way, the muscle action potential elicited by S(A2) corresponds to the remaining slow-conducting fibers that selectively transmit the orthodromic impulses (Fig. 11-19).

Table 11-1 Range of Conduction Velocity in Motor Fibers of the Ulnar Nerve

AUTHORS	FASTEST FIBERS	SLOWEST FIBERS	RANGE
Poloni and Sala[114]			35%–39%
Nix, Luder,Hopf, et al[101]	60.0 ± 3.2		4–7 m/s
Skorpil[138]	61.1 ± 4.5	37.7 ± 7.1	22.4 m/s

This technique allows direct determination of the amplitude and latency of the slowest conducting fibers. The muscle action potential elicited by S(A2) shows progressive diminution of amplitude as the antidromic impulse of S(W) eliminates an increasing number of fast-conducting fibers. The latency changes, however, do not always coincide exactly with the values expected from the time interval between S(A1) and S(W), presumably because the impulses in the slowest conducting fibers do not necessarily arrive at the motor endplate last. The conduction time must depend not only on the speed of the propagated impulse but also, and perhaps more important, on the length of fine terminal branches, which characteristically lack myelin sheath. Even though they vary in length only on the order of a few millimeters, this degree of difference can still give rise to a

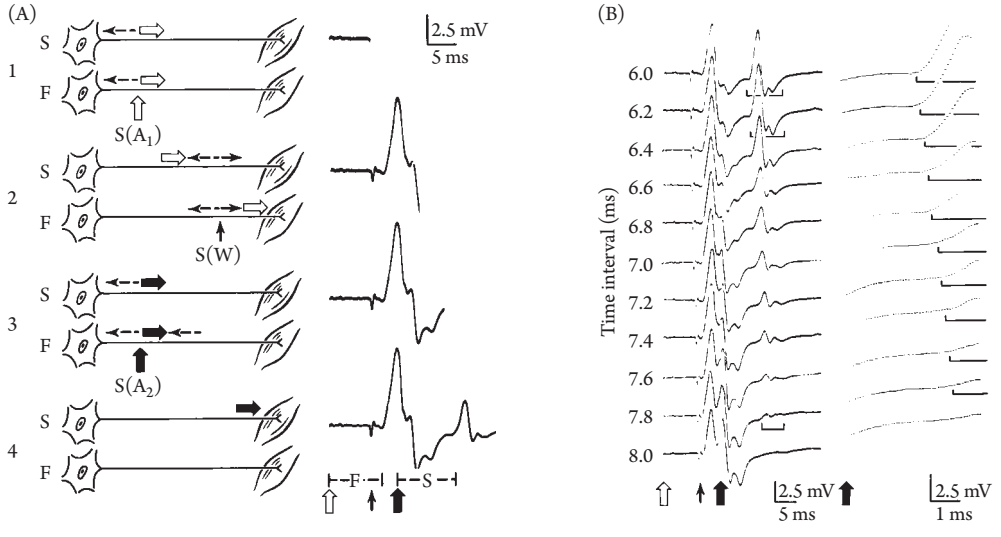

FIGURE 11-19 (***A***) Compound muscle action potential recorded by surface electrode placed over the abductor digiti minimi after stimulation of the ulnar nerve. The diagrams on the left show orthodromic (solid line) and antidromic (dotted line) impulses generated by three stimuli, S(A1), S(W), and S(A2), delivered at the axilla, wrist, and axilla, respectively. Note the collision between the orthodromic impulse from S(A1) and antidromic impulse of S(W) in slow-conducting fibers (S), and between the orthodromic impulse of S(A2) and antidromic impulse of S(W) in the fast-conducting fibers (F). The orthodromic impulse of S(A2) propagates along the slow-conducting fibers and elicits the second compound muscle action potential. (***B***) Paired axillary shocks of supramaximal intensity combined with a single shock at the wrist. The first axillary stimulation, S(A1), preceded the wrist stimulation, S(W), by intervals ranging from 6.0 to 8.0 ms in increments of 0.2 ms. Adjusting the second axillary shock, S(A2), to recur always 6.0 ms after S(W) automatically determined interstimulus interval between S(A1) and S(A2). The figures on the left show the entire tracing with a slow sweep (5 ms/divison) triggered by S(A1) for amplitude measurement. The figures on the right illustrate latency determination with a fast sweep (1 ms/division) triggered by S(A2) and displayed after a predetermined delay of 6.0 ms.

substantial latency change at this level, where the impulse normally conducts at a very slow rate.

Volitionally Generated Nerve Impulses

Many studies have elucidated the relationship between electrical and mechanical events in contracting muscle. Full wave rectified EMG commonly used to measure the electrical activity resulting from asynchronous firing of many motor units provides a correlation between the electrical potential and the muscle force, but only indirectly. A collision technique (Fig. 11-20 A,B), in effect, converts asynchronous nerve impulses into a synchronous volley. The muscle action potential elicited by this means yields a true electrical corollary of voluntary muscle contraction.

Recording from the first dorsal interosseous muscle, supramaximal stimulation delivered to the ulnar nerve either at the wrist or axilla evokes nearly identical CMAP, M(W), or M(A) (Fig. 11-20A). A paired stimulus, if applied simultaneously at the wrist and axilla with the subject at rest, elicits M(W) but not M(A) because the orthodromic impulse from the axilla collides with the antidromic impulse from the wrist. During muscle contraction, antidromic impulses from the wrist first collide with voluntary impulses in some motor axons. Therefore, the distal shock cannot completely block the impulse evoked by axillary stimulation. The fraction of M(A) so recorded, termed M(V), represents the number of the motor axons carrying a voluntary impulse. This technique produces, in effect, a synchronized equivalent to the asynchronous motor neuron activity associated with voluntary contraction.[64] As expected, the amplitude M(V) relates linearly to the force of contraction under isometric conditions (Fig. 11-20B). Using M(V), an approximate percentage of motoneuron pool discharging during a 10-ms period increased linearly with muscle force from 2.4% ± 1.4% at 0.5 kg to 23.5% ± 9.6% at 4.5 kg in 10 healthy subjects.

Needle study during weak voluntary contraction best characterizes the recruitment and discharge pattern of individual motor units. Strong muscle contraction interferes with the identification of a single MUP in the presence of a large shower of spikes from many different units. Moreover, the few motor units selected for observation do not necessarily reveal the behavior of the total population of motoneurons. The collision technique provides a direct means of elucidating the relationship between the discharge pattern of the motoneuron pool and muscle force over a wide range of voluntary contraction. This method also serves as a good measure of the central drive to assess supraspinal components of human muscle fatigue.[37]

7. LONG AND SHORT OF NERVE CONDUCTION STUDIES

Inching Technique for Short Segment

Ordinary conduction studies suffice to approximate the site of involvement in entrapment neuropathies. More precise localization requires inching the stimulus in short increments along the course of the nerve for isolation of a focal lesion.[65,70] In the evaluation of a localized pathology such as a compressive neuropathy, inclusion of the unaffected segments in calculation dilutes the effect of abnormalities, lowering the sensitivity of the test. Incremental stimulation across the shorter segment helps isolate a focal lesion that may otherwise escape detection (see Chapter 6-3). Thus, the study of short segments provides better resolution of restricted lesions. Assume a nerve impulse conducting at a rate of 0.2 ms/cm (50 m/sec) except for a 1-cm segment where demyelination has doubled the conduction time to 0.4 ms/cm. In a 10-cm segment, normally covered in 2.0 ms, a 0.2-ms increase would amount to only a 10% change. This delay, approximately equal to one standard deviation of any measure, falls well within the normal range of variability. The same 0.2-ms increase, however, would represent a 100% change in latency if measured over a 1-cm segment, signaling a clear abnormality. The large per-unit increase in latency more than compensates for the inherent measurement error associated with multiple stimulation in short increments.[13,39,65]

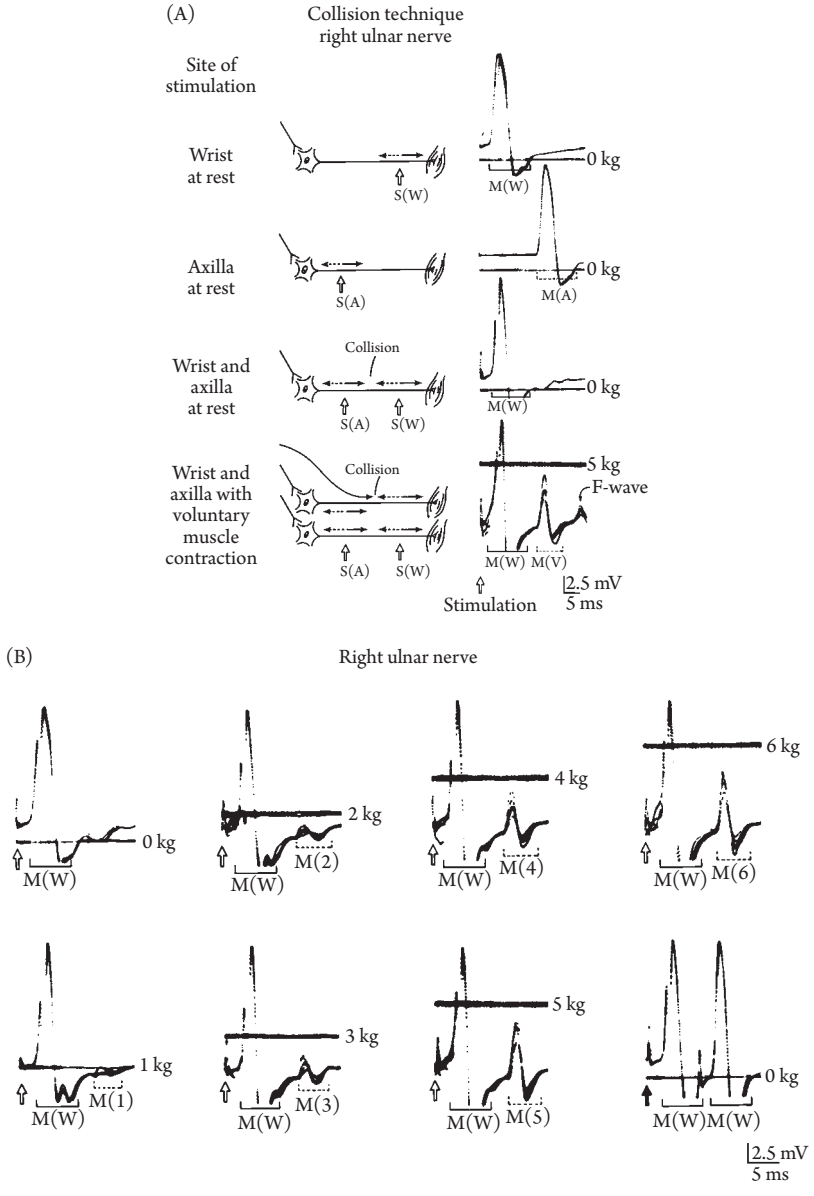

FIGURE 11-20 (***A***) Compound muscle action potentials, M(W) and M(A), from the first dorsal interosseous and muscle force (straight line). At rest, the antidromic impulse from stimulation at the wrist eliminated the orthodromic impulse from the axilla by collision. With muscle contraction (bottom tracing), M(V) appeared in proportion to the number of axons in which the voluntary impulse first collided with the antidromic impulse from the wrist. (***B***) Correlation between muscle force and electrical activity, with the same stimulation (open arrow) and recording as in the bottom tracing of (***A***). Muscle force ranged from 0 to 6.0 kg (straight line). In the last tracing, paired stimuli (closed arrow) delivered at the wrist elicited the second M(W) to appear with the same time delay as M(V). The second M(W) equaled the first in amplitude, indicating the integrity of the neuromuscular excitability. (Modified from Kimura.[64])

This technique is best suited for assessing a possible compressive lesion such as median nerve entrapment in the palm,[65,121,135] ulnar neuropathy at the elbow[13,61,98,159] or peroneal nerve compression at the knee.[60] With stimulation of the median nerve every 1 cm across the wrist, the latency increments average 0.16 to 0.21 ms/cm from the mid-palm to the distal forearm. An abrupt change in waveform nearly always accompanies a sharply localized nonlinear latency increase across the site of compression, indicating a focal abnormality.[65] An excessive latency shift may result from inaccurate advances of the stimulating electrodes or inadvertent spread of stimulus current activating a more excitable neighboring segment. In questionable cases, studies of the more proximal and distal segments suffices to clarify the ambiguity. If the observed nonlinear shift results from a focal process, rather than technical errors, the latencies of successive responses above and below the affected zone must form two parallel lines rather than one. These findings localize a focal lesion within the short interval in question encompassed by normal segments proximally and distally.

Late Responses for Long Segment

A number of neurophysiological methods supplement the conventional techniques for the assessment of longer pathways.[35] The selection of such techniques necessarily reflects the special orientation of each laboratory. Those of general interest include the F wave and the H reflex (see Chapters 7-4 and 9-2). In assessing a diffuse or multisegmental process such as polyneuropathies, the longer the segment under study, the more evident the conduction delay. In other words, this approach has an advantage of accumulating all the segmental abnormalities, which individually might not show a clear deviation from the normal range. If a nerve impulse conducts at a rate of 0.2 ms/cm (50 m/s), a 20% increase for a 10-cm segment, for example, yields an unimpressive delay of only 0.4 ms, whereas the same change for a 100-cm segment amounts to an easily detectable 4.0 ms.

In addition, evaluating a longer, as compared to shorter, segment improves the accuracy of latency and distance measurements because the same absolute difference constitutes a smaller percentage error. In determining the length of a 10-cm nerve segment, distance values measured over the surface may vary between 9.5 and 10.5 cm. A 1-cm difference constitutes a 10% error, leading to the range of calculated conduction velocities of 50 m/s to 55 m/s. The same 1-cm difference in measuring a 100-cm segment represents only 1% change, or the range of 50 m/s to 50.5 m/s. Using the same argument, percentage errors in latency measurement also diminish for a longer, as compared to shorter, nerve segment. Consequently, the study of a longer path offers a better sensitivity and higher accuracy and, as stated in the next section, an improved reproducibility in serial studies.

Reliability and Reproducibility

Nerve conduction study, as a sensitive and objective measure, can document serial changes of neuropathic process.[76] Its accuracy primarily depends on the adherence to technical details, as any deviations from the standards result in inconsistencies of the results.[18] This aspect particularly influences a multicenter clinical trial, which involves many investigators of different background and training. Technical factors also determine the degree of reproducibility for any measures used in the evaluation of polyneuropathy,[155] as reported, for example, in patients with diabetes.[9,20,128] In most studies,[5,20,155] nerve conduction velocity and F-wave latencies varied less than motor and sensory amplitude. The use of large electrodes improved reproducibility of CMAP amplitude.[150] Of a few reported studies on F waves, all but one[155] dealt with the experience at a single laboratory, showing variation of up to 10 m/s.

We also conducted a multicenter analysis on intertrial variability of nerve conduction studies to determine the confidence limits of the variations for use in future drug assessments for diabetic polyneuropathy.[69,79] All measurements, repeated twice at a time interval of 1 to 4 weeks, followed a standardized method in the study of 132 healthy subjects (63 men) and 172 patients (99 men) with diabetic polyneuropathy. In both the controls and the patient group, amplitude

varied most followed by terminal latency, and motor and sensory conduction velocity. In contrast, minimal F-wave latency showed the least change, with the range of variability of only 10% for the study of the median nerve and 11% for the tibial nerve in normals and 12% and 14% in patients with diabetic polyneuropathy.

These results support the contention that minimal or mean F-wave latency serves as the most stable and consequently reliable measure for a sequential nerve conduction study of the individual subjects.[113] The same does not hold, however, when evaluating single patients against a normal range established in a group of subjects. Here F-wave conduction velocity suits better, minimizing the effect of limb length. Alternatively, the use of nomogram suffices in clinical practice, plotting the latency against the height as a simple, albeit indirect, measure of limb length.[102,116] Any indices based on height, however, have an inherent limitation because limb lengths vary in different individuals with the same height. Similarly, the slope of the regression line in the nomograms, indicating the linear relationships between the latency and height, varies from country to country, reflecting ethnic differences in conduction characteristics and other factors such as motoneuron excitability.[110]

In the assessment of reproducibility, we use two independent indices: relative intertrial variation (RIV) and intraclass correlation coefficiency (ICC). Of the two, RIV directly represents a variation of measurements expressed as the percentages of the difference between V1 and V2 over the mean value of the two. Thus,

$$RIV(\%) = 100x(V2 - V1)/0.5(V1 + V2)$$

where V1 and V2 represent the values of the first and the second measurements of the pair. The ranges of RIV between –10% to +10% usually indicate a higher precision.

Measures having larger interindividual differences usually show a greater intraindividual variability as well. The calculation of ICC takes this into consideration as follows to partially offset the effects of a large variability among different subjects. Thus,

$$ICC = \sigma s^2/(\sigma s^2 + \sigma \varepsilon^2)$$

where σs^2 and $\sigma \varepsilon^2$ represent among-subject variance and experimental error. The values exceeding 0.9 indicate a reliable measure, although, as seen from the formula, this may indicate a large among-subject variance rather than a small experimental error.[47]

Figure 11-21 shows the 5th to 95th percentiles of RIV and ICC in both groups, whereas Fig. 11-22 illustrates some examples of the individual data from the patients. The measures showing the range of RIV of less than ±10% included F-wave latency and F-wave conduction velocity of both median and tibial nerve; and sensory conduction velocity of the median nerve. In general, amplitudes showed a greater variation than latencies or nerve conduction velocities. Similarly, ICC exceeded 0.9 for F-wave latency of the median and tibial nerves in both the healthy subjects and the patients. Median nerve SNAP and median and tibial CMAP had a large range of RIV despite a high ICC. In these amplitude measurements, a large among-subject variance of the amplitudes made σs^2 much greater than $\sigma \varepsilon^2$, leading to a high ICC despite a considerable intertrial variability.

Although a high ICC indicates a statistical correlation between two measurements,[32] it does not necessarily imply a good reproducibility. Thus, to achieve an optimal comparison, a sequential study must exclude any measurements with a wide RIV regardless of ICC values. The calculation of RIV in addition to ICC helps detect the indices with an acceptable degree of reproducibility. In our data, F-wave latencies of the median and tibial nerves qualified as a reliable measure showing a large ICC (>0.9) with a small RIV (< ± 10%). Main factors contributing to an intertrial variability include inadequate control of skin temperature, insufficient stimulus intensity, errors in determining the latency and the surface distance, and difficulty in placing recording electrodes exactly at the same place on two separate occasions.[18] Amplitudes vary most probably because of an unavoidable shift in the recording site.

Clinical Consideration

A question often posed in regard to the accuracy and sensitivity of latency or velocity

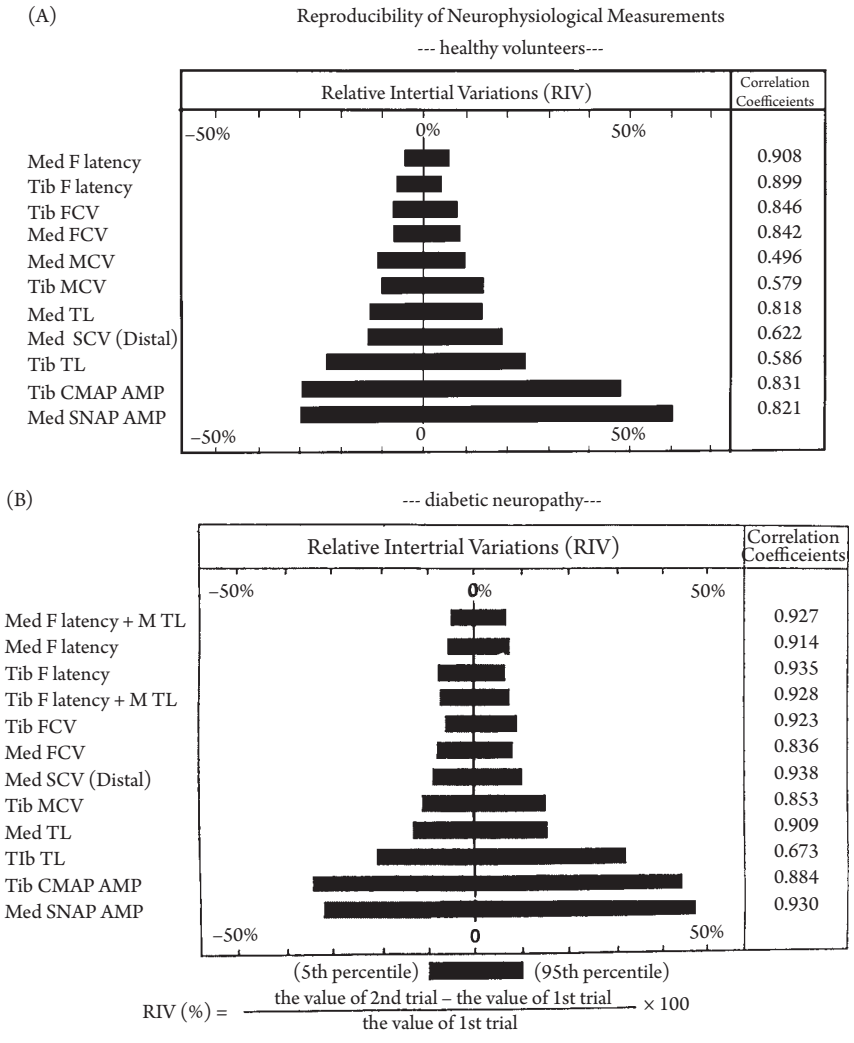

FIGURE 11-21 Reproducibility of various measures in healthy volunteers (***A***) and patients with diabetic neuropathy (***B***), repeated twice at a time interval of 1 to 4 weeks to calculate relative intertrial variations as an index of comparison. (Modified from Kimura[69]; courtesy of Kohara, Kimura, Kaji, et al.,[79] from a multicenter reliability study sponsored by Fujisawa Pharmaceutical Co., Ltd.).

measurements relates to the length of the segment under study. Other factors being equal, should one study shorter or longer segment for better results? Although both approaches have merits and demerits, the choice depends entirely on the pattern of the conduction change. Short segmental approaches uncover a focal lesion involving a very restricted zone better than evaluating across a longer distance, which tends to obscure the abnormality. In contrast, studies of a longer segment detect diffuse or multisegmental abnormalities better, increasing sensitivity, and decreasing measurement errors, which, in percentage, diminish in proportion to the overall latency and surface distance. The increased accuracy of the techniques in turn improves the reproducibility of the results. In summary, short distances magnify focal conduction abnormalities despite increased measurement error, and long distances, though insensitive to focal lesions, provide better yields and reliability for a diffuse or multisegmental process.

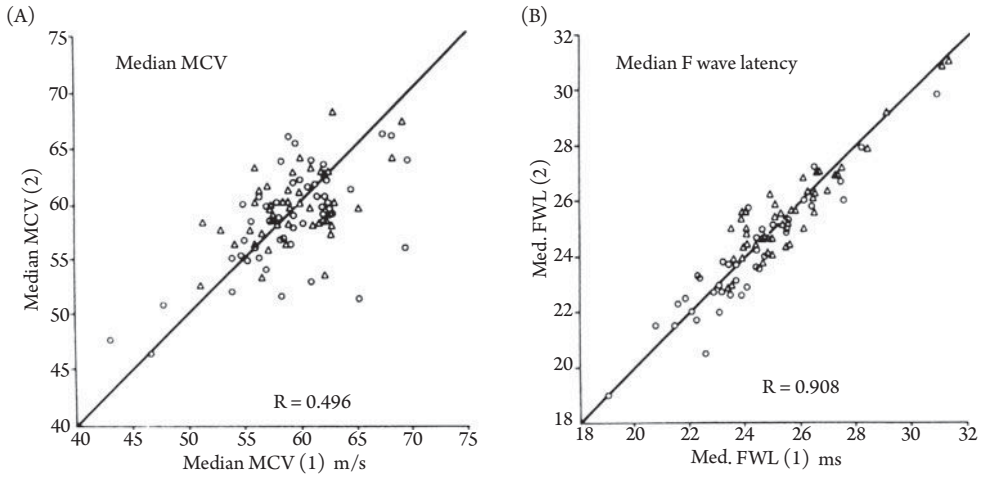

FIGURE 11-22 Comparison between the first and the second measures of median nerve motor conduction velocity (***A***) and F-wave latency (***B***). Individual values plotting the first study on the abscissa and second study on the ordinate show a greater reproducibility of the F-wave latency compared to the motor nerve conduction velocity (cf. Fig. 11-21) (Modified from Kimura[69]; courtesy of Kohara, Kimura, Kaji, et al.[79]; data from a multicenter reliability study sponsored by Fujisawa Pharmaceutical Co., Ltd.).

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PART IV

Electromyography

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12

Anatomy and Physiology of the Skeletal Muscle

Abbreviations: ACh—acetylcholine, ATP—adenosine triphosphate, ATPase—adenosine triphosphatase, DPNH—diphosphopyridine nucleotide, ECC—excitation contraction coupling, EMG—electromyography, FF—fast fatiguing, FG—fast glycolytic, FOG—fast oxidative glycolytic, FR—fast resistant, MND—motoneuron disease, NADH—nicotinamide adenine dinucleotide dehydrogenase, NMT—neuromuscular transmission, S—slow, SFEMG—single-fiber electromyography, SO—slow oxidative

1. INTRODUCTION

The skeletal muscles comprise the extrafusal and intrafusal fibers, each with distinct anatomic and physiologic features. The alpha motoneurons innervate the extrafusal fibers that occupy the bulk of muscle mass as contractile elements. The skeletal muscles usually have the innervation zones with abundant motor endplates in the middle length of the muscle, though the detailed configurations vary among different subjects.[76] Many limb muscles have multiple motor points,[117] which in part dictate their contraction characteristics.[69] Mammalian skeletal muscles may consist of two or more separate subdivisions known as neuromuscular compartments with unique structural and functional characteristics.[25,68,104] The gamma motoneurons subserve the stretch-sensitive intrafusal fibers that constitute the muscle spindles found in parallel with the extrafusal fibers, which contract to generate force. The Golgi tendon organs, aligned in series with the tendon of the extrafusal fibers, also respond to stretch. The spindles and Golgi tendon organ continuously monitor and regulate the tonus of the reflexive or volitional muscle

contraction. The motor unit, the smallest contractile element, consists of a single motoneuron and all the muscle fibers innervated by its axon.

A nerve impulse initiates muscle contraction in two distinct steps: neuromuscular transmission (NMT) and electromechanical or excitation contraction coupling (ECC) (see Chapter 17-3 and 17-4). Acetylcholine (ACh), released at the neuromuscular junction, depolarizes the endplate region, generating an action potential, which then propagates along the muscle membrane. As the impulse reaches the triad, depolarization of the transverse tubules releases ionized calcium into the sarcoplasm. The interaction between calcium and the thin filaments triggers electromechanical coupling, leading to the formation of bridges between the thin and thick filaments. The sliding of thin filaments between the thick filaments shortens the muscle fibers. This section will describe the anatomy of the contractile elements, the mechanism underlying the shortening of the muscle fibers, and the anatomy and physiology of motor units.[66]

2. FUNCTIONAL ANATOMY

Gross Anatomy of Muscle

A connective tissue called epimysium covers the surface of each muscle. Inside this sheath, the coarse sleeves of the connective tissue called perimysium bind individual fascicles (Fig. 12-1). Each fascicle contains many muscle fibers surrounded by a delicate network of fine connective tissue or endomysium. A muscle fiber, the smallest anatomic unit capable of contraction, averages 10 μm in diameter in a newborn and 50 μm in an adult.[11] Individual muscle fibers range from 2 to 12 cm in length, some extending the entire length of the muscle and others only through a short segment of the total length. The sarcolemma on the surface membrane of a muscle fiber contains multiple nuclei distributed beneath the thin sheath. The skeletal muscle extracellular matrix plays an important role in muscle fiber force transmission, maintenance, and repair[41].

Excitability and Conductivity

The muscle membrane has functional properties of excitability and conductivity similar to those of an axon. Thus, a myoelectric signal originating from a neuromuscular junction propagates in both the proximal and distal directions.[75] Compared to the nerve axons, the muscle fibers have a considerably slower rate of conduction (see Chapter 13-8) in the range of 3 to 5 m/s.[11,74,106,136] An averaging method with arrays of surface electrodes shows a high correlation of conduction velocity with twitch and threshold forces but not with rise time.[94]

Myofibrils and Myofilaments

The semifluid intracellular content of a muscle fiber, called sarcoplasm, contains many bundles of cylindrical myofibrils. They appear as a thin, threadlike substance with light and dark bands of striations under the light microscope. Myofibrils consist of two types of myofilaments, which represent the basic substrates for the contraction of muscle fibers. The transverse striations seen by light microscopy result from their specific arrangements of the structural subunit, called the sarcomere, defined by two adjacent Z lines. The center of the sarcomere contains the longitudinally oriented origin of thick myosin myofilaments, which extend transversely toward the Z line on both sides. The thin actin filaments extend from either side of the Z line into the two adjacent sarcomeres to interdigitate with the myosin filaments.

The thick filaments consist only of myosin molecules, which form parallel elongated rods. The thin filaments contain not only actin molecules but also two other proteins, troponin and tropomyosin. Globular-shaped troponins cover each end of the elongated tropomyosin molecule, which, in turn, intimately binds to several actin molecules along its interwoven course (Fig. 12-2). During muscle fiber contraction, actin filaments slide relative to the myosin filaments. This brings the adjacent Z lines closer together, shortening the sarcomere, rather than individual filaments.[12]

Mechanism of Contraction

The mechanism of the sliding begins with the formation of calcium-dependent bridges that link the actin and myosin filaments (see Chapter 17-4). At rest, tropomyosin physically blocks the formation of bridges between myosin and actin.

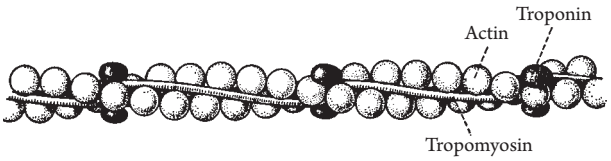

FIGURE 12-2 Fine structure of the thin actin filament with actin molecules attached to globular-shaped troponin and rod-shaped tropomyosin in an orderly arrangement. (From Ebashi, Endo, and Ohtsuki,[32] with permission.)

The propagation of the action potential into the sarcoplasmic reticulum via the transverse tubules releases calcium from the terminal cistern of the longitudinal tubules.[99] The free calcium binds to troponin, the only calcium-receptive protein in the contractile system. This interaction shifts the position of tropomyosin relative to the actin molecule, allowing the globular heads of myosin to gain access to the actin molecules. Myosin-actin cross-bridges pull the actin filaments past the myosin filaments.

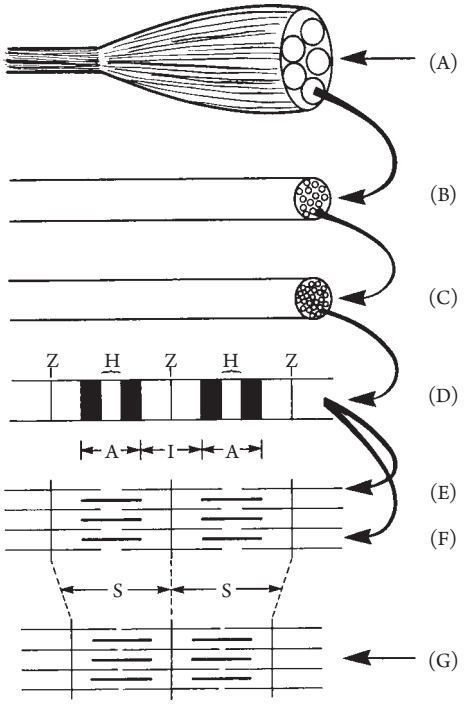

FIGURE 12-1 Anatomic composition of the skeletal muscle. The epimysium surrounds the entire muscle (*A*), which consists of many fascicles bound by perimysium (*B*). Individual muscle fibers (*C*), covered by endomysium, contain many bundles of myofibrils (*D*), which in turn consist of thin (*E*) and thick (*F*) myofilaments. Thin actin filaments slide relative to thick myosin filaments during muscle contraction (*G*).

The tension develops in proportion to the number of cross-bridges formed by this chemical interaction. The dissociation of actin and myosin by adenosine triphosphate (ATP) shears old bridges to allow further sliding with new bridges.

Muscle contractility depends in part upon extracellular calcium concentration.[70] Without a sustained muscle action potential, ATP-dependent active transport sequesters calcium into the sarcoplasmic reticulum. The removal of calcium from troponin allows tropomyosin to return to the resting position, and the muscle relaxes. In McArdle's disease, characterized by deficiency of muscle phosphorylase, this initial step of muscle relaxation does not occur, presumably because of an insufficient amount of ATP (see Chapter 27-4). Failure of relaxation results in persistent shortening of the muscle in the absence of ongoing muscle action potentials. This condition, called contracture, typically develops when patients exercise under ischemic conditions (Fig. 12-3). In porcine malignant hyperthermia, a mutation of the calcium channel in the skeletal muscle sarcoplasmic reticulum causes excessive release of calcium into the myoplasm, leading to contracture.[109] Although the degree of muscle contraction determines strength and endurance, the amount of force generated also depends on other factors, for example, sarcopenia or loss of lean tissue with aging.[31,107]

3. TYPES OF MUSCLE FIBERS

Important determining factors for histologic and physiologic subdivision of muscle fibers include enzymatic properties demonstrated by histochemical reactions; rate of rise in twitch tension regulating the speed of contraction; degree of fatigability; and the nature of motor innervation.[111] Table 12-1 summarizes the profiles commonly used in the classification of muscle fibers: Type I and Type II as

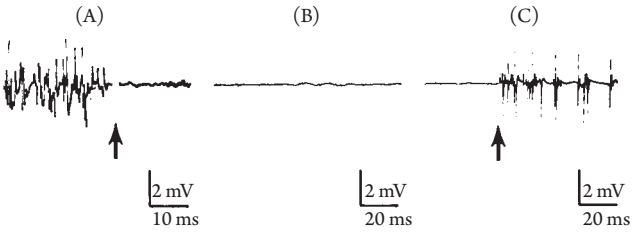

FIGURE 12-3 Contracture during ischemic exercise in a 66-year-old man with McArdle's disease. The patient exercised the forearm flexors with an inflated pressure tourniquet placed around the arm and a concentric needle electrode inserted in the flexor digitorum profundus. Contracture began 45 seconds after the start of ischemic exercise (arrow in *A*) and persisted (*B*). Electrical activity returned 15 minutes after the release of the cuff (arrow in *C*). (Courtesy of E. Peter Bosch, MD, Mayo Clinic, Scottsdale, AZ.)

determined by histochemical reactions,[29] slow (S), fast resistant (FR), and fast fatiguing (FF) by twitch and fatigue characteristics; and slow oxidative (SO), fast oxidative glycolytic (FOG), and fast glycolytic (FG) by twitch and enzymatic properties.[96]

Type I and Type II Fibers

Histochemical reactions (Fig. 12-4) reveal two types of human muscle fibers. Type I fibers react strongly to oxidative enzymes such as nicotinamide adenine dinucleotide dehydrogenase (NADH) and reduced diphosphopyridine nucleotide (DPNH) and weakly to both phosphorylase and myofibrillar adenosine triphosphatase (ATPase). Type II fibers, with reverse reactivity, consist of three subtypes, IIA, IIB, and IIC, according to their ATPase reactions (Table 12-1) after preincubation at different pH values.[7] Type IIC fibers rarely seen in adult muscles constitute fetal precursor cells.

The myosin ATPase content dictates the speed of contraction, which forms the basis for physiologic subdivision of muscle fibers. Thus, in general, the slow twitch fibers correspond to histochemical Type I, and fast twitch fibers to Type II.[19] The intensity of histochemical ATPase reaction, however, cannot serve as the sole criterion in distinguishing fast and slow twitch fibers as exceptions abound. For example, histochemically mixed extensor digitorum longus of the rat contains only fast fibers. Similarly, slow soleus muscle of eels shows greater myosin ATPase activity than fast gastrocnemius muscle.

The growth of muscle cross-sectional area from childhood to adult age reflects an increase in mean fiber size from 10–12 μm shortly after birth to 40–60 μm at age 15–20 years.[95] Accompanying functional development includes a change of the fiber population with an increase of Type II fibers from about 35% at age 5 to 50% at age 20, most likely by a transformation of Type I to Type II fibers.[64] Aging atrophy or sarcopenia begins around age 25 and then accelerates,[31,107] mainly reflecting a loss of fibers of all types and, to a lesser extent, reduction in fiber size mostly of Type II fibers.

Fast and Slow Twitch Fibers

Muscle fibers differ in their contraction time, force-velocity curves, and rates of decay. Slow fibers (S) with high oxidative properties (SO) resist fatigue. Fast resistant (FR) fibers with high oxidative and glycolytic properties (FOG) also resist fatigue, whereas the fast fatigue (FF) fibers with high glycolytic activity but low oxidative enzyme (FG) do not.[18] These findings suggest that glycolytic capacity generally relates to twitch characteristics, and oxidative capability dictates fatigability. Compared with slow fibers, fast glycolytic fibers have greater resting membrane potential, a larger amplitude of the action potential, higher maximum rates of depolarization and repolarization, and a more variable shape of the repolarization phase.[128] The slow twitch fibers have higher antioxidative capacity than the fast twitch fibers.[55] The production of lipid peroxides parallels the exercise-induced increase of oxygen uptake in the muscle, showing higher values in more oxidative and better perfused, oxygen-consuming muscle fibers.[62]

Table 12-1 Types of Muscle Fibers

Commonly used designations			
Fiber types	Type I	Type II A	Type II B
Twitch and fatigue characteristics	Slow (S)	Fast resistant (FR)	Fast fatigue (FF)
Twitch and enzymatic properties	Slow oxidative (SO)	Fast oxidative-glycolytic (FOG)	Fast glycolytic (FG)
Properties of muscle fibers			
Resistance to fatigue	High	High	Low
Oxidative enzymes	High	High	Low
Phosphorylase (glycolytic)	Low	High	High
Adenosine triphosphate	Low	High	High
Twitch speed	Low	High	High
Twitch tension	Low	High	High
Characteristics of motor units			
Size of cell body	Small	Large	Large
Size of motor unit	Small	Large	Large
Diameter of axons	Small	Large	Large
Conduction velocity	Low	High	High
Threshold for recruitment	Low	High	High
Firing frequency	Low	High	High
Frequency of miniature endplate potentials	Low	High	High

Fast and Slow Muscles

In animals, most muscles consist mainly of one muscle fiber type. Slow muscles appear deeper red in color, reflecting a higher myoglobin content, whereas fast muscles tend to show a whitish hue. Functionally, slow muscles have a tonic postural role, like that of the soleus in the cat, whereas fast muscles provide willed phasic movements, like those of the wing muscles of a chicken. This distinction, however, blurs in the human because most human limb muscles consist of slow and fast twitch motor units in various combinations.[14] For example, the slow fibers with contraction times longer than 60 ms constitute a majority in triceps surae, one-half in tibialis anterior, one-third in biceps brachii, and a small percentage in triceps brachii.[13] Slow oxidative fibers occupy 38% and 44% of superficial and deep areas in the vastus lateralis and 47% and 61% in the vastus medialis.[56] Furthermore, fibers of the same types do not necessarily share the same contractile speed in different muscles.[100]

Injury, Denervation, and Innervation

Focal injury to a long multinucleated muscle fiber could destroy it totally unless repair takes place immediately at the site of the lesion, sealing the remainder of its length. The satellite cell-derived myoblasts fuse with the injured muscle fiber to undertake such localized repair[4,110] without affecting the major gene expression in the uninjured parts of the fiber.[138] Transient loss of functional innervation has a permanent effect on the myosin composition.[54] Denervation-induced

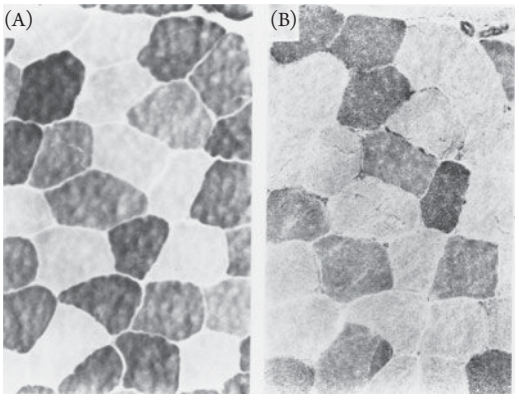

FIGURE 12-4 Cross-section of a normal skeletal muscle stained with adenosine triphosphatase (ATPase) at pH of 9.4 in (*A*) and nicotinamide adenine dinucleotide dehydrogenase (NADH) in (*B*). The darker fibers represent Type II in (*A*) and Type I in (*B*). (Courtesy of Linda Ansbacher, MD, and Michael N. Hart, MD, Department of Pathology, University of Iowa Hospitals and Clinics.)

pattern of phosphorylation in fast muscle resembles that of slow muscle, a finding consistent with changes observed with other phenotypic markers.[83,92,130] Denervation usually causes irreversible muscle atrophy unless reinnervation ensues promptly.[53] In one study, muscle graft with nerve implants generated twice the force compared with denervated muscle receiving only nerve implants.[3] Functional recovery also depends critically on the duration of denervation before nerve repair.[61] A specific force deficit exists in skeletal muscle after repair of injured peripheral nerve.[57]

The rate of stimulation dictates the contractile characteristics of muscle fibers in animals[97,103] as well as in humans.[21,47] Brachial plexus palsy at birth alters isometric contraction time and half-relaxation time of the affected muscles.[115] The finding suggests that denervation during infancy impairs normal development of muscle contractile properties. In fact, congenital abnormality of innervation seems to result in disturbance of muscle fiber differentiation.[118] In patients with chronic neuromuscular diseases, normal muscle fiber histochemistry persists as long as motoneuron differentiation remains. In patients with long-term spastic hemiplegia, some motor units show greater fatigability and longer twitch contraction times than normal. Neuronal influence on the muscle fiber phenotype persisted even after inactivity induced by spinal cord isolation in the cat soleus muscle.[139]

Alterations in histochemical properties may reflect the firing pattern and axonal conduction velocity of the motoneurons. Athletes engaged in endurance training have a greater number of slow fibers,[43] whereas weight lifters have more fast fibers.[123] Exercise training alone, however, induces little change in basic muscle contractility in humans. Hence, motoneuron activity does not suffice in itself to alter the distribution of fast and slow fibers in a muscle. The findings in favor of additional neurotrophic influences include effects of neurons on muscle in tissue cultures[137] and the inverse relationship of nerve length on the time interval before the development of muscle membrane changes after nerve section.[20] The hypertrophy with Type I fiber predominance, seen in some patients with neuromyotonia, may represent conversion of Type II fibers based on similar physiologic mechanisms as described in animal models.[45] Reactive hypertrophy of the masticatory muscle, induced by increased workload, also accompanies progressive Type I fiber predominance and Type II fiber atrophy.[48]

After the transplantation of the nerve normally innervating a fast fiber to a slow fiber, the originally slow muscle fiber will acquire the properties of a fast muscle fiber.[58] Such a relationship between the type of innervation and muscle activity also determines the mechanical characteristics of contraction in some fibers but not others.[131] For example, motoneurons innervating fast twitch muscles have shorter afterhyperpolarization than those supplying slow twitch muscles.[33] A cross-innervation study in patients with muscle transfer for facial palsies has shown considerably less plasticity than in animal models in the conversion of slow to fast twitch fibers.[49] Also minimal changes take place in the spatial distribution of fiber types following self-reinnervation in adults. This finding suggests a limited degree of conversion of muscle fibers to myosin heavy

chain phenotype matching the motoneuron characteristics.[126]

Studies using inactivity with and without cross-reinnervation have shown that electrically silent motoneurons can influence type-related skeletal muscle properties.[101] Furthermore, activity-dependent fiber type modulations differ substantially among fibers in a relatively homogeneous muscle.[119] Thus, the driving forces for this regulation, though not yet elucidated, probably include not only the discharge pattern of the motoneuron but also the axoplasmic transplantation of trophic substances from the nerve to the muscle. Conversely, after complete resection and suturing, a motoneuron of a given type has a high probability of projecting back to the original region, suggesting the presence of guidance cue.[34,129] Many other factors influence the twitch and other characteristics of muscle fibers. In one study,[9] capsaicin treatment, which selectively eliminated fibers belonging to the Group III and IV muscle afferents,[24,132] induced muscle fiber transformation from fast contracting fatiguing fibers to slowly contracting nonfatiguing ones. Muscle fiber types also correlate with innervation topography as shown in the rat serratus anterior muscle.[44] Muscle fiber hypertrophy or altered central drive may account for a larger CMAP and interference pattern recorded in trained as compared with untrained subjects.[30]

4. STRETCH-SENSITIVE RECEPTORS

Anatomy of Muscle Spindles

Muscle spindles consist of small specialized muscle fibers encapsulated by connective tissue. The intrafusal fibers measure only 4–10 mm in length and 0.2–0.35 mm in diameter, in contrast to the much larger extrafusal fibers of striated muscle.[37] The connective tissue capsule surrounding the intrafusal fiber joins the sarcolemma of the extrafusal fibers attached to the origin and insertion of the muscle. The muscle spindles lie parallel to the striated muscle fibers. The nuclear arrangement in their equatorial region distinguishes two types of intrafusal fibers: nuclear bag and nuclear chain (Fig. 12-5). Both dynamic and static bag fibers expand near their midpoint over a short length of about 100 μm by a collection of some 50 nuclei. The smaller nuclear chain fibers contain a linear array of nuclei along the center of the fiber.

The afferent and efferent nerves that supply muscle spindles each have two different kinds of endings: primary (annulospiral) and secondary

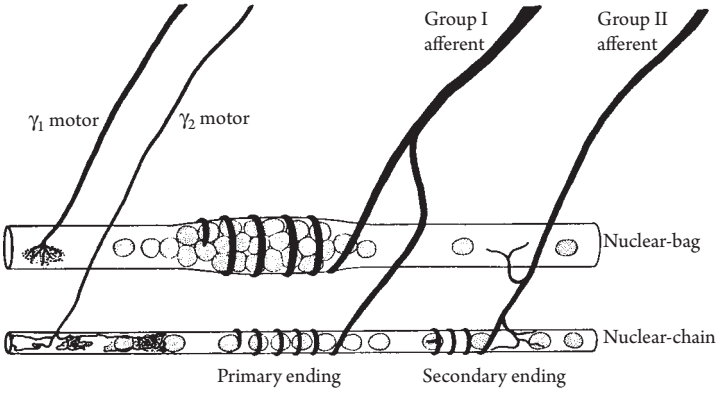

FIGURE 12-5 Simplified diagram of the central region (about 1 mm) of the nuclear bag fiber (top) and nuclear chain fiber (bottom), showing two types of motor endings, two types of afferent fibers, and two types of gamma motoneurons. (Modified from Matthews.[77])

(flower-spray) sensory endings; and plate (single, discrete) and trail (multiple, diffuse) motor endings. The primary sensory ending spirals around the center of the bag and chain fibers. In contrast, the secondary ending terminates more peripherally and chiefly on nuclear chain fibers. The large-diameter, fast-conducting Group IA afferent nerve fibers from the primary endings subserve the monosynaptic stretch reflex. In contrast, the secondary ending gives rise to Group II afferent nerve fibers that terminate on the interneurons in the spinal cord.[93] Although both kinds of motor endings can innervate either type of intrafusal fiber, the plate endings tend to supply preferentially the nuclear bag, whereas the trail endings mainly subserve the chain fibers.

Function of Muscle Spindles

The dynamic afferent fibers respond to the velocity of the actively stretching spindles. The static afferent fibers detect a sustained change in the length. The primary ending has both dynamic and static function, but the secondary ending mainly mediates static changes (Fig. 12-6). The dynamic and static axons of the fusimotor system influence the dynamic and static muscle spindles, respectively.[77] The plate endings primarily control dynamic changes, whereas the trail endings mediate static changes.[79] The bag fibers receive a sufficiently distinctive motor innervation to subserve preferentially dynamic fusimotor effect, and the chain fibers, static fusimotor effect.[6] Muscle spindles, using the contraction-dependent discharge pattern, monitor activity of motor units in the vicinity.[15] Receptor feedback, however, has a negligible effect on the motoneuron pool, compared with the excitatory drive induced by voluntary contraction.[82] During sustained muscle contractions, when a large number of motor units fire at a high frequency, the spindle afferents tend to inactivate, giving the impression of an α-γ dissociation. The decline in spindle discharge, however, may result from a progressive failure in the peripheral mechanisms by which the fusimotor system normally excites the spindle endings.[46,72]

Table 12-2 shows a simplified summary of sensory endings found in muscle spindles. The basic structural elements comprise two types of

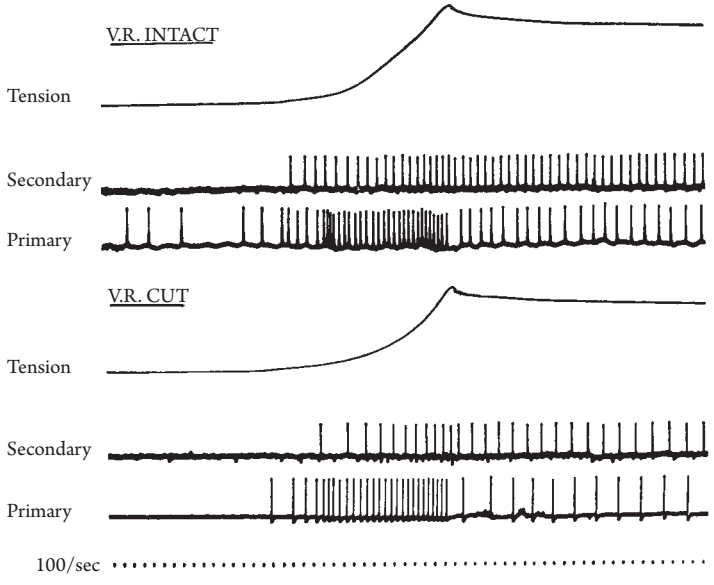

FIGURE 12-6 Responses of primary and secondary endings to a rapidly applied stretch before (top) and after (bottom) cutting the ventral root. Spontaneous fusimotor discharge maintained a steady intrafusal contraction in the decerebrate cat. The primary endings show a greater sensitivity to stretch than the secondary endings, but both types respond equally to changes in muscle length. (From Matthews,[78] with permission.)

Table 12-2 Sensory Endings of Muscle Spindles

	PRIMARY SENSORY ENDING	SECONDARY SENSORY ENDING
Location	Both bag and chain fibers	Mainly chain fibers
Sensitivity	Both length and velocity	Mainly length
Fusimotor system	Both dynamic and static	Mainly static
Form of ending	Half rings in annulospirals	Spirals and flower sprays
Length of ending	About 300 μm	About 400 μm
Type of afferent fiber	Group IA	Group II
Diameter of afferent fiber	12–20 μm	6–12 μm

intrafusal fibers, nuclear bag and nuclear chain; two types of sensory receptor endings, primary and secondary, giving rise to Group IA and Group II afferent fibers; and two types of fusimotor endings, plate and trail, which preferentially subserve dynamic and static function. The dynamic bag fibers receive innervation from the fusimotor fibers with plate endings and modulate dynamic function via the primary sensory endings. The static bag fibers and chain fibers, innervated mainly by fusimotor fibers with trail endings, give rise to both types of sensory afferents to regulate static muscle length. Muscle receptors play a role in proprioception,[98] as evidenced by sensory effects of pulling or vibrating exposed tendons in humans,[80] although cutaneous afferents may also provide a dominant input.[89]

Golgi Tendon Organ

The Golgi tendon organ, arranged in series with extrafusal striated muscle fibers, monitors not only active muscle contraction but also passive stretch. The Group IB afferent fibers originating herein subserve disynaptic inhibition of the motoneurons that innervate the stretched muscle. According to the traditional view, this inhibitory mechanism provides a safety function to prevent an excessive muscle tension when motoneuron firing reaches a certain level. The threshold tension, much less than previously believed, however, excites the tendon organ, especially during active stretch.[51] The activation of Group IB afferent fibers during mild tension helps continuously monitor and adjust the magnitude of muscle activity for smooth contraction even at a low level of tension.

5. ANATOMY OF THE MOTOR UNIT

As defined by Liddell and Sherrington,[65] the motor unit consists of an axon and the few hundred muscle fibers that it supplies, although most authors now consider the motoneuron as its integral part.[91] A single discharge of a motoneuron gives rise to synchronous contraction of all muscle fibers innervated by the axon. Hence, even though individual muscle fibers represent the anatomic substrate, the motor unit constitutes the smallest functional element of contraction.

Innervation Ratio

The innervation ratio relates to the average size of a motor unit expressed as a ratio between the total number of extrafusal fibers and the number of innervating motor axons.[36] Depending on the type of muscle, the ratio ranges from 3:1 in extrinsic eye muscles, which require fine gradations of movement, to 30:1 to 120:1 in some limb muscles subserving only coarse movement.[121] Table 12-3 summarizes the results of one study.[39] Table 12-4

Table 12-3 Summary of Innervation Ratio

MATERIAL	MUSCLE	NO. OF LARGE NERVE FIBERS	NO. OF MUSCLE FIBERS	CALCULATED NO. OF MOTOR UNITS	MEAN NO. OF FIBERS PER MOTOR UNIT	MEAN DIAMETER OF MUSCLE FIBERS (μm)	CROSS-SECTIONAL AREA OF MOTOR UNITS (mm^3)
♂22	Platysma	1,826	27,100	1,096	25	20	0.008
♂40	Brachioradialis	Right 525	>129,200	315	>410	34	
		Left 584		350			
♂22	First dorsal interosseous	199	40,500	119	340	26	0.18
♂54	First lumbrical	155	10,038	93	108	19	0.031
♂29	Anterior tibial	164	10,500	98	107	21	0.037
♂40	Anterior tibial	742	250,200	445	562		
♂22	Anterior tibial		292,500		657	57	1.7
♂28	Gastrocnernius	965	1,120,000	579	1,934		
♂22	medial head		946,000		1,634	54	3.4

(Modified from Feinstein, Lindegard, Nyman, et al.[39])

Table 12-4 Mean Values of Motor Unit Territory

MUSCLE	NO. OF MUSCLES	NO. OF MOTOR UNITS	SPIKE LEVEL (μV)	TERRITORY AT SPIKE LEVEL (mm)	STANDARD DEVIATION (mm)
Biceps brachii	24	129	100	5.1 ± 0.2	2.4
Deltoid	7	52	100	6.7 ± 0.4	3.0
Extensor digitorum communis	11	43	100	5.5 ± 0.3	2.1
Opponens pollics	10	34	150	7.4 ± 0.4	2.6
Rectus femoris	9	65	100	10.0 ± 0.6	4.6
Biceps femoris	5	35	150	8.8 ± 0.7	4.1
Tibialis anterior	8	47	100	7.0 ± 0.4	3.0
Extensor digitorum brevis	5	25	200	11.3 ± 0.8	4.1

(Modified from Coers and Woolf.[23])

shows the territory of motor units estimated histologically[23] or electrically.[10] Numerous regional variations characterize skeletal muscle, with larger motor units located more superficially than smaller units.[60]

Distribution of Muscle Fibers

Muscle fibers of a given motor unit have identical histologic characteristics. Therefore, the apparent random distribution of different histologic fiber types seen in muscle cross-sections indicates considerable overlap in the territories of adjacent motor units. In general, motor unit fibers show cluster arrangement in subgroups of varying size, rather than a wide distribution throughout the territory of the unit.[5] Single-fiber electromyography (SFEMG)[114] and electrophysiologic cross-section analysis[113] have demonstrated the scattering of muscle fibers belonging to a given motor unit. Indeed, a muscle fiber of a single motor unit rarely makes direct contact with other fibers of the same unit. One study even refutes a random arrangement of mammalian muscle fibers but argues for a more orderly disposition at certain stages of development to minimize adjacencies of individual muscle fibers of the same motor unit.[134] Such specification may have the functional advantage of maximizing muscle action potential dispersal for smooth muscle contraction, especially in compensating for lost motor units.

Another mapping technique has also substantiated motor unit overlap.[5,35] Repetitive stimulation of an isolated single ventral root nerve fiber exhausts glycogen storage in all the muscle fibers belonging to the motor unit of the stimulated axon. The muscle, excised immediately after tetanic stimulation and stained for glycogen in a frozen section, shows a scattered distribution of unstained muscle fibers. This method not only confirms the territorial overlapping of adjacent motor units but also the histochemical uniformity of a given motor unit.

Three-dimensional reconstruction from tracings of the glycogen-depleted fibers in the cat tibialis anterior revealed a close relationship between the area of a motor unit territory and the number of fibers in the motor unit.[102] As the density of unit fibers remains unchanged, the same factor must regulate the number of fibers innervated by a motoneuron and its territory. Many muscles have divisions that may function independently, showing motor unit territories often confined to

a compartment bounded by anatomical structures.[124] In the skeletal muscles, fibers rarely run from origin to insertion in parallel arrays. Instead, they comprise relatively short, serially arranged muscle fibers with interdigitated ends.[125] Under this arrangement, a motor unit acts in concert with other units, transmitting forces generated to the tendon via adjoining muscle fibers.[42]

Histologic findings in partially denervated muscle once prompted some investigators to propose that the fibers of each motor unit might consist of many subunits, each containing an average of 10 to 30 fibers. According to this theory, the motor unit potential recorded during routine electromyography (EMG) results from completely synchronized firing of all fibers belonging to a subunit. Human studies with SFEMG revealed no evidence of muscle fiber grouping within a motor unit in normal extensor digitorum communis or biceps brachii muscles.[112] Moreover, high-amplitude spikes do not necessarily imply a synchronized discharge from a subunit, because a single muscle fiber can give rise to such a potential if recorded by a needle placed in close proximity. These findings have led most electromyographers to abandon the concept of subunits in the normal human muscle.

6. PHYSIOLOGY OF THE MOTOR UNIT

The same criteria apply to the classification of motor units (Table 12-1) as muscle fibers, because all the muscle fibers of a given motor unit have identical histologic and physiologic properties.[73] The animal and human data briefly reviewed next pertain to the understanding of motor unit potentials in clinical EMG.[8] In brief, the potential field generated during the discharge of a motor unit evolves in the following successive stages[63]: a standing quadruple wave at the endplate initiated by excitation, bidirectional traveling quadruple waves propagated along the muscle fibers, and two standing dipole waves at the muscle-tendon junction with termination of action potential.

Size Principle and Recruitment

Series of animal experiments have clearly established a close relationship between the fundamental physiologic properties of motor units and the size of the motoneuron (Table 12-1). The large neurons have fast-conducting, large-diameter axons[84] and a higher innervation ratio, or a greater number of muscle fibers supplied by one axon.[135] Larger motor units have, in turn, greater twitch tensions, faster twitch contractions, and a greater tendency to fatigue.[17] According to the size principle of Henneman, the motoneuron recruitment occurs not at random but in an orderly manner, determined by the fixed central drive that preferentially activates small neurons first.[50,59]

Studying human motor units with intraneural microstimulation has revealed some differences from animal data,[86] although most findings apply to both. In brief, the larger the cell body, the greater the conduction velocity, the stronger the twitch tension, the faster the twitch contraction, and, in general, the greater the tendency to fatigue. Smaller motoneurons, innervating smaller motor units, discharge initially with minimal effort, before a greater effort of contraction activates larger neurons.

When measured by macro EMG, motor units recruited at low force have smaller amplitude and area as compared to those recruited at high force. This reflects, as expected from the size principle, the motor unit territory rather than fiber density, which remain the same at different force output.[38,71] In the first dorsal interosseous muscle, the motor units activated early at low threshold have lower twitch tensions and slower twitch contractions than those units recruited at higher levels of effort.[16] Factors correlated with motoneuron excitability include axon diameter, conduction velocity, and motor unit size.[88] High- and low-threshold motor units also differ histochemically. Earlier studies hinted at a distinction between tonic and phasic motor units on the basis of their firing pattern and the order of recruitment. Later studies, however, have shown a relatively continuous rather than bimodal pattern of recruitment.[73]

Despite certain exceptions documented under some experimental circumstances, the size principle generally applies to any voluntary activation of motor units, including rapid ramp or ballistic contractions.[28] The same rule governs the order of presynaptic inhibition after activation of Group 1A afferent fibers by tonic vibration.[27] Neither neuropathy nor motoneuron

disease (MND) alters the size principle, but a previously transected peripheral nerve may show a random pattern of recruitment.[88] The size principle holds after nerve injury in humans, if motor axons reinnervate their original muscles or those with a closely synergistic function, as seen with complete median nerve section at the wrist.[122] Thus, misdirection of motor axons account for the absence of orderly recruitment after complete above-elbow ulnar or median nerve sections.

Twitch Characteristics

Although the contractile properties of the whole muscle serve as a useful function indicator, they may not accurately reflect the heterogeneity of the constituent motor units and their changes in health and disease.[22] Different human muscles contain either fast or slow units whose twitch contraction approximates the contraction time of the whole muscle. An averaging technique, using repetitive discharges from a single muscle fiber as a trigger, can provide a selective summation of the muscle twitch attributable to that motor unit. Twitch tensions analyzed by this means range from 0.1 to 1.0 g, with contraction times varying between 20 and 100 ms. Spike-triggered averaging, however, often extracts the characteristics of the unfused force transient, instead of the desired single motor unit twitch.[67] Thus, in some muscles such as human masseter, this method may prove inappropriate for determining highly task-dependent single motor unit force.[85]

In humans, as in animals, the twitch tension generated by a motor unit increases in proportion to its action potential amplitude measured by macroEMG.[127] The units recruited with slight contraction have smaller twitch tensions, slower contraction times, and greater resistance to fatigue, compared with the units that appear with stronger contraction.[116] The twitch tension of individual motor units may become larger[81] or smaller[88] after denervation. Partially denervated muscle, however, generally have a prolonged contraction time and reduced twitch tension.[87] Peak twitch torque and twitch characteristics also show age-related changes.[133]

In one animal experiment,[2] reinnervation after nerve section normalized the distribution of motor unit force in adult rats but not in neonates. Thus, nerve injury during the neonatal period resulted in permanent abnormalities of motor unit size and twitch force. Denervated skeletal muscle can restore normal or nearly normal levels of force production as the remaining intact motoneurons sprout to reinnervate denervated fibers. Daily locomotor activity can enhance the tension-generating capacity of chronically enlarged motor units.[108] Different types of training may selectively change different aspects of function in disused muscles.[40] Skeletal muscles become less efficient as force production increases, reflecting a greater participation of more fatiguable Type II muscle fibers.[52]

Rate Coding

The muscle force increases either by recruitment of previously inactive motoneurons or through more rapid firing of already active units. In early studies, discharge frequency ranged from 5 to 30 Hz during early phases of voluntary contraction and stabilized thereafter.[120] These findings suggested to some that rate coding mostly regulated fine control at the beginning of contraction and during maximal effort. Work in humans,[90] however, has emphasized the importance of rate coding for increasing force, as originally suggested by Adrian and Bronk.[1] Recruitment must play an important role at low levels of contraction, when all units fire at about the same rate, ranging from 5 to 15 Hz.[26] After the activation of most motor units, additional increases in force must result from faster firing of individual units. With stronger contraction, more synchronized inputs contribute to greater motoneuron drive to generate more synchronous motor unit discharges.[105] In strong or ballistic contractions, instantaneous firing may reach 60 to 120 Hz at the onset.[26]

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13

Electromyography and Other Measures of Muscle Function

Abbreviations: ACh—acetylcholine, ALS—amyotrophic lateral sclerosis, CK—creatine kinase, CMAP—compound muscle potential, EMG—electromyography, INR—international rating, MND—motoneuron disease, MUP—motor unit potential, NMT—neuromuscular transmission, RRP—relative refractory period, SFEMG—single-fiber electromyography

1. INTRODUCTION

Electromyography (EMG) tests the integrity of the entire motor system, which consists of upper and lower motoneurons, neuromuscular junction, and muscle. Further subdivision in each category reveals seven possible sites of involvement that may cause muscle weakness (Fig. 13-1). To localize the responsible lesion in one of these sites, a trained physician must conduct EMG as an extension of the physical examination, rather than as a laboratory procedure. The clinical symptoms and

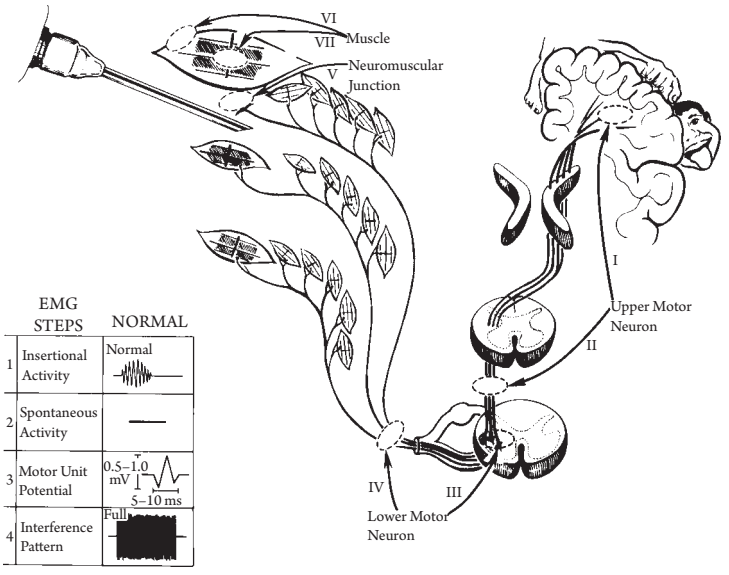

FIGURE 13-1 Schematic view of the motor system with seven anatomic levels. They include (1) upper motoneuron from the cortex (I) to the spinal cord (II); (2) lower motoneuron with the anterior horn cell (III) and nerve axon (IV); (3) neuromuscular junction (V); and (4) muscle membrane (VI) and contractile elements (VII). The insert illustrates diagrammatically four steps of electromyographic examination and normal findings. The figure of cortical representation is modified from Netter.[146]

signs guide the optimal selection of specific muscle groups. An adequate study consists of multiple sampling at rest and during different degrees of voluntary contraction.[43,193]

Electromyographers must first learn surface anatomy of muscles for accurate needle placement[80,152] and physiology of normal voluntary contraction to understand disorders of the motor system.[42] In one study using cadavers, ultrasound-guided needle placement improved accuracy compared to no-guided insertion, particularly in the hand of less experienced trainees.[19] Multiple factors that affect the outcome of recordings include patients' age and muscle properties under study in addition to the types of the needle electrode and recording apparatus (see Chapter 3-2). The findings in the initially tested muscle dictate the course of subsequent exploration. Thus, no rigid protocol applies for a routine EMG examination. Certain basic principles hold, but a flexible approach best fulfills the needs of individual patients.

Although patients have some apprehension before the study, adequate information about the procedure will decrease their anxiety. In one study of low-back disease,[108] predictors for the degree of discomfort during the procedure included the patients' assessment of their back pain, their trait-anxiety levels, and female gender. The concentric and monopolar needles may[199] or may not[219] differ in pain perception. Small needle movements tend to cause less pain.[199] A simultaneous finger slapping seems to reduce pain inflicted by needle insertion.[163] Ibuprofen (400 mg) administered 2 hours before the procedure may reduce immediate recall of pain.[57] Somewhat counterintuitively, our survey indicates most patients consider nerve conduction studies more uncomfortable than needle EMG during routine clinical investigations.[198]

2. PRINCIPLES OF ELECTROMYOGRAPHY

Physiologic Basis

The electrical properties of the cells (see Chapter 2-2) form the basis of clinical EMG. Normally, a single neural impulse gives rise to synchronous discharges of all muscle fibers innervated by the

axon, producing a motor unit potential (MUP). In an unstable denervated muscle, however, individual muscle fibers fire independently in the absence of neural control. The detection of these spontaneous single-fiber potentials constitutes one of the most important findings in EMG (see Chapter 14-4). Extracellular recording of a muscle action potential through a volume conductor reveals an initially positive triphasic fibrillation potential as the impulse approaches, reaches, and leaves the active electrode. The muscle fiber, if traumatized by the needle, cannot generate a negative spike at the damaged membrane. In this case, a positive sharp wave appears as a large initial positivity followed by a low-amplitude, slow negativity. An action potential detected in the external field also varies in size and waveform depending on the spatial relationship between the cell and the tip of the needle electrode. For example, when recorded by an electrode with a small lead-off surface, the amplitude falls off sharply to less than 10% at a distance of 1 mm from the generator source.

Surface recording, though rarely employed for diagnostic EMG,[52] may have use for kinesiologic studies (see Chapter 13-8) and other special purposes such as noninvasive estimation of motor unit size[201] or longitudinal tracking of the same single motor unit.[79]

Contraindications and Precautions

Contraindications for EMG examination include bleeding tendencies and unusual susceptibility to recurrent systemic infections.[2,5] Specific inquiries often reveal pertinent information that the patient may not volunteer. A consultation with the referring physician helps weigh the diagnostic benefits against the risks to prevent unnecessary complications, which include bleeding, infection, nerve injury, pneumothorax, and other local trauma.[5] Although rare,[76] hemorrhagic complications[82] induce acute compartment syndrome of the leg.[67] A patient taking anticoagulants should have appropriate laboratory tests for bleeding tendency prior to a needle study.[122] The empirical guidelines used in our laboratory call for, with heparin infusion, partial thromboplastin time not exceeding 1.5 times control value and, with warfarin (Coumadin) therapy, an international rating (INR) measured at the time of study less than 2.0. The same precautions should apply to those with other coagulopathy, such as hemophilia.[179] For thrombocytopenia, unless the platelet count falls below 20,000/mm,[20] local pressure can usually counter the minimal hemorrhage. Largely based on the rarity of anecdotal reports, others restricts needle studies with INR greater than 3.0 or platelets less than 10,000/mm.[32] Testing the degree of bleeding tendency with a superficial muscle like tibialis anterior can help determine the feasibility of further study of a deeper muscle like tibialis posterior not readily accessible to external compression. Dermatologic conditions that lead to limitation of needle study include skin infection, cellulitis, lymphedema, varicose vein, and thin skin such as from corticosteroid use.[43] Transient bacteremia following needle examination could cause endocarditis in patients with valvular disease or prosthetic heart valves. This not withstanding, few recommend prophylactic administration of antibiotics for the needle studies.[1]

In response to an anonymous survey, a majority of physicians (64%) reported at least one needle stick injury to themselves during EMG.[131] Wearing a pair of rubber gloves minimizes the risk of accidentally transmitting infectious agents to the examiner. This precaution applies especially in studying cases of hepatitis, AIDS, and prion diseases. One must also protect sensitive patients from allergens of rubber gloves, which, if introduced under the skin during the study, may cause local or systemic acute hypersensitivity reaction. In fact, the use of latex gloves has occasionally caused anaphylaxis and local hypersensitivity, especially in patients with myelodysplasia. To prevent this type of avoidable risk, we now resort to the use of vinyl gloves in all patients.[130]

Needle studies, if conducted prematurely, could interfere with the interpretation of subsequent histologic or biochemical findings that supplement clinical evaluation. Repeated trauma during insertion and movement of the needle electrode consistently induces localized inflammation, appropriately labeled "syringomyositis" in our laboratory, and, less frequently, focal myopathic changes. These abnormalities may

contaminate the results of muscle biopsy often required for confirmation of clinical diagnosis. With the anticipated need for pathologic studies, needle examination should therefore explore various muscles on one side, sparing the other side for histologic evaluations.

Serum creatine kinase (CK) increases in certain muscle diseases, such as muscular dystrophy and myositis, and in other conditions, including cardiac ischemia, hypothyroidism, and sustained athletic participation. The enzyme level may also rise considerably in normal muscles from the combination of EMG, diurnal variation, and prolonged exercise.[22] Needle examination by itself, however, should not elevate the enzyme to a misleading level in normal persons. In one series, no significant changes occurred within 2 hours after EMG.[38] The value reached a peak of 1.5 times baseline in 6 hours and returned to baseline 48 hours after the procedure. Testing enzyme levels prior to needle examination avoids any confusion, but a sufficient elevation of CK activities indicates abnormality, even for the serum drawn after the procedure.

Recording Techniques

Sequence of examination comprises four steps:

1. Insertional activity caused by movement of a needle electrode placed in the muscle
2. Spontaneous discharges recorded at rest with the needle stationary in each position
3. Voluntary firing of motoneurons to induce an isolated MUP during mild muscle contraction
4. Recruitment of motor units during progressively greater muscle contraction and an interference pattern at the maximum effort

Needle insertions, guided by the adequate knowledge of anatomy and function of the muscle, usually suffice, although electrical stimulation may help identify the target in patients with motor deficit.[216] The use of ultrasonography may also improve the accuracy of needle insertion for quantitative assessments.[105] Routine settings consist of a sweep speed ranging from 2 to 20 ms/cm and an optimal gain to maximize the recorded potentials without truncating the peaks. The sensitivity varies from 50 to 500 μV/cm for insertional and spontaneous activities and from 100 μV to 1 mV/cm for MUP. Obviously, a lower amplification suffices for the study of larger potentials. Most investigators use the low-frequency filter of 10–20 Hz and high-frequency filter of 10 kHz, but some prefer lowering the lower limit to 2 Hz or less when determining the low-frequency component of an MUP. In contrast, elevating the lower limit to 500 to 1000 Hz allows better assessment of high-frequency components (see Chapter 16–2). For routine purpose we use 100 μV/cm studying spontaneous discharges and 500 μV/cm for MUP analyses with the frequency bandpass of 10 Hz to 10 KHz.

3. INSERTIONAL ACTIVITY

Origin and Characteristics

Moving the needle electrode inserted into the muscle normally gives rise to brief bursts of electrical activity with each repositioning. The insertional activity, on average, lasts a few hundred milliseconds, slightly exceeding the movement of the needle (Fig. 13-2). It appears as positive or negative high-frequency spikes in a cluster, accompanied by a crisp static sound over the loudspeaker. As implied by the commonly used term *injury potential*, the discharges originate from muscle fibers injured or mechanically irritated by the penetrating needle. Unequivocal recording of insertional activities signals the entry of the needle tip into a muscle, as opposed to the surrounding adipose tissue. Voluntary contractions help confirm the proper location of the electrode in the target muscle.

Clinical Significance

The waveforms seen on the oscilloscope and, perhaps more important, the sounds over the loudspeaker allow a somewhat loose but useful categorization of the insertional activity into normal, diminished, and enhanced patterns. The level of response depends, among other things, on the magnitude and speed of needle movement. Nonetheless, semiquantitative analysis provides an important measure of muscle

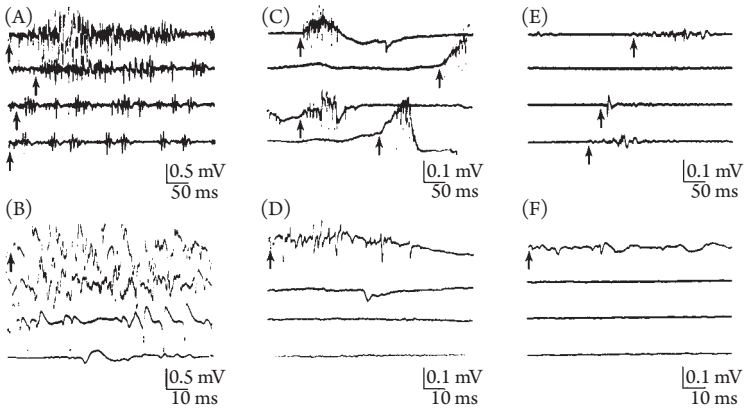

FIGURE 13-2 Increased (*A, B*), normal (*C, D*), and decreased (*E, F*) insertional activities (arrows) from the first dorsal interosseus in tardy ulnar palsy, tibialis anterior in a control, and fibrotic deltoid in severe dermatomyositis.

excitability, reduced in fibroses and exaggerated in denervation or inflammatory processes. Such findings often provide the first clue to the nature of the lesion, directing the examiner toward the proper course of action. The needle electrode registers electrical activities only from a restricted area of the muscle. An adequate survey, therefore, calls for frequent needle repositioning in small steps for multiple sampling. Exploration in four directions from a single puncture site minimizes patient discomfort. Studies of larger muscles require additional insertions in proximal, central, and distal portions. Otherwise, patchy areas of abnormalities, if present, may escape detection.

In denervated muscles, insertion of the exploring needle may provoke positive sharp waves and, less frequently, fibrillation potentials (see Chapter 14-4). These early abnormalities of denervation resemble a normal insertional activity that may also take the form of positive sharp potentials. In a quantitative analysis using a mechanical electrode inserter, one or two isolated positive waves commonly appeared in normal muscles at the end of insertional activity.[220] None of these potentials, however, fired repetitively or in a train, or in a reproducible fashion with further insertions, lacking the typical pitch of positive sharp waves associated with denervation. These findings suggest nonspecificity of isolated positive waves induced by insertion, unless they give rise to reproducible trains with characteristic audio displays reminiscent of the spontaneous discharge.

4. ENDPLATE ACTIVITIES

With the needle held stationary, normal resting muscles show no electrical activity except with the electrode tip at the endplate region. Here, irritation of the small intramuscular nerve terminals by the needle tip induces ongoing low-amplitude, undulating endplate noise (Fig. 13-3), intermittent high-amplitude irregularly discharging endplate spikes, or both (Fig. 13-4). These two types of potentials occur conjointly or independently. The patient usually experiences a dull pricking pain, which dissipates with slight withdrawal of the needle.[181] Endplate activities, although physiologic in nature, tend to become excessive in denervated muscles.

Endplate Noise

The background activity in the endplate region consists of frequently recurring irregular negative potentials, 10–50 μV in amplitude and 1–2 ms in duration, producing over the loudspeaker a characteristic sound much like a live seashell held to the ear. The same potentials, if recorded intracellularly with microelectrodes, show monophasic positivity of about 1 mV in amplitude, corresponding to the miniature endplate potentials (MEPPs). Thus, endplate noise represents extracellular recording of MEPP, or nonpropagating depolarizations caused by spontaneous release of acetylcholine (ACh) quanta.[221] Endplate noise, generally considered normal, has had limited clinical applications. Some

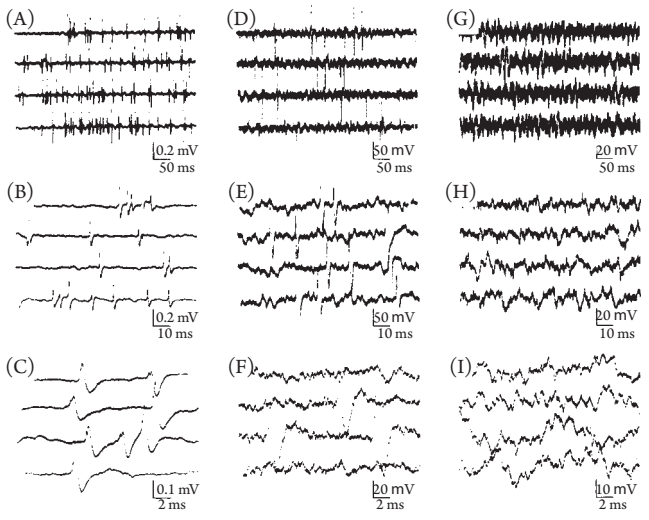

FIGURE 13-3 Endplate activities recorded from the tibialis anterior in a healthy subject. Two types of potentials shown represent the initially negative, high-amplitude endplate spikes (*A, B, C*) and low-amplitude endplate noise (*G, H, I*). The spikes and endplate noise usually, though not necessarily, appear together (*D, E, F*).

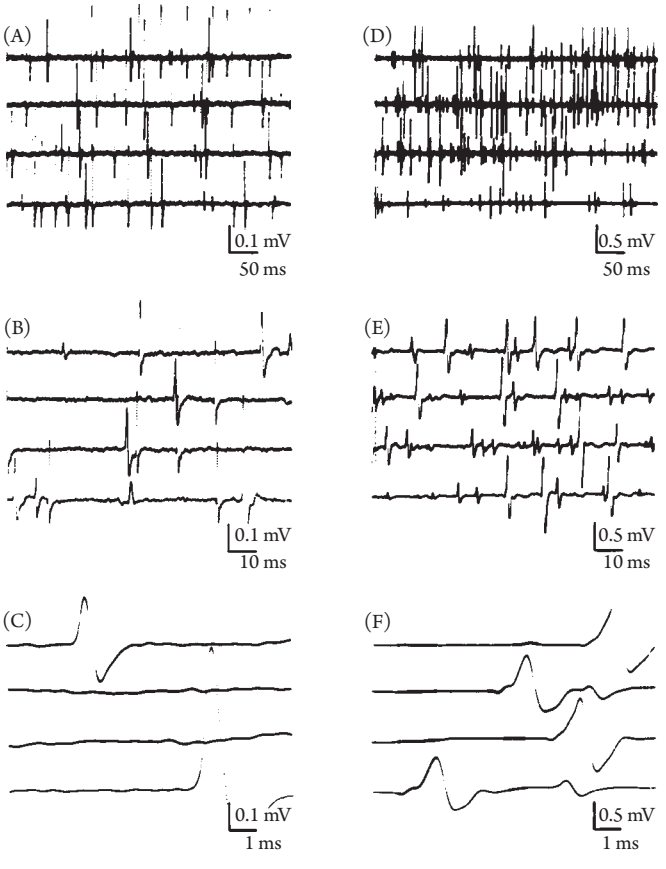

FIGURE 13-4 Endplate spikes recorded from the abductor pollicis brevis in a normal subject (*A, B, C*) and in a patient with carpal tunnel syndrome (*D, E, F*). An unusual prominence of endplate activities in denervated muscle, although common, carries little diagnostic value.

believe it represents exaggerated release of ACh with a possible, but unproven, link to myofascial trigger points.[186] Its enhancement combined with the absence of endplate spikes may characterize an attack of periodic paralysis (see Chapter 28-2).[60] This finding supports the notion that the generation of adequate endplate potential (EPP) fails to trigger a propagating muscle action potential in this disorder. Power spectral analysis of endplate noise permits rapid estimation of the dominant ACh receptor ion channel kinetics.[129] Thus, the technique may provide a useful measure to evaluate neuromuscular transmission (NMT) for example, after injection of botulinum neurotoxin.[214]

Endplate Spike

The endplate spikes result from discharges of single muscle fibers excited by the approaching tip of the needle.[30] Intermittent spikes, 100–200 μV in amplitude and 3–4 ms in duration, fire irregularly at 5–50 Hz. The typical pattern with an initial negativity indicates that the spikes originate at the tip of the recording electrode. They have the same waveform as fibrillation potentials, which also show an initial negativity when recorded with the needle at the endplate region. In contrast, fibrillation potentials, recorded elsewhere, have a small positive phase preceding the major negative spike. Similarity of the firing patterns of endplate spikes to discharges of muscle spindle afferents led some investigators to postulate their origin in the intrafusal muscle fibers[150] but without subsequent confirmation.

Repositioning of the recording needle may injure the cell membrane at the endplate region. Slight relocation of the needle tip near the source of discharge may then reverse the polarity of the ordinarily negative endplate spikes. Small irregularly occurring positive potentials also appear in the endplate region when recorded with a concentric needle electrode. Here, the positive discharges probably represent cannula-recorded endplate spikes, hence reversed in polarity and reduced in amplitude. The irregular pattern of firing and shorter duration distinguish the physiologic positive discharges at the endplate from positive sharp waves seen in denervation or other pathologic conditions.

5. MOTOR UNIT ACTION POTENTIAL

The motor unit consists of a group of muscle fibers innervated by a single anterior horn cell (Fig. 13-5). Its anatomic and physiologic properties are determined by the innervation ratio, fiber density, propagation velocity, and integrity of NMT. These characteristics vary not only from one muscle group to another but also with other factors such as age for a given muscle. Isolated potentials attributed to an individual motor unit represent the sum of all single muscle fiber spikes that occur nearly synchronously within the recording radius of the electrode. Refined techniques for longitudinal tracking of the same motor unit may enable serial measures of these aspects for quantitative assessment of the disease process.[34] Surface recording (see Chapter 13-8), though not suitable for routine use,[84] may suffice to characterize enlarged motor units after reinnervation as reported in poliomyelitis.[169]

Motor Unit Profile

The shape of recorded potentials reflects, in addition to the inherent properties of the motor unit itself, many other physiologic factors. These include the resistance and capacitance of the intervening tissue and intramuscular temperature.[15,47] The amplitude decreases slightly with hypothermia because differential slowing and desynchronization among individual muscle fibers more than counter the anticipated facilitatory effect on the muscle membrane potentials. Cooling from 37°C to 30°C, for example, causes the duration to increase by 10%–30% and the amplitude to decrease by 2%–5% per 1°C. The number of polyphasic potentials increases as much as tenfold with a 10°C decrease.[29]

Nonphysiologic factors also influence the configuration of the recorded potentials. Of these, the spatial relationships between the needle and individual muscle fibers play the crucial role in determining the waveform.[28] Thus, slight repositioning of the electrode, altering the spatial orientation, introduces a new profile for the same motor unit. Other important variables include the type of needle electrode, size of the recording surface or lead-off area, electrical

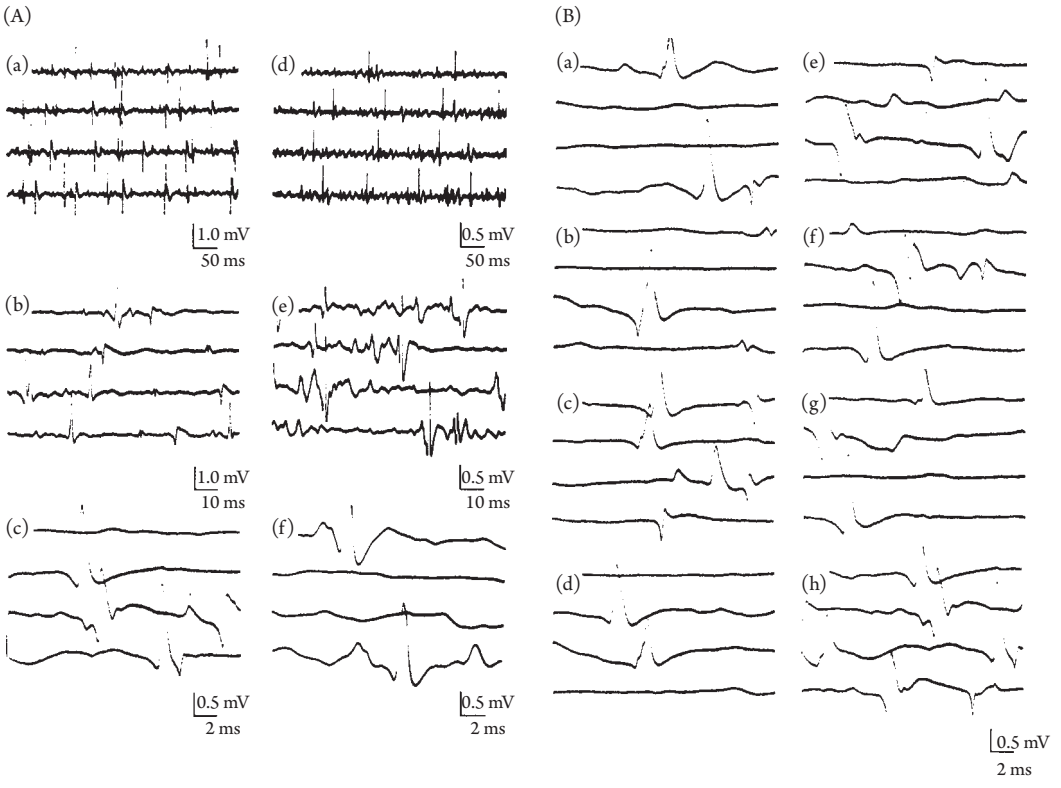

FIGURE 13-5 (*A*) Normal motor unit potentials from mildly contracted biceps in a 40-year-old healthy man (a, b, c) and maximally contracted tibialis anterior in a 31-year-old woman with hysterical weakness (d, e, f). In both, low firing frequency indicates weak voluntary effort. (*B*) Waveform variations of motor unit potentials generated by the same motor unit in the normal biceps. Tracings (a) through (h) represent eight slightly different recording positions while the patient maintained isolated discharges of a single motor unit.

properties of the amplifier, choice of oscilloscope setting such as the filter band path, and the methods of storage and display. These factors together dictate the amplitude, rise time, duration, number of phases, and other characteristics of an MUP.

Amplitude

All of the individual muscle fibers in a motor unit discharge in near synchrony, but only a limited number located near the tip of the recording electrode determine the MUP amplitude (Fig. 13-6). Single muscle fiber potentials fall off in amplitude to less than 50% at a distance of 200–300 μm from the source and to less than 1% a few millimeters away with the use of an ordinary concentric needle.[55] Fewer than five muscle fibers lying within a 500 μm radius of the electrode tip contribute to the high voltage spike.[195] In fact, computer simulation indicates that the proximity of the electrode to the closest muscle fiber determines the amplitude.[196] Therefore, the same motor unit can give rise to many different profiles depending on the position of the needle tip. The amplitude normally varies from several hundred microvolts to a few millivolts with the use of a concentric needle, and a similar range with a substantially greater average when recorded with a monopolar needle.[110,112] In one study using simultaneous recording by two types of electrodes,[35] the same motor unit showed a significantly higher mean amplitude (2.05 times), larger surface area (2.64 times), longer duration (1.86 times), and increased number of phases (1.58 times) and turns (1.35 times) with monopolar as compared to concentric needles.

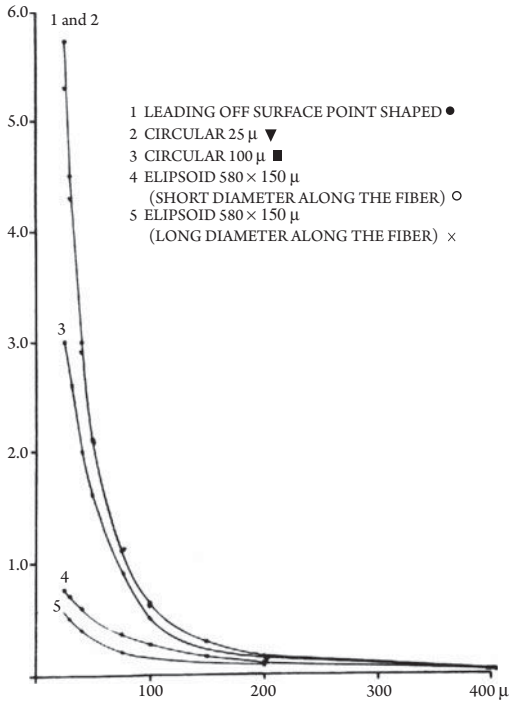

FIGURE 13-6 Reduction in amplitude of recorded response with a gradual shift of the electrode position away from the source. The needle with a large leading-off surface registers a low amplitude even near the spike generator and shows only minor reduction as it moves away from the source. In contrast, the initially large amplitude declines steeply per unit distance with a smaller leading-off surface, which does not extend across the many isoelectric lines (see Fig. 16-1). (Modified from Ekstedt and Stalberg.[55])

Rise Time

The rise time, measured as a time lag from the initial positive peak to the subsequent negative peak (see Fig. 2-7 in Chapter 2), helps estimate the distance between the recording tip of the electrode and the discharging motor unit. A distant unit has a greater rise time because the resistance and capacitance of the intervening tissue act as a high-frequency filter. Such a discharge, accompanied by a dull sound, indicates the need to reposition the electrode closer to the source. In general, a rise time less than 500 μs ensures recording from within the motor unit territory[95] but some argue for less restrictive criteria.[10] Such a motor unit produces a sharp, crisp sound over the loudspeaker, an important clue for the proximity of the unit to the electrode.[148] The measurement of the rise time confirms the suitability of the recorded potential for quantitative assessment of the amplitude.

Duration

Duration of an MUP measured from the initial takeoff to the return to the baseline indicates the degree of synchrony among many individual muscle fibers with variable conduction velocity, membrane excitability, and fiber length.[53] Unlike the spike amplitude, exclusively determined by a very small number of muscle fibers near the electrode, it reflects the activity from a greater number of muscle fibers within the uptake area of the recording surface, which in a concentric needle, extends 2.0–2.5 mm from the core.[195] Therefore, a slight shift or rotation of the needle influences the duration much less than the amplitude. The duration normally varies from 5 to 15 ms, depending on the age of the subject. In one study,[27] the values measured at the ages of 3 and 75 years were 7.3 and 12.8 ms in biceps brachii, 9.2 and 15.9 ms in tibialis anterior, and 4.3 and 7.5 ms in the facial muscles. Another study dealing with four proximal and distal muscles of the upper and lower limbs in 111 healthy subjects between 20 and 80 years of age[16] revealed no marked increase of mean duration before the age of 55. Those older than 55 showed a slight tendency toward increased duration. The use of a wide-open amplifier bandpass combined with enhanced signal-to-noise ratio results in a much longer duration, approaching 30 ms recorded either with a single-fiber electrode or macroelectrode. Under this circumstance, the total time of single action potential from endplate zone to musculotendinous junction may dictate overall duration of motor unit action potential.[54]

Area

Clinical experience and computer simulation indicate that area measurement may help differentiate neuropathy from myopathy. Compared to the amplitude, a greater number of muscle fibers lying within a 2 mm radius of the electrode tip contribute to this measure. The value, however, varies

markedly, with a slight move of the recording electrode mainly reflecting a change in amplitude. The ratio between area and amplitude measures the "thickness" of the potential, which varies much less with changes in electrode position.[143] The combination of amplitude and area/amplitude ratio improves discrimination considerably,[189] detecting around 70% of neurogenic changes, compared to only 15%–30% by duration criteria alone. Compared to studies with concentric needles, macro EMG measures the size of the motor unit better, reflecting a larger recording radius of the needle, which also induces less phase cancellation of single-fiber action potentials.[177]

Phases and Satellite Potential

A phase, defined as that portion of a waveform between the departure from and return to the baseline, also characterizes the waveform. The number of phases, determined by counting negative and positive peaks to and from the baseline, equals the number of baseline crossings plus one. Normally, an MUP has four or fewer phases. Polyphasic potentials with more than four phases often seen in neuropathy and myopathy result from desynchronized discharges of individual muscle fibers, probably based on fiber size variability rather than random loss of fibers. These potentials do not exceed 5% to 15% of the total population in a healthy muscle, if recorded with a concentric needle electrode. Polyphasic activities occur more commonly with the use of a monopolar needle, although no studies have established the exact incidence. Some action potentials show several "turns" or directional changes without crossing the baseline. The serrated action potentials or, less appropriately complex or pseudopolyphasic potentials, probably indicate desynchronization among discharging muscle fibers. These irregular potentials appear more commonly in acute processes.[226] A late component of MUP occurs both in pathologic and normal muscle. In one study,[118] satellite latencies ranged from 8.8 to 32 ms, too long for regenerating axons or atrophic muscle fibers. The spike-to-satelite time intervals suggested retrograde propagation in a noninnervated muscle connected with an innervated muscle fiber at one of muscle junctions.

6. QUANTITATIVE MEASUREMENTS

Methods of Assessment

In clinical EMG, we assess various features of an MUP by visually inspecting oscilloscope displays of waveforms and listening to their audio characteristics. Using these simple means, an experienced examiner can detect abnormalities with reasonable certainty. Such subjective assessment, though satisfactory for the detection of unequivocal abnormalities, may fall short of delineating less obvious deviations or mixed patterns of abnormalities. These ambiguous circumstances call for quantitative measurement of motor unit potentials.[26,73,144,194] An objective approach also allows meaningful comparison of test results obtained sequentially or in different laboratories. The use of standardized recording sites within the muscle reduces location-dependent variability and increases diagnostic sensitivity.

Physiologic properties that characterize an MUP include duration, amplitude, area, phases, turns, number of satellites, and degree of waveform variability.[31,190] Additional measures of interest include spike duration, thickness[143] and size index[189] using special computer algorithms. Quantitative studies customarily analyze at least 20 different units to compare the mean with reference values. An alternative method relies on identifying extreme values, which fall outside the normal range.[191] This outlier technique helps identify abnormalities limited to a few motor unit potentials that escape detection in the assessment solely based on mean values.

Currently available quantitative techniques include spike-triggered averaging with a delay line,[113] two-channel recording using a concentric needle for pickup, and a single-fiber electrode for trigger,[116] template matching,[7] and decomposition technique based on multiple template matching.[11,17,50,97,162,202]

Selection and Analysis

Table 13-1 summarizes the duration of motor unit potentials recorded with a concentric needle in normal subjects of different ages.[27] These values,

Table 13-1 Mean Action Potential Duration (in Milliseconds) in Various Muscles at Different Ages (Concentric Electrodes)

	ARM MUSCLES						LEG MUSCLES					FACIAL MUSCLES
AGE IN YEARS	DELTOIDEUS	BICEPS BRACHII	TRICEPS BRACHII	EXTENSOR DIGITORUM CONUNUNIS	OPPONENS POLLICIS; INTEROSSEUS	ABDUCTOR. DIGITI QUINTI	BICEPS FEMORIS; QUADRICEPS	GASTROCNEMIUS	TIBIALIS ANTERIOR	PERONEUS LONGUS	EXTENSOR DIGITORUM BREVIS	ORBICULARIS ORIS SUPERIOR; TRIANGULARIS; FRONTALIS
0	8.8	7.1	8.1	6.6	7.9	9.2	8.0	7.1	8.9	6.5	7.0	4.2
3	9.0	7.3	8.3	6.8	8.1	9.5	8.2	7.3	9.2	6.7	7.2	4.3
5	9.2	7.5	8.5	6.9	8.3	9.7	8.4	7.5	9.4	6.8	7.4	4.4
8	9.4	7.7	8.6	7.1	8.5	9.9	8.6	7.7	9.6	6.9	7.6	4.5
10	9.6	7.8	8.7	7.2	8.6	10.0	8.7	7.8	9.7	7.0	7.7	4.6
13	9.9	8.0	9.0	7.4	8.9	10.3	9.0	8.0	10.0	7.2	7.9	4.7
15	10.1	8.2	9.2	7.5	9.1	10.5	9.2	8.2	10.2	7.4	8.1	4.8
18	10.4	8.5	9.6	7.8	9.4	10.9	9.5	8.5	10.5	7.6	8.4	5.0
20	10.7	8.7	9.9	8.1	9.7	11.2	9.8	8.7	10.8	7.8	8.6	5.1
25	11.4	9.2	10.4	8.5	10.2	11.9	10.3	9.2	11.5	8.3	9.1	5.4
30	12.2	9.9	11.2	9.2	11.0	12.8	11.1	9.9	12.3	8.9	9.8	5.8
35	13.0	10.6	12.0	9.8	11.7	13.6	11.8	10.6	13.2	9.5	10.5	6.2
40	13.4	10.9	12.4	10.1	12.1	14.1	12.2	10.9	13.6	9.8	10.8	6.4
45	13.8	11.2	12.7	10.3	12.5	14.5	12.5	11.2	13.9	10.1	11.1	6.6
50	14.3	11.6	13.2	10.7	12.9	15.0	13.0	11.6	14.4	10.5	11.5	6.8
55	14.8	12.0	13.6	11.1	13.3	15.5	13.4	12.0	14.9	10.8	11.9	7.0
60	15.1	12.3	13.9	11.3	13.6	15.8	13.7	12.3	15.2	11.0	12.2	7.1
65	15.3	12.5	14.1	11.5	13.9	16.1	14.0	12.5	15.5	11.2	12.4	7.3
70	15.5	12.6	14.3	11.6	14.0	16.3	14.1	12.6	15.7	11.4	12.5	7.4
75	15.7	12.8	14.4	11.8	14.2	16.5	14.3	12.8	15.9	11.5	12.7	7.5

The values given are mean values from different subjects without evidence of neuromuscular disease. The standard deviation of each value is 15% (20 potentials for each muscle). Therefore, deviations up to 20% are considered within the normal range when comparing measurements in a given muscle with the values of the table. (From Buchthal,[27] with permission.)

measured from the point of takeoff to return to the baseline, exclude late or satellite components seen as a separate peak.[117]

In quantitative analysis, most investigators use the standard concentric needle electrode with a lead-off surface of about 0.07 mm^2. The optimal recording calls for an amplifier frequency range of 10 Hz–10 KHz and standard sensitivity of 100–500 μV/cm, as well as the selection of an MUP with a rise time of less than 500 μs. A storage oscilloscope with a delay line offers a distinct advantage for quick identification of such potentials. Recorded waveforms vary a great deal from one motor unit to another and within the same unit, depending on the relative position of the needle tip to the source of discharge.[25] Thus, an ideal quantification requires counting at least 20 different units in each muscle, using multiple needle insertions.

In one study,[58] the 95% tolerance limits for mean total duration progressively narrowed from 6.6 to 14.2 ms for 5 units to 7.4 to 13.0 ms for 20 units in normal subjects. Quantitative studies of duration supported the presence of myopathy in 2 of 10 patients with analyses of 5 units and in 9 patients with analyses of 20 units. Thus, compared to sampling 5 units, which may allow diagnosing some cases, studying 20 potentials narrows the tolerance limits. Increasing the sample to more than 20, though impractical as a clinical study, further reduces intertrial variability and improves diagnostic sensitivity.[161] As discussed earlier, the normal ranges depend on many factors other than simply the characteristics of the motor unit itself. Hence, each laboratory should ideally construct its own table of normal values. A close scrutiny of the technique that duplicates the original process, however, allows the use of any available norms published by others.

Automated Methods

Different investigators have explored the possibility of automatically analyzing the MUP.[160,168] Such a system converts the recorded potentials to a digital equivalent for computer analysis. The usual measurements include duration, amplitude, polarity, number of phases, and integrated area under the waveform. One of the inherent difficulties with this approach centers on the selection of the signals. In early methods, the examiner screened the potentials by visual inspection, using a monitor scope, before processing them for automated analysis. Another technique uses automatic qualification of peak-to-peak amplitudes exceeding 50 or 100 μV for inclusion of a greater number of potentials. This system measures the duration of the discharge at 20 μV above the baseline and counts the number of phases as a deflection exceeding 40 μV.

Most studies have shown no major discrepancy between the results of manual quantification and quick automatic analysis. Indeed, the computer can accurately and efficiently discriminate typical neuropathic and myopathic changes. These techniques, however, may or may not resolve borderline cases in which conventional methods fail to provide useful information. For example, an automatic analysis failed to separate female relatives of patients with Duchenne dystrophy from healthy subjects individually, despite a statistically significant difference between the two as a group.[206]

Routine studies rarely include quantitative analysis, which takes time to select and measure 20 individual motor units. Of various approaches discussed earlier, decomposition techniques probably are best suited for automatic analysis, avoiding a time-consuming quantification process.[17,128,142] Although pilot studies show promising results, none of the techniques has found wide acceptance. Their implementation and evaluation must wait for further dissemination of special computer algorithms as part of commercially available software. Some authors recommend visual inspection and remarking of the characteristics for each MUP before making clinical judgment from the data.[21]

Frequency Spectrum

The waveform of any action potential comprises many sine waves of different frequencies. Thus, a frequency spectrum provides another objective means of characterizing an MUP. This type of analysis reveals an inverse relationship between the MUP duration and the amount of high-frequency components. Several investigators have studied frequency spectra, or a histogram of

activities against frequency, in normal and diseased muscles.[37,132] The highest peak seen during maximal contraction falls between 100 and 200 Hz in normal subjects. This peak shifts to a higher frequency in subjects with myopathy and to a lower frequency in subjects with anterior horn cell lesions. The clear difference seen in typical cases does not imply its practical value as a diagnostic test.[72] The reproducibility of results depends primarily on controlling the variables, such as needle position or level of muscle contraction, that appreciably influence the results.

7. DISCHARGE PATTERN OF MOTOR UNITS

Recruitment

A healthy subject can initially excite only one or two motor units before recruiting additional units in a fixed order.[87] The units activated early consist primarily of small, Type I muscle fibers according to the size principle during isometric or lengthening contractions.[40,180,197] A single motor unit normally begins to discharge at 5 to 7 Hz, typically semirhythmically, with slowly increasing, then decreasing interspike intervals, despite constant contraction. Any potential that fires slower than this rate represents spontaneous rather than voluntary discharges. As the subject contracts the muscle more, the first motor unit increases its firing rate and then a second motor unit begins to fire. Thus, an attempt to generate a stronger force brings about two separate but related changes in the pattern of motor unit discharge: (1) more rapid firing of already active units and (2) recruitment of previously inactive units (Fig. 13-7).

At minimal levels of muscle contraction, changes in firing rate grade the muscle force. Which of the two plays a greater role thereafter remains unknown, but both mechanisms operate simultaneously. The physiologic rank order of motor unit discharge during slowly graded or ballistic increase in force (see Chapter 12-6) depends, in addition to soma diameter, on other factors such as synaptic density and efficacy as well as specific membrane resistance. Ranking of recruitment also relates to the type of motor units; slow, fatigue-resistant units first, followed by fast fatigue units. A monopolar or concentric electrode with a small uptake area fails to assess the motor unit territory.[59] Thus, it takes a macro electrode or a specially constructed quadrifilar electrode[4] to confirm the size principle from low to high threshold motor units. Increasing muscle tension activates the large high threshold Type II motor units. The force of single units then increases exponentially when plotted against the enlarging MUP size measured by macro technique.[217]

A normal recruitment pattern implies the discharge of an appropriate number of motor units for the effort (Fig. 13-8A). A reduced (Fig.13-8B) or increased pattern (Fig. 13-8C) indicates a fewer or greater number of discharging units than expected. A loss of motor units results in late and sparse recruitment compensated by increased rates of firing, showing a strong nonlinear correlation to the estimated loss of motor units.[178] In contrast, a random loss of muscle fibers from each motor unit gives rise to an early and excessive recruitment at minimal and moderate levels of effort (see Chapter 14-56). For accurate assessment, the examiner must know the approximate number of active motor units expected for a given force generated by

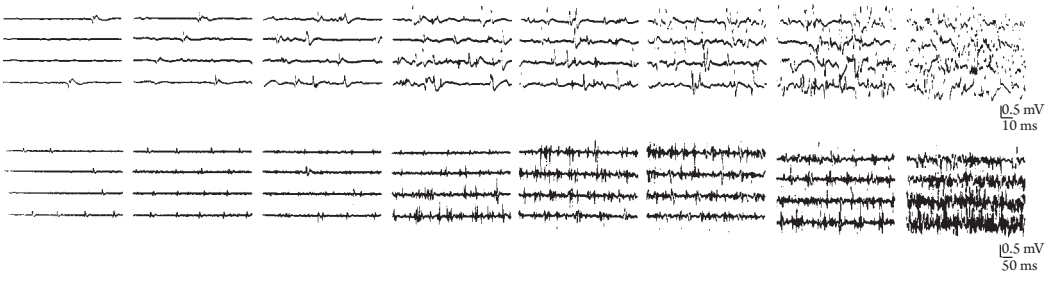

FIGURE 13-7 Normal recruitment and full interference pattern with increasing strength in the same healthy subject as shown in Figure 13-5A. The tracings depict the same activity recorded with fast (top) and slow (bottom) sweep.

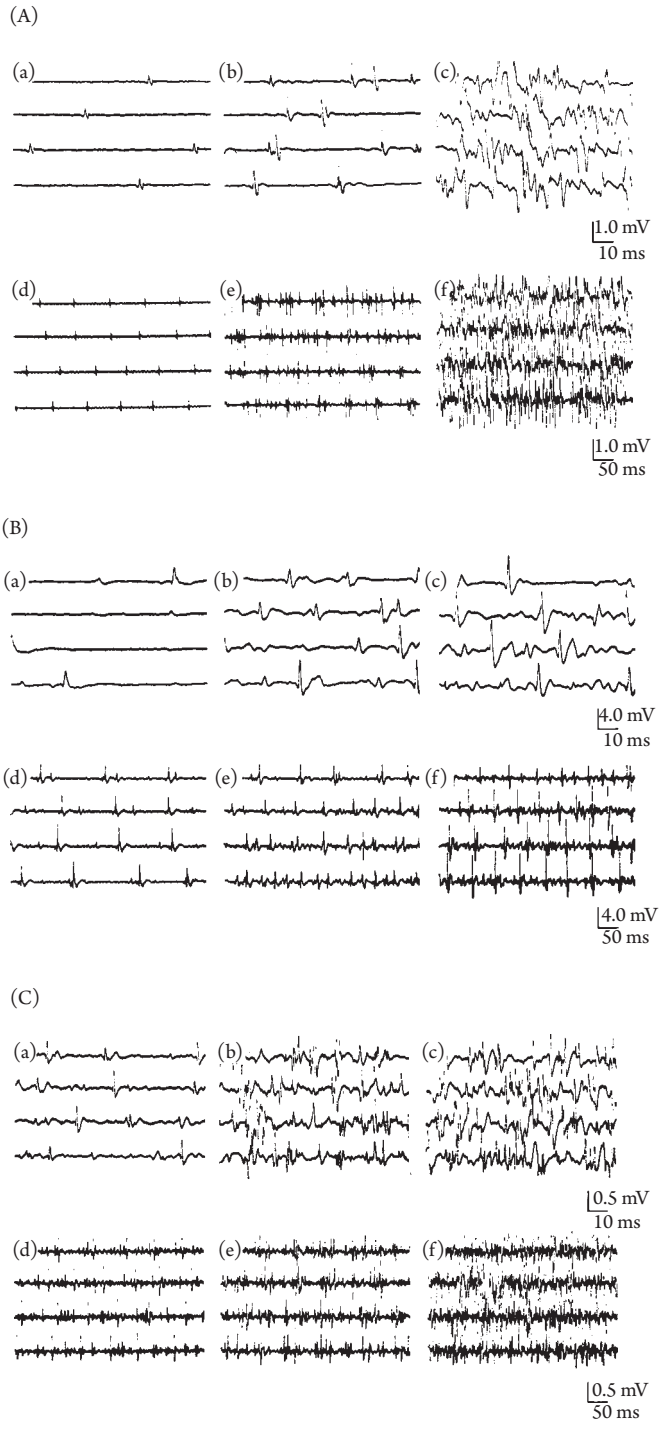

FIGURE 13-8 (*A*) Normal recruitment in the triceps of a 44-year-old healthy man, recorded with fast (top) and slow sweep (bottom) during minimal (a, d), moderate (b, e), and maximal contraction (c, f). (*B*) Reduced recruitment in the tibialis anterior of a 44-year-old man with amyotrophic lateral sclerosis. A single motor unit discharged rapidly to compensate for the lack of recruitment during a strong contraction. (*C*) Early recruitment and full interference pattern in the quadriceps of a 20-year-old patient with limb-girdle dystrophy. The tracings show early recruitment, or the presence of an excessive number of motor units for the amount of voluntary force exerted during weak contraction.

the muscle. Motor units may fire irregularly in basal ganglia disorders such as parkinsonism or chorea at or above physiologic tremor rate. Upper motoneuron lesions such as spinal cord injury may alter motor unit forces and recruitment patterns.[203]

The recruitment frequency, defined as the firing frequency of the initially activated unit at the time an additional unit kicks in, measures the pattern of motor unit discharge. Normal values determined during mild contraction average 5 to 10 impulses per second, depending on the types of motor units under study.[83,154] The reported ranges show a considerable overlap between healthy subjects and patients with neuromuscular disorders. Some electromyographers prefer the ratio of the average firing rate to the number of active units. Normal subjects should have a ratio less than 5 with, for example, three units firing less than 15 impulses per second each.[41] If two units are firing, one at 20 Hz and the other at 10 Hz, the average rate of firing of the two units equals 15 Hz. The recruitment ratio (15/2) exceeds 5, indicating a loss of motor units. Studying discharge pattern of single motor units may help distinguish firing behavior in patients with upper motoneuron lesions.[61,200]

Interference Pattern

With greater contraction, many motor units begin to fire very rapidly (Fig. 13-9). Simultaneous activation of different units precludes recognition of each individual MUP, hence the name *interference pattern*. A number of factors determine the spike density and the average amplitude of the summated response. These include descending input from the cortex, number of motoneurons capable of discharging, firing frequency of each motor unit, waveform of individual potentials, and probability of phase cancellation. Despite such complexity, its analysis provides a simple quantitative means of evaluating the relationship between the number of firing units and the muscle force exerted with maximal effort. For example, in hemiparetic patients, isometric contraction of paretic muscles shows frequent lapses in the interference pattern. This inability to sustain muscle activity serves as quantitative confirmation of clinical motor impersistence.

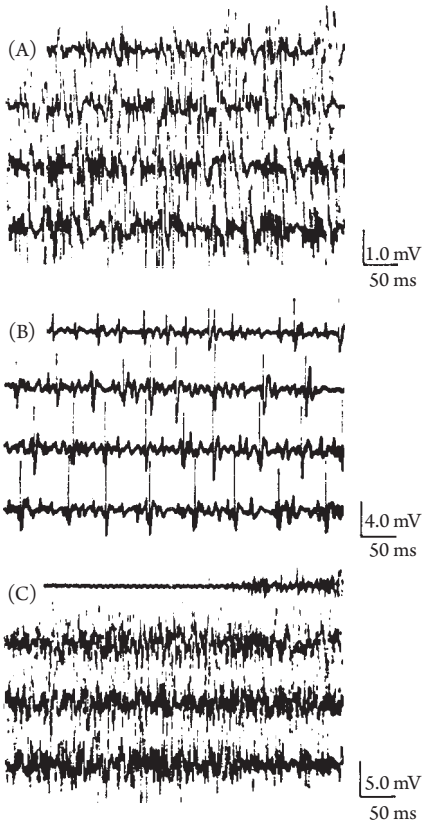

FIGURE 13-9 Interference patterns seen in the triceps of a 44-year-old healthy man (A); tibialis anterior of a 52-year-old man with amyotrophic lateral sclerosis (B); and quadriceps of a 20-year-old man with limb-girdle dystrophy (C). Discrete single motor unit discharge in (B) stands in good contrast to abundant motor unit potentials with reduced amplitude in (C).

Computer simulation may help automatic analysis of interference patterns.[61] Decomposition of interference patterns into the constituent MUP allows measurement of their configurational and behavioral properties.[39,188] Such analysis showed contrasting changes of amplitudes and firing rates in motoneuron disease (MND) and myopathies, confirming many of the traditional criteria.

Measurements of Turns and Amplitude

Examination of an individual MUP during weak voluntary effort only relates to low-threshold Type I muscle fibers. Studies of the interference pattern induced by strong muscle contraction

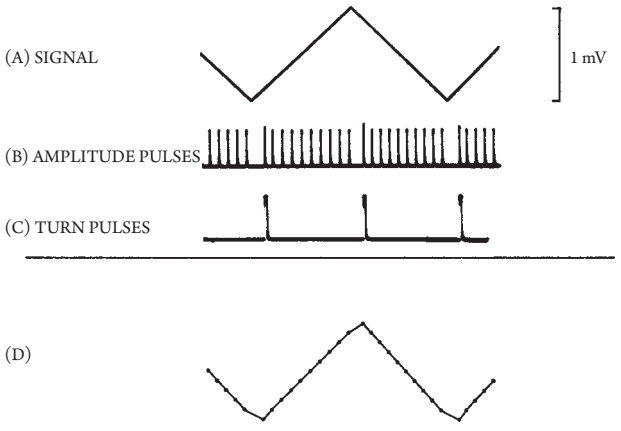

FIGURE 13-10 Conversion of calibration waveform (*A*) into two serial pulse trains: amplitude (*B*) and turns (*C*). The outputs of these two pulse generators characterize the original input accurately, as evidenced by graphical reconstruction of the waveform (*D*) from (*B*) and (*C*). (From Hayward and Willison,[86] with permission.)

allow quantitative assessment over a wider range.[185] One such analysis utilizes an automated technique designed to count the number of "turns" or directional changes of a waveform that exceeds a minimum excursion without necessarily crossing the baseline.[222] This method (Fig. 13-10) measures the amplitude from a point of change in direction to the next, not from baseline to peak, selecting potentials greater than 100 μV to avoid contamination from noise.[85] During a fixed time epoch, the subject must push against a force transducer to maintain constant levels of muscle contraction, although the technique may yield comparable data when testing facial muscles without force monitoring.[68,104] Turns and spectral analyses of interference pattern, though efficient, only indirectly relate to the physiologic properties of the motor units. Reported measures include turn frequencies,[99] the maximal ratio of turns to mean amplitude, or peak ratio, and the number of time intervals between turns.[121] In this type of analysis, a decrease in peak-ratio and number of time intervals supplement each other in identifying neurogenic involvement.[70,71]

Quantitative measurements of recruitment patterns complement studies of single motor units. Evaluation of individual potentials allows a precise description of normal and abnormal motor units and their temporal stability. Analysis of recruitment reveals an overall muscle performance by demonstrating the number and discharge pattern of all the motor units. Despite the theoretical interest, however, these methods have found limited acceptance as supplements to routine EMG.

8. OTHER MEASURES OF MUSCLE FUNCTION

Muscle Fiber Conduction

Direct muscle stimulation by monopolar needle distally and recording of muscle action potentials proximally by concentric electrode placed at a known distance of 50–60 mm allow calculation of muscle fiber conduction velocity.[212] The first and last peak of the recorded response represents the muscle fibers of the fastest and slowest conduction velocity. Muscle fiber conduction velocity also changes with the fiber length.[24,114] In one study using single-fiber electromyography (SFEMG)[208] propagation velocity increased by 33% on shortening and decreased by 22% on elongating the muscle fiber. These length-dependent changes may contribute to the supernormal phase of muscle fiber propagation velocity and interdischarge interval-dependent myogenic jitter seen in single-fiber studies.

Computerized data analyses of frequency and time domain give rise to an average estimate

of muscle fiber conduction velocity from many motor units at different contraction levels.[109] During submaximal contractions, two opposing factors influence the average values. It increases with recruitment of fresh motor units and decreases with fatigue of already active motor units. On the average, the conduction velocity increases with the level of contraction force either measured with surface or needle electrode.[141] Thus, the measurements with electric stimulation of single or a bundle of fibers at rest, in general, yield lower values than those obtained during voluntary contraction.[62] The use of multichannel recording may improve reproducibility of the results.[66]

The propagation velocities increases with age, body height, and muscle diameter in the growing normal child.[124] Surface and needle recording[213] may reveal a reduced muscle fiber conduction velocity in myopathies,[18] diabetic polyneuropathies,[136] and high-dose methylprednisolone therapy.[212] Other related topics of interest include velocity recovery function assessed with preconditioning activation, including doublet and triplet stimulation,[102,103] correlation between conduction characteristics and MUP properties,[64] relationship between muscle and nerve fiber conduction velocities,[56] effect of space mission or bed rest [172] and surface EMG signals during explosive dynamic contractions.[164] Despite some encouraging results, muscle fiber conduction studies have found only limited clinical value as a diagnostic measure.

Velocity Recovery Cycles of Muscle Fibers

Similar to the threshold tracking (see Chapter 10-3, 10-4), estimating changes of muscle membrane excitability after a conditioning stimulus may serve as a measure of muscle function in health and disease. Direct muscle stimulation through needle electrodes in the brachioradialis revealed a relative refractory period (RRP) lasting 3.27 ± 4.5 ms (mean ± SD) and a phase of supernormality showing a velocity increase of 9.3% ± 3.4% at 6.1 ± 1.3 ms. After gradual recovery over the next second, a broad hump of additional supernormality appeared at around 1000 ms. The two phases of supernormality resemble early and late after-potentials attributable, respectively, to the passive decay of membrane charge and potassium accumulation in the t-tubules. Five minutes of ischemia prolonged RRP and reduced supernormality, confirming the role of depolarization for these measures.[228] Patients with chronic renal failure showed muscle membrane depolarization by hyperkalemia, which may account for some of the functional deficits in uremic myopathy. Dialysis transiently normalized muscle membrane potential, although the late component of supernormality remained abnormally low.[115,227]

Integrated Electrical Activity and Muscle Force

During maximal effort, discharge frequencies of motor units reach 50 impulses per second. This gives rise to a tetanic contraction by high degrees of fusion, producing more than twice the tension of a single twitch. Despite intermittency of electrical impulses, the accompanying mechanical response fuses at high discharge frequencies to maintain a relatively smooth tension. In contrast, unfused twitches of intermittently firing motor units induce a tremor during isometric contraction. Spectral analysis of muscle force therefore helps estimate overall motor unit activity.[96] Smooth contraction of the whole muscle also results from asynchronous firing of different motor units. Isokinetic measurements of muscle strength reveal the level of consistency in normal motor performance and aid in the identification of unusual patterns, for example, those seen in hysterical paresis.

Different surface measures of electrical activity can quantify muscle function and determine discharge pattern of motor units.[145,182,209,223] Waveform integration may also help correlate the muscle force and the electrical activity, although the results vary considerably with repeated trials.[138,187] For determining the total area, a process called full-wave rectification reverses the polarity of all positive peaks. The tracing then consists only of negative deflections, allowing their integration without phase cancellation. The integral of a waveform increases in proportion to the amplitude, frequency, and duration of the original potential, usually relating linearly to the isometric tension up to the maximal contraction.[205] Surface recording

can also provide useful information in estimating motor unit size.[170] Diagnostic yield of surface studies in various neuromuscular disorders,[94] although not comparable to needle examination, may improve with the use of high spatial resolution recording and high-pass filtering.[23]

Testing muscle force in the management of neuromuscular diseases[204] requires rigorous quality assurance to improve its reliability.[88] During dynamic contraction, power spectra of surface myoelectric signals change depending on the applied torque, muscle length, and velocity of contraction. Muscle force generally declines with age in both sexes.[81,171] Fallout of motor units contributes to the reduction in torque when compensatory reinnervation begins to fail.[192] Other factors that influence muscle force include muscle fiber contractility, metabolic changes, and central mechanisms.

Muscle Contraction and Fatigue

Despite substantial reduction in torque after fatigue, compound muscle action potentials (CMAPs) change little in area, although they become slightly reduced in amplitude.[183] During fatiguing contractions, EMG activities gradually decline in the contracted muscle and, to a lesser extent, in the synergists probably through an inhibitory reflex.[175] Progressive increase in mean firing rate and recruitment of additional larger motor units results in fatigue-induced increase in the surface EMG.[33] A decreased contraction-relaxation rate of muscle fibers during fatigue reduces the fusion frequency. In this setting, lower rates of motor unit activation suffice in the maintenance of constant force. In most studies, therefore, the number of motor unit discharges needed to maintain a constant force declined after maximal contraction, causing reduction in the surface recorded integral of the rectified electrical activities.[229]

Human muscle fatigue may also result from failure of central motor drive, which results in less than maximal activation of muscle).[106] The technique termed *twitch interpolation* provides quantitative estimate of the amount of volitional effort by superimposing electrical stimulation during voluntary contraction.[6,139] In one study using this method, corticomotor excitability increased during a sustained submaximal voluntary contraction followed by progressive intracortical inhibition as fatigue developed.[176] In some central nervous system disorders such as multiple sclerosis, motor unit activation may require a relatively greater central motor drive.[147] Patients with chronic fatigue syndrome complain of persistent asthenia that no known medical disease can account for. Careful analysis of symptoms should facilitate the clinical evaluation, often preventing unnecessary physiologic or biochemical procedures.[119]

Other reports of interest related to this topic include fatigue during electrically stimulated contraction,[78,123,125] MUP tracking during fatigue,[13] surface EMG changes associated with eccentric exercise,[156] activation pattern on muscle force,[69,207] muscle force and endurance,[230] and motor unit recruitment during a sustained contraction.[166]

Kinesiology and Motor Control

Surface EMG plays a unique role in kinesiology, measuring the output of α-motoneurons in normal subjects as well as in patients with a variety of motor disorders,[231] although the currently available data do not support its use as a sole test in the diagnosis and study of neuromuscular disorders.[135, 210] Electrical signals and twitch torque recording have provided insight into the function of the normal and the disordered neuronal system as well as motor control.[153,165] Its application includes studies of motor unit short-term synchronization,[49] decoding the neural drive to muscles,[65] firing pattern of fasciculations in amyotrophic lateral sclerosis (ALS),[111] motor unit discharge pattern,[91] locomotion,[77,92,149,151] concentric and eccentric dynamic contraction,[45] effect of age,[137] muscle pain,[63] hypoxia,[51] effect of training,[126] Parkinson's disease,[127,167] dystonia,[44] and poststroke hemiparesis.[48,101]

Acoustic Signals

Skeletal muscle emits acoustic signals during voluntary contraction providing a measure of force production, fatigue, and pathology of muscle. A composite probe used for surface

acoustic recordings contains a piezo ceramic transducer glued to a flexible printed circuit board.[36] Frequency spectrum reveals relatively high-amplitude peaks below 20 Hz with the most prominent peak occurring at around 10 Hz and additional peaks on either side of the major peak. Muscle activities induced by nerve stimulation also produce sounds for evaluation with an accelerometer, which registers muscle vibration induced by twitches. This approach not only eliminates movement artifacts but also allows the use of fundamental, nontransducer-dependent units. It also provides quantitative data to relate electric signal to contractile muscle activity.[215]

One study[12] reported latencies of 5.7 ± 0.6 ms and 5.1 ± 0.6 ms (mean ± SD) from the median and ulnar nerve stimulation at the wrist to the onset of the acceleration waveform obtained from abductor pollicis brevis and abductor digit quinti. In another study,[155] phrenic nerve stimulation at the neck induced diaphragmatic acoustic signal with the latency of 12.4 ± 0.6 ms as compared to electrical response with the latency of 7.3 ± 0.7 ms. The ratio of acoustic myographic amplitude to surface electrical signals serves as a measure of mechanical output compared with electrical activity of the contractile system. Its clinical application as a diagnostic test, however, needs further scrutiny.

Sonographic Imaging

Despite potentially substantial errors in measurement of muscle geometry,[14] sonographic imaging of muscle may help evaluate the location and type of pathology. Quantification of muscle echo intensity provides more reliable information compared with visual evaluation of the images.[157,159] This test improves clinical assessment of patients by supplying precise muscle size measurements and identification of structural abnormalities. Sonography also can image fasciculations[140,218] as well as fibrillations.[158,211] It may distinguish between healthy and affect muscles without identifying specific disease entities.[75] Other studies of interest include assessing contractile ability of the quadriceps muscles,[46] normal values for quantitative analyses,[9] muscle changes in ALS,[8,120] electromechanical delay,[93] muscle stiffness distribution,[184] calibrated quantitative imaging,[224] isometric muscle contraction,[89] and evaluation of focal abnormalities in acid maltase deficiency.[225]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) offers structural information on the muscular system noninvasively with direct measurement of the muscle tissue using nonionizing radiation.[90,100,107] Clinical application used in conjunction with electrophysiologic study of muscle function includes assessment of contractile and noncontractile components,[90] detection of muscle denervation,[98,134] and measurement of mechanical properties of muscle, for example, in myositis.[133]

Electrical Impedance Myography

This noninvasive technique relies upon the application and measurement of high-frequency, low-intensity electrical current. It assesses disease-induced changes to the normal composition and architecture of the muscle based on electrical impedance across a spectrum of applied frequencies.[173,174] As a group average, ALS patients demonstrated increased and distorted anisotropy pattern, whereas myopathic patients showed a normal or reduced anisotropy.[74] Anisotropy of muscle conductivity increases markedly after subacute denervation injury.[3] This technique has some promise in exploring electrical characteristics of muscle, but its clinical application as a diagnostic test remains unclear.

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14

Types of Electromyographic Abnormalities

Abbreviations: ACh—acetylcholine, AChE—acetylcholinesterase, ALS—amyotrophic lateral sclerosis, CMT—Charcot-Marie-Tooth disease, CRD—complex repetitive discharge, DMI—myotonic dystrophy Type I, DMII—myotonic dystrophy Type II, DMD—Duchene muscular dystrophy, EMG—electromyography, FSH—facioscapulohumeral, GBS—Guillain Barré syndrome, HyperPP—hyperkalemic periodic paralysis, LEMS—Lambert Eaton myasthenic syndrome, LG—limb girdle, MC—myotonia congenita, MG—myasthenia gravis, MND—motoneuron disease, MS—multiple sclerosis, MUP—motor unit potential, NMT—neuromuscular transmission, PMC—paramyotonia congenita, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy

1. INTRODUCTION

Needle study of muscle action potentials, or electromyography (EMG), constitutes an integral part of neuromuscular assessment as an extension of clinical assessments (see Chapter 13-2). It serves as a clinical tool only in the light of the patient's history and physical examination and not as an independent laboratory test. The four steps of EMG (see Fig. 13-1) help categorize motor dysfunction into upper and lower motoneuron disorders and myogenic lesions. Each entity has

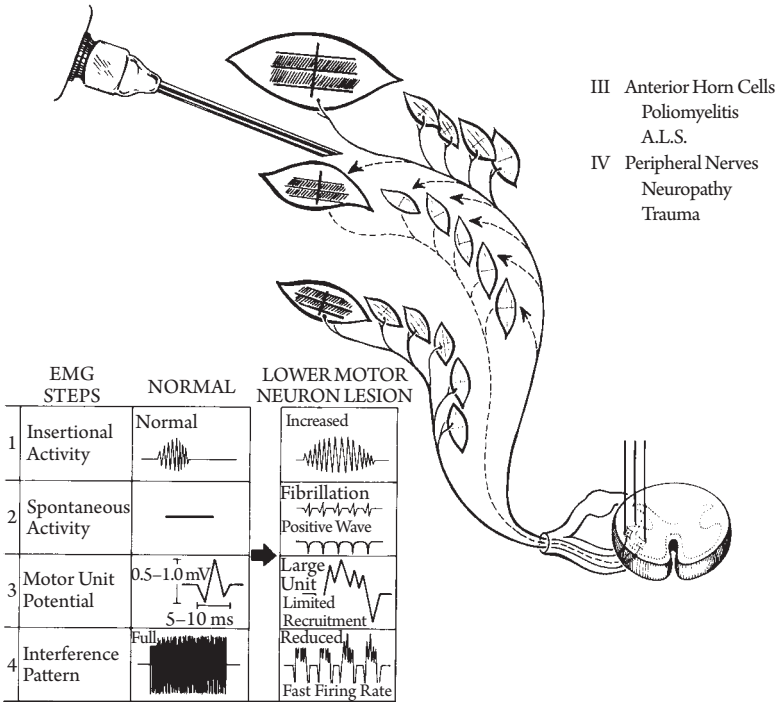

FIGURE 14-1 Typical findings in lower motoneuron lesions. They include (1) prolonged insertional activity; (2) spontaneous discharges in the form of fibrillation potentials and positive sharp waves, (3) large-amplitude, long-duration polyphasic motor unit potentials; and (4) late recruitment and, in advanced cases, discrete single unit activity firing rapidly during maximal effort of contraction. The diagram depicts reinnervation of muscle fibers supplied by a diseased axon (cf. Fig. 13-1). Although not apparent in this illustration, the sprouting axon respects the anatomical constraint, incorporating only those muscle fibers found within its own boundary. Thus, a large motor unit potential reflects increased muscle fiber density rather than motor unit territory, which remains the same.

typical findings, as shown in Figures 14-1 through 14-3 and summarized in Figure 14-4.

The initial two steps test a relaxed muscle, which shows no electrical activities except for brief injury potentials coincident with the insertion of the needle and endplate noise and spikes recorded at the motor points. Several types of spontaneous discharges seen at rest, therefore, all signal diseases of the nerve or muscle. Both fibrillation potentials and positive sharp waves result from excitation of individual muscle fibers. Complex repetitive discharges (CRDs) comprise high-frequency spikes derived from multiple muscle fibers, which fire sequentially, maintaining a fixed order. In contrast, fasciculation potentials and myokymic and neuromyotonic discharges represent spontaneous activation of motor units as the result of hyperexcitable motor axons.

The last two steps assess motor units, the smallest functional element during volitional contraction. Isolated discharges of single motor axons induced by voluntary effort give rise to motor unit potentials (MUPs). Diseases of the nerve or muscle cause structural or functional disturbances of the motor unit, which in turn lead to alterations in the waveform and discharge patterns of their electrical signals. Because certain characteristics of such abnormalities suggest a particular pathologic process, the study of MUP provides information useful in elucidating the nature of the disease. The illustrations used to describe various types of abnormalities (Figs. 14-1 through 14-4) in this chapter emphasize the basic principles at the risk of oversimplification. The description in the text amplifies these points and clarifies certain variations and exceptions not apparent in the diagrams.

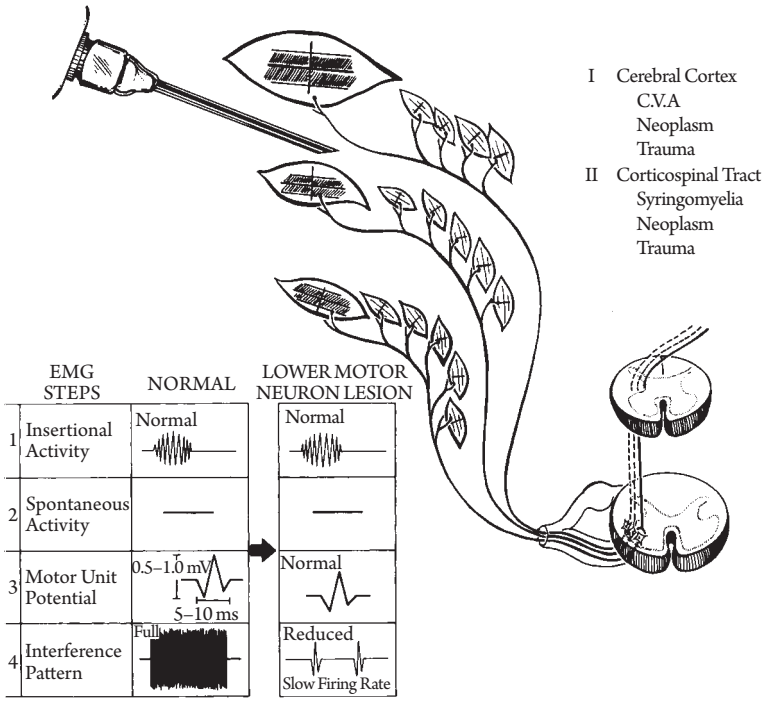

FIGURE 14-2 Typical findings in upper motoneuron lesions. They include (1) normal insertional activity, (2) no spontaneous discharges, (3) normal motor unit potential if detected in an incomplete paralysis, and (4) reduced interference pattern with slow rates of motor unit firing in the absence of a central drive. The diagram illustrates degeneration of the corticospinal tract resulting in a reduced number of descending impulses reaching the anterior horn cells, which in turn activate a small number of motor unit potentials.

2. INSERTIONAL ACTIVITY

Decreased versus Prolonged Activity

A marked diminution of insertional activity usually indicates a reduced number of healthy muscle fibers in fibrotic or severely atrophied muscles (see Fig. 13-2 in Chapter 13). Functionally inexcitable muscle fibers will also show the same abnormality, for example, during attacks of familial periodic paralysis. Absence of any activity, however, more often than not signals technical problems such as switched-off amplifier, broken lead wire, and faulty needle. Underestimating the depth of the muscle in an obese patient leads to inadvertent exploration of the subcutaneous fat, as we commonly experience in Iowa (but not in Kyoto). If the longest needle available (75 mm) barely reaches the intended target, further effort usually proves untenable, indicating the need to switch to more superficial muscles, if any.

Abnormally prolonged insertional activity, outlasting the cessation of needle movement, indicates irritability of the muscle or, more specifically, instability of the muscle membrane (Fig. 14-1). This type of activity often accompanies denervation, myotonic disorders, or certain other myogenic disorders such as myositis. Some healthy individuals may have one or two isolated positive potentials at the end of the discharge. The lack of reproducibility distinguishes this variant of normal insertional activity from qualitatively similar, but abnormally enhanced, insertional positive waves, as described in the next section.

Insertional Positive Waves

A briefly sustained run of positive waves may follow insertional activity, lasting several seconds to minutes after cessation of the needle movement.

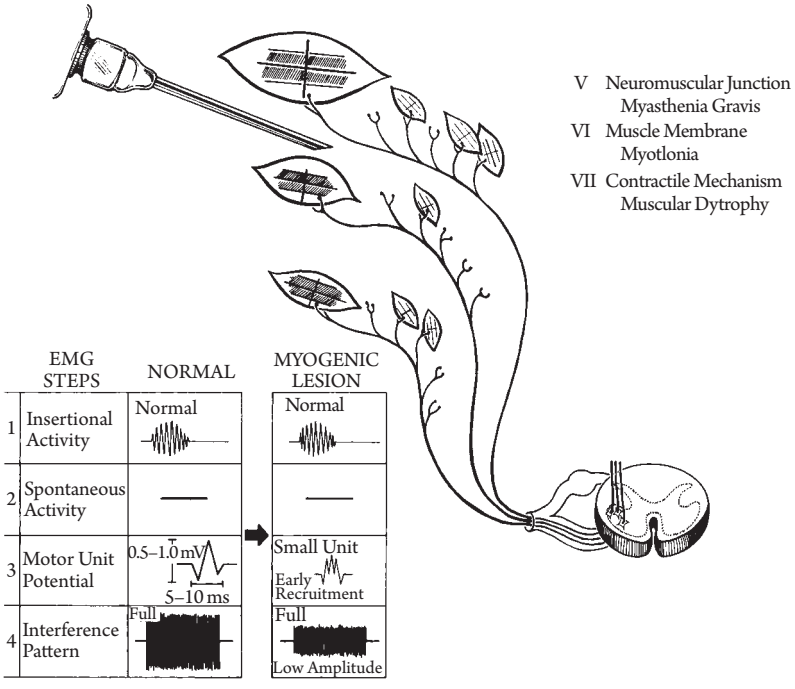

FIGURE 14-3 Typical findings in myogenic lesions. They include (1) normal insertional activity; (2) no spontaneous discharges, with some notable exceptions; (3) brief-duration, small-amplitude, polyphasic motor unit potentials; and (4) early recruitment leading to a low-amplitude, full-interference pattern at a less than maximal effort of contraction. The diagram illustrates a random loss of individual muscle fibers, resulting in a reduced number of fibers per motor unit.

EMG FINDINGS

	LESION / EMG Steps	NORMAL	NEUROGENIC LESION		MYOGENIC LESION		
			Lower Motor	Upper Motor	Myopathy	Myotonia	Myositis
1	Insertional Activity	Normal	Increased	Normal	Normal	Myotonic Discharge	Increased
2	Spontaneous Activity	—	Fibrillation Positive Wave	—	—	—	Fibrillation Positive Wave
3	Motor Unit Potential	0.5–1.0 mV 5–10 ms	Large Unit Limited Recruitment	Normal	Small Unit Early Recruitment	Myotonic Discharge	Small Unit Early Recruitment
4	Interference Pattern	Full	Reduced Fast Firing Rate	Reduced Slow Firing Rate	Full Low Amplitude	Full Low Amplitude	Full Low Amplitude

FIGURE 14-4 Typical findings in lower and upper motoneuron disorders and myogenic lesions, as shown in Figures 14-1 through 14-3. Myotonia shares many features common to myopathy in general in addition to myotonic discharges triggered by insertion of the needle or with voluntary effort to contract the muscle. Myositis shows combined features of myopathy and denervation, including (1) prolonged insertional activity; (2) abundant spontaneous discharges; (3) brief-duration, small-amplitude, polyphasic motor unit potentials; and (4) early recruitment leading to a low-amplitude, full-interference pattern.

Less frequently, a train of negative spikes with or without initial positivity may develop instead of positive sharp waves. These discharges, ranging from 3 to 30 impulses per second in firing frequency, closely resemble the spontaneous discharges recorded at rest from frankly denervated muscles. In fact, abnormal insertional activity commonly appears during the early stages of denervation, 10 days to 2 weeks after nerve injury, as a prelude of spontaneous activity. Denervated or degenerated muscles also show increased insertional potential in association with positive sharp waves appearing spontaneously—not initiated by needle movement (Fig. 14-5). By definition, insertional activity immediately follows the mechanical stimulus by the needle, even if it continues after cessation of needle movement, whereas true spontaneous activities need no triggering mechanisms. Needle movement also enhances spontaneous activity, thus making differentiation between insertional and noninsertional activities somewhat arbitrary.

Insertional positive sharp waves seen in denervated muscles may have a waxing and waning quality characteristic of myotonic discharge. Similarly, an abortive form of myotonic discharge, sometimes seen in patients with myotonia immediately after a prolonged exercise, resembles insertional positive waves of early denervation. Asymptomatic patients with a forme fruste of myotonia congenita (MC) may show insertional positive sharp waves diffusely, including paraspinal muscles.[135,137]

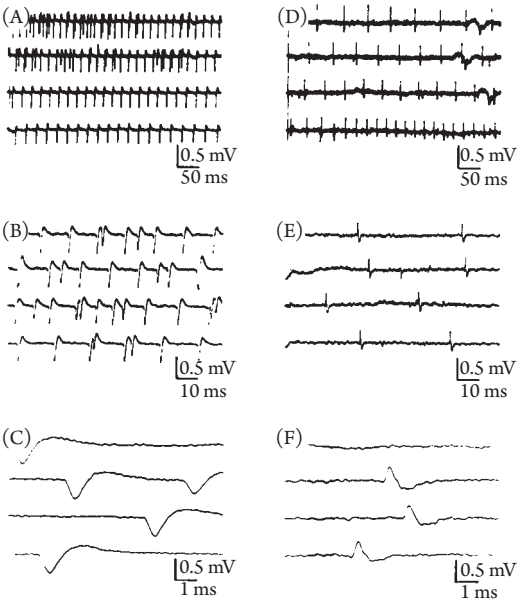

FIGURE 14-5 Spontaneous single muscle fiber discharges from the right paraspinal muscle in a 62-year-old woman with myositis. The tracings show two types of discharges: trains of positive sharp waves (*A*, *B*, *C*) and negative spikes (*D*, *E*, *F*) initiated by insertion of the needle electrode. The lack of initial positivity indicates the recording of the negative spikes near the endplate region, although their rhythmic pattern speaks against the physiologic endplate spikes. Note the slight waxing and waning quality, although not to the extent typically associated with myotonic potential (cf. Fig. 14-7).

3. MYOTONIC DISCHARGE

In a group of disorders characterized by clinical myotonia (Table 14-1), a sustained contraction of the muscle follows voluntary movement or electrical or mechanical stimulation. These include myotonic dystrophy Type I and Type II (DMI

Table 14-1 Disorders with Myotonic Discharges

1) With Clinical Myotonia
- Myotonia Dystrophica (DMI)
- Proximal Myotonic Myopathy (DMII)
- Myotonia Congenita (MC)
- Paramyotonia Congenita (PMC)
- Hyperkalemic Periodic Paralysis (HyperPP)

2) Without Clinical Myotonia
- Myositis
- Acid Maltase Deficiency
- Cytoplasmic Body Myopathy
- Hyperthyroidism
- Hypothyroidism
- Familial Granulovacuolar Lobular Myopathy
- Malignant Hyperpyrexia
- Multicentric Reticulohistiocytosis
- Myopathies induced by:
  - Glycyrrhizin
  - Hypocholesterolemic Agent
  - Diazacholesterol
  - Colchicine

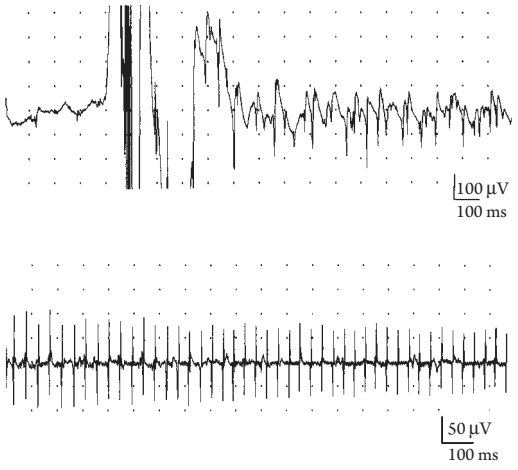

FIGURE 14-6 A 40-year-old woman with hypothyroidism. Electromyography showed increased insertional activities followed by sustained repetitive positive sharp waves, at times generating a transient myotonic discharge.

and DMII), myotonia congenita (MC), paramyotonia congenita (PMC),[133] and hyperkalemic periodic paralysis (HyperPP)[20,42] (see Chapter 28-2). The EMG correlates of clinical myotonia consist of sustained rhythmic discharges of single muscle fibers triggered by insertion of the needle electrode or mild voluntary muscle contraction. As such, myotonic discharges share the identical waveform with fibrillation potentials and positive sharp waves, which, however, fire spontaneously without an apparent trigger and at a much slower pace.

Myotonic discharge varies qualitatively and quantitatively among different disorders. For example, it tends to wax and wane in DMI, but characteristically only wane in DMII.[78] Its severity correlates with muscle weakness and CTG length expansion (see Chapter 28–2).[99] Myotonic discharges may accompany disorders showing no clinical myotonia (Table 14-1), prompting the now abandoned term, *pseudomyotonia*. These include myositis, Type II glycogen storage disease with acid maltase deficiency,[63,87] X-linked myopathy with excessive autophagy, cytoplasmic body myopathy resembling myotonic dystrophy,[88] and conditions associated with chronic denervation. Some metabolic disorders such as myopathies associated with hypothyroidism may also show exaggerated insertional positive waves forming myotonic discharges (Fig. 14-6).

Positive versus Negative Discharge

Myotonic discharges take two forms, depending on the spatial relationship between the recording surface of the needle and the discharging muscle fibers. One type of myotonic discharge occurs as a sustained run of sharp positive waves, each followed by a slow negative component of much longer duration (Fig. 14-7a,b,c). These waveforms, like those of positive sharp waves seen in denervation, represent recurring single-fiber potentials recorded from an injured area of the muscle membrane. A second type of myotonic discharge consists of a sustained run of initially positive triphasic spikes (Fig. 14-7d,e,f). These negative spikes, like fibrillation potentials, represent a single muscle fiber discharge recorded as the impulses approach, arrive at, and depart from the recording tip of the needle (see Chapter 2-4).

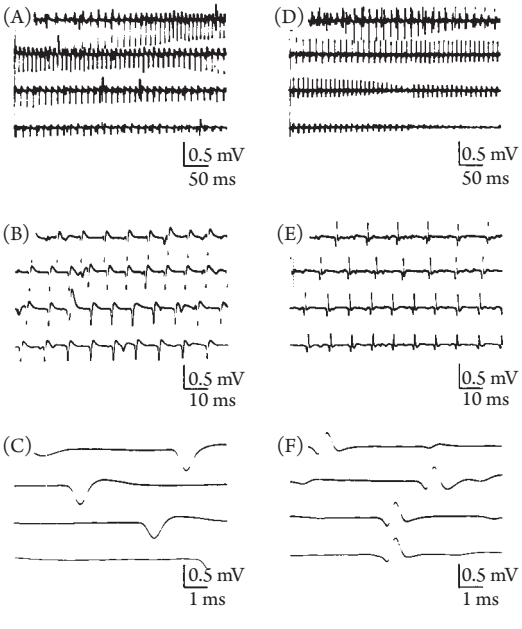

FIGURE 14-7 Myotonic discharges from the right anterior tibialis in a 39-year-old man with myotonic dystrophy. The tracings show two types of discharges: trains of positive sharp waves (*A*, *B*, *C*) and negative spikes with initial positivity (*D*, *E*, *F*). The discharges in (*A*) and (*D*) reveal a waxing and waning quality.

In contrast to the positive sharp waves usually initiated by needle insertion, negative spikes tend to occur at the beginning of slight volitional contraction.

Both positive sharp waves and negative spikes typically wax and wane in amplitude over the range of 10 μV to 1 mV often, though not always, varying inversely with the rate of firing. Their frequency may increase or decrease within the range of 50 to 100 Hz, giving rise to a unique sound over the loudspeaker. Despite common belief, a myotonic discharge does not simulate a dive-bomber, based on my extensive personal experience (with dive-bombers), which, after diving, pull up only once, if at all. Recurrent characteristic of myotonic discharge more closely resembles the sounds of an accelerating and decelerating motorcycle or chain saw. A variant called "slow" myotonic discharges,[7] usually seen after the patient "loosens up" the muscle with exercise, closely mimics abnormally enhanced insertional positive waves and may lead to a mistaken impression of denervation or myositis.

Pathophysiology

The pathophysiology of myotonic discharge (see Chapter 28-2), although not yet completely established in humans, relates to abnormalities of chloride and sodium channels. A decrease in resting chloride conductance results in repetitive electrical activity in isolated frog and mammalian skeletal muscles. Electrophysiologic studies show abnormalities attributable to decreased density of chloride channels in hereditary myotonia of goats. In normal fibers, the presence of chloride conductance stabilizes the membrane potential by shunting the depolarizing current and dampening its effect. Conversely, its absence in effect raises the membrane resistance, *R*, which in turn reduces the amount of current, *I*, necessary to initiate a threshold depolarization, *E*, according to Ohm's law ($E = IR$).

The critical level of depolarization opens the sodium channel with a rapid change in sodium conductance, initiating an action potential, which falls with inactivation of sodium channels. Delayed activation of potassium conductance tends to hyperpolarize the membrane. As potassium conductance slowly returns to its resting value, the cell becomes slightly depolarized, with accumulation of potassium in the transverse tubule system. In an unstable membrane without chloride shunting the current, this slow change may trigger another action potential, and the cycle repeats itself. Thus, the process of depolarization begins as soon as repolarization ends, leading to a series of repetitive action potentials. The explanation of myotonic phenomena based on low chloride conductance seems to apply to human myotonia congenita. Pharmacologic blocking of the acetylcholine receptor or atropine binding site effectively silences fibrillation potentials, but not myotonic discharges.

Patients with PMC and hyperPP typically show a number of mutations in the adult skeletal muscle sodium channel gene, located on chromosome 17q 23-25 (see Chapter 28-2). For reasons not completely understood, patients with the same mutation may have variable clinical findings. Conversely, different mutations may account for the same signs and symptoms. Nonetheless, experts agree that sodium channel mutation results in muscle membrane instability, which in turn causes temperature-sensitive myotonic discharges triggered by muscle activation.[133] Cooling the patient with this disorder depolarizes the muscle membrane slightly, initiating the entry of sodium ions into the muscle fiber. This leads to more sustained depolarization through regenerative activation of abnormal, noninactivating sodium channels.[110] Inactivation of normally functioning sodium channels by further cooling or exercise results in inexcitability of the muscle fiber and paralysis.

4. SPONTANEOUS ACTIVITY

Excitability of Denervated Muscle Fibers

In the first 2 weeks after denervation, the sensitivity of a muscle fiber to acetylcholine (ACh) increases by as much as 100-fold.[128] This phenomenon, known as denervation hypersensitivity, may in part explain spontaneous discharges of denervated muscle fibers in response to small quantities of circulating ACh. The disappearance

of fibrillation potentials in isolated muscle fibers[125] also supports the presence of some circulating substance. In rats, fibrillation potentials cease after application of alpha-bungarotoxin or atropine sulfate.[14] The receptor molecules for these agents therefore must play an essential part in the production of spontaneous activity.

Experimental data marshaled against the ACh hypersensitivity hypothesis include the following: (1) the large amount of circulating ACh reaching the endplate combines with acetylcholinesterase (AChE) concentrated in this region. This results in continuous hydrolysis of ACh to choline and acetate. (2) Denervation hypersensitivity reflects the development of many highly reactive sites along the entire length of the denervated muscle fiber rather than a specific change localized to the endplate region.[130] Spontaneous activity, however, seems to originate only in the endplate zone and not elsewhere along the nonjunctional membrane.[8] Furthermore, the infusion of curare blocks the endplate receptors but fails to abolish spontaneous discharges. (3) Denervation of frog muscle may cause increased sensitivity to ACh but produces no spontaneous activity.[82] These findings suggest that ACh hypersensitivity alone cannot explain the generation of spontaneous activity.

Alternative hypotheses invoke slowly changing membrane potentials of metabolic origin that may periodically reach the critical level and evoke propagated spikes.[125] Other possibilities include denervation-induced changes in the mechanisms that control refractory periods of sodium channels[71] and reduction of extracellular calcium concentration based on suppressing effects of dantrolene sodium on fibrillation potentials.[62]

Fibrillation Potentials

Fibrillation potentials range from 1 to 5 ms in duration and from 20 to 500 μV in amplitude when recorded with a concentric needle electrode (Table 14-2). These potentials, variable in waveforms,[37,90] have initially positive diphasic or triphasic pattern (Fig. 14-8) unless the tip of the needle electrode faces the endplate zone, registering an initial negativity. Physiologic endplate spikes also have an initial negativity, but unlike fibrillation potentials recorded at the endplate, they fire irregularly at a very high rate (see Chapter 13-4). Over the loudspeaker, fibrillation potentials produce a crisp clicking noise reminiscent of the sound caused by wrinkling tissue paper. The discharges increase after warming the muscle or with administration of cholinesterase inhibitors, such as edrophonium (Tensilon) and neostigmine (Prostigmin), and decrease after moderate cooling of the muscle or hypoxia. Thus, warming the muscle under study enhances the chance of detecting this abnormality.

When triggered by spontaneous oscillations in the membrane potential, fibrillation potentials typically fire in a regular pattern at a rate of 1–30 Hz, with an average frequency of 13 Hz.[111] This rate possibly reflects oxygen supply, which presumably determines the scope of aerobic metabolism.[61] The decreased resting membrane potential in the denervated muscle plays a critical role as the cause of the oscillations.[126] A new class of sodium channels that develops after denervation may cause reduced sodium inactivation. Increased sodium conductance would account for progressive lowering of the firing threshold, giving rise to cyclical activities. Although a very irregular firing pattern usually represents discharges from more than one fiber, the same muscle fiber may occasionally fire irregularly in the range of 0.1–25 impulses per second.[19,83] These potentials result from random, discrete, spontaneous depolarization of nearly constant amplitude.[19]

Voluntarily activated single-fiber potentials and fibrillation potentials have the same shape and amplitude distribution when studied with single-fiber electromyography (SFEMG).[118] Close scrutiny of a train reveals no change in shape between the first and the last discharges. These findings indicate that fibrillation potentials originate from single muscle fibers, a view consistent with the observation that they represent the smallest unit recorded by the needle electrode.

Positive Sharp Waves

Positive sharp waves, which also represent single-fiber activation (Table 14-2), have a sawtooth appearance with the initial positivity and a subsequent slow negativity, much lower in amplitude but longer

in duration.[38] They often follow insertion of the needle, which triggers hyperexcitable but not spontaneously firing muscle fibers during the early stage of denervation. This accounts for its earlier appearance than fibrillation potentials (Fig. 14-8). A single muscle fiber discharge originating in close proximity to a crushed membrane may propagate away from the electrode, giving rise to an initially positive waveform.[41] If the tip of the needle damages the membrane, the sustained standing depolarization here precludes the generation of a negative spike at this point. Thus, a propagating action potential that approaches the site of injury also results in a sharp positive spike followed by a low-amplitude negative deflection as predicted by the theory of solid angle approximation (see Chapter 2-4). Therefore, the absence of a negative spike implies recording near the damaged part of the muscle fiber. As discussed earlier (Fig. 14-7), positive sharp waves also form part of myotonic discharges, triggered by insertion of the needle or by mild voluntary contraction. Despite the identical waveform, representing single muscle fiber potentials, myotonic discharges do not appear spontaneously.

Table 14-2 Responsible Sites of Hyperexcitability for Spontaneous Muscle Activities

1) Muscle Fiber	
Insertional Positive Wave	Briefly sustained single muscle fiber discharge triggered by needle movement or muscle contraction
Endplate Noise	Miniature endplate potentials recorded extracellularly at motor point
Endplate Spikes	Single muscle fiber discharges triggered by needle movement at motor point
Myotonic Discharge	Repetitive single muscle fiber discharge triggered by needle movement
Fibrillation Potential	Spontaneous single muscle fiber discharge, negative type
Positive Sharp Wave	Spontaneous single muscle fiber discharge, positive type
Complex Repetitive Discharge	A group of emphatically activated spontaneous single muscle fiber discharges
2) Lower Motoneuron	
Fasciculation Potential	Spontaneous motor unit discharge, involving a single unit, totally or fractionally
Myokymic Discharge	Clusters of repetitive firing of the same motor unit, usually from demyelination
Neuromyotonic Discharge	Continuous high-frequency discharge, involving many motor units
Cramp Discharge	Briefly sustained high-frequency discharge, involving many motor units
Hemifacial Spasm	Intermittent, unilateral contraction of facial muscles, either idiopathic or post Bell's palsy
Hemimasticatory Spasm	Intermittent, unilateral contraction of masseter muscle
3) Upper Motoneuron	
Stiff-man Syndrome	Sustained discharges of motor units in many agonistic and antagonistic muscles
Involuntary Movement	Tremor, chorea, hemiballisms, athetosis, dystonia, myoclonus
Seizure Disorder	Epilepsia partialis continua

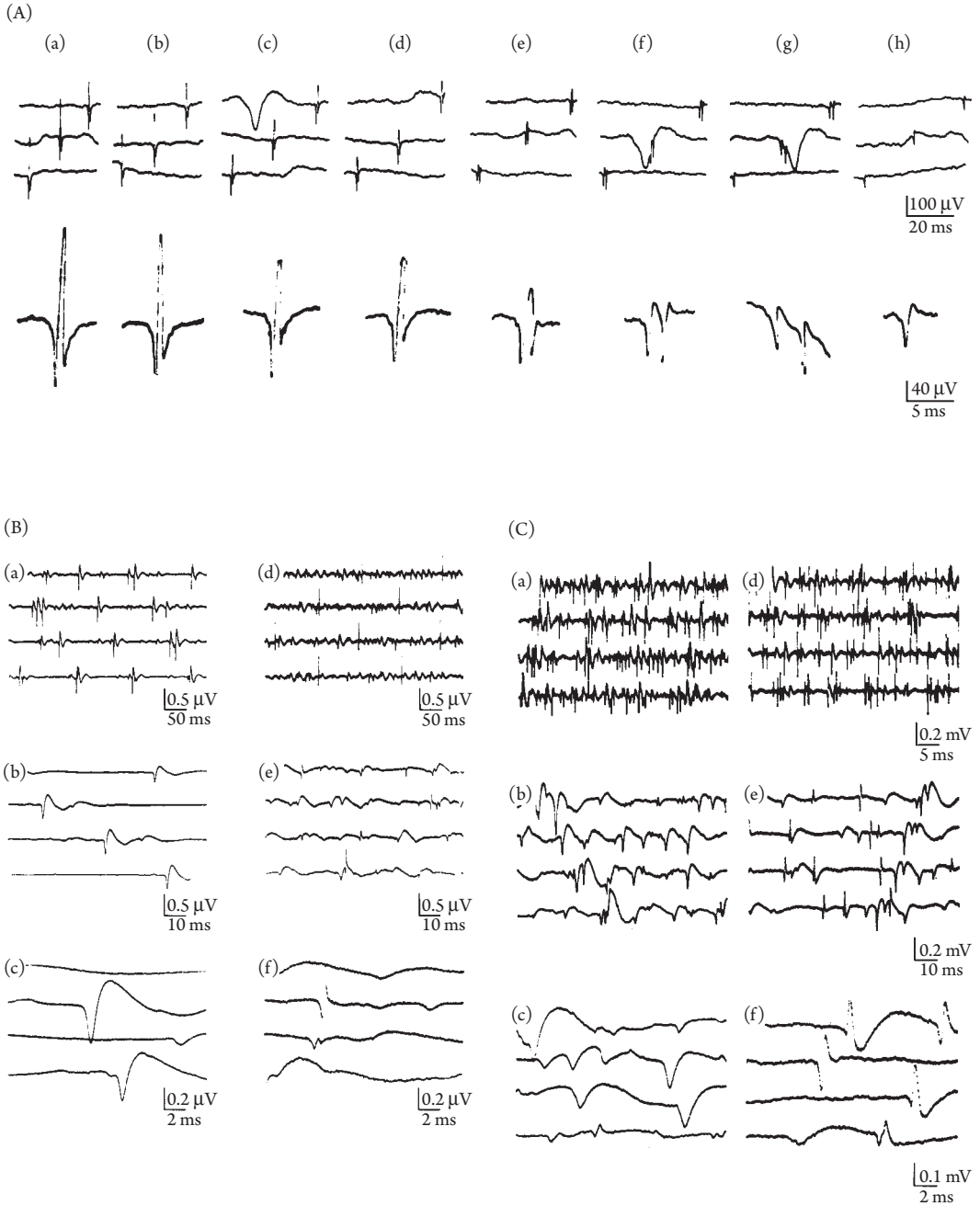

FIGURE 14-8 Spontaneous single muscle fiber discharges recorded from the (*A*) tibialis anterior in a 67-year-old man with acute onset of footdrop, (*B*) tibialis anterior in a 68-year-old woman with amyotrophic lateral sclerosis, (*C*) paraspinal muscle in a 40-year-old man with radiculopathy, (*D*) deltoid in a 9-year-old boy with a 6-week history of dermatomyositis, and (*E*) tibialis anterior in a 7-year-old boy with Duchenne dystrophy. In (*A*), note gradual alteration of the waveform from triphasic spike with major negativity to paired positive potentials and finally to a single positive sharp wave over the time course of some 8 seconds without movement of the needle. This fortuitous recording provides direct evidence that the same single-fiber discharge can be recorded either as fibrillation potentials or as positive sharp waves. Long-duration positive deflections seen in (c), (f), and (g) represent a pulse artifact. The tracings in (*B*), (*C*), (*D*) and (*E*) show two types of spontaneous single muscle fiber discharges: positive sharp waves (a, b, c) and fibrillation potentials (d, e, f).

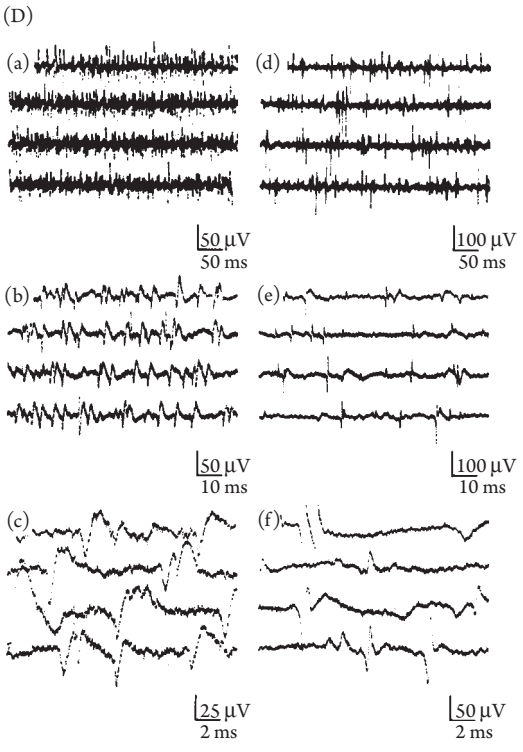

FIGURE 14-8 (*Continued*)

Complex Repetitive Discharges

In the complex repetitive discharge (CRD), a group of denervated muscle fibers fire in near synchrony, ranging from 50 µV to 1 mV in amplitude and up to 50–100 ms in duration (Figs. 14-9 and 14-10A,B). The entire sequence repeats itself at slow or fast rates, usually in the range of 5–100 impulses per second. The polyphasic and complex waveform remains uniform from one group of discharges to another, with periodic shifts to a new pattern. These discharges typically begin suddenly, maintain a constant rate of firing for a short period, and cease as abruptly as they started. Over the loudspeaker, they mimic the sound of a machine gun. The unique repetitive pattern once prompted the use of a now discarded term, *bizarre high-frequency discharges*. Superficial similarities to myotonic sound led to the even less appropriate term, *pseudomyotonia*, in the absence of waxing and waning. The rate of repetition and an identical waveform from one burst to the next make the CRD distinct from myokymic, neuromyotonic, or cramp discharges despite their superficial resemblance (see Chapter 28-5, 28-6, and 28-7).

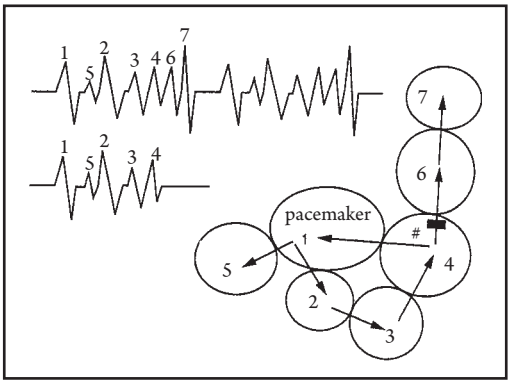

FIGURE 14-9 Schematic illustration of complex repetitive discharges involving seven hyperexcitable single muscle fibers. A pacemaker fiber (1) fires spontaneously, initiating a train of ephaptic activation of the remaining muscle fibers (2 through 7). The fiber (4) reactivates the pacemaker, and the sequence repeats itself, giving rise to an identical waveform. The pattern may change abruptly if emphasis fails between the adjacent muscle fibers (for example 4 and 6 as shown in this diagram). (Adopted from Kimura and Kohara.[69])

In single-fiber recordings, a CRD often consists of several distinct unit potentials separated

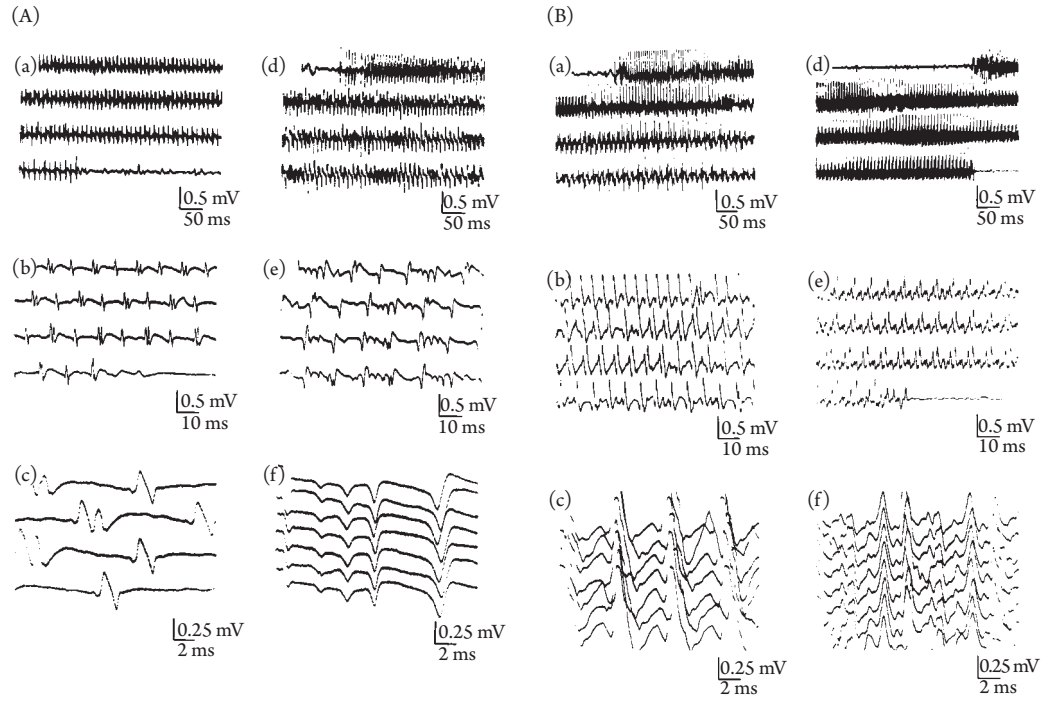

FIGURE 14-10 (*A*) Complex repetitive discharges of the left quadriceps in a 58-year-old man with herniated lumbar disc. The tracings show two types of discharges: trains of single- or double-peaked negative spikes (a, b, c) and complex positive sharp waves (d, e, f). In (f), each sweep, triggered by a recurring single fiber potential, shows remarkable reproducibility of the waveform within a given train. (*B*) Complex repetitive discharges with trains of negative spikes from the same muscle shown in (*A*). Note characteristically abrupt onset and cessation (a, d, e). In (c) and (f), each sweep, triggered by a recurring single fiber potential, shows a detailed waveform of the repetitive patterns, which superimpose precisely.

by intervals ranging from less than 0.5 ms to more than 200 ms. The individual spikes within the complex fire in the same order, as the discharge recurs repetitively (Fig. 14-9). One fiber in the complex serves as a pacemaker, initiating the burst, and driving one or several other fibers ephatically.[130] In successive cycles, one of the remaining fibers activated late in the previous cycle re-excites the principal pacemaker to repeat the whole cycle until the pacemaker fibers eventually fail. The electrical field associated with each of these repetitive discharges must effectively induce ephaptic activation of neighboring muscle fibers. Thus, a CRD often gives rise to high-amplitude spikes, compared with fibrillation potentials.

Disorders associated with a CRD (Table 14-3) include muscular dystrophy and myositis in addition to a wide variety of denervating conditions such as motoneuron disease, radiculopathy, chronic polyneuropathy, myxedema, and the Schwarz-Jampel syndrome.[109] The presence of a CRD may[3,31] or may not[47] suggest the chronicity of the underlying process. In a large series,[44] an overall analysis of the prevalence revealed its highest incidence in Duchene muscular dystrophy (DMD), spinal muscular atrophy (SMA), and Charcot-Marie Tooth disease (CMT). Women with urinary retention may have profuse activity of this type in the striated muscle of the urethral sphincter.[50] Apparently healthy subjects may occasionally show a CRD as an unexpected finding. These foci of a clinically silent irritative process tend to involve deeper muscles in general and the iliopsoas in particular.

Fasciculation Potentials

Clinicians once referred to visible twitching of muscle bundles as *fibrillation*, a term now reserved for the EMG description of spontaneously firing

Table 14-3 Disorders Associated with Common Types of Spontaneous Discharges

1) Fibrillation Potentials and Positive Sharp Waves
- Neuropathic Condition
- Muscular Dystrophy
- Myositis

2) Complex Repetitive Discharges
- Motoneuron Disease
- Radiculopathy
- Chronic Polyneuropathy
- Myositis
- Muscular Dystrophy
- Myxedema
- Schwarz-Jampel Syndrome

3) Fasciculation Potentials
- Motoneuron Disease
- Radiculopathy
- Entrapment Neuropathy
- Muscular Pain–Fasciculation Syndrome
- Healthy Subjects

4) Myokymic Discharges
- Guillain-Barré Syndrome
- Radiation Plexopathy
- Spinal Stenosis
- Nerve Root Compression
- Bell's Palsy
- Multiple Sclerosis
- Syringobulbia

5) Neuromyotonic Discharges
- Neuromyotonia

single muscle fibers. To avoid confusion, the term *fasciculation* refers to spontaneous contraction of motor units seen by clinical inspection, and fasciculation potentials, its electrical counterpart (Fig. 14-11). An isolated motor unit discharge deep in the muscle may not necessarily induce visible twitches. In such instances, EMG allows detection of this spontaneous activity, which would otherwise remain unrecognized.

Unlike a normal MUP, fasciculation potentials may undergo slight changes in amplitude and waveform from time to time. Mild voluntary contraction of agonistic or antagonistic muscles fails to alter the firing rate or discharge pattern. The generator source remains unknown, although the existing evidence favors a very distal site of origin at or near the motor terminals.[68,75,76] The neural discharge may, however, originate in the spinal cord or anywhere along the length of the peripheral nerve. In one study using a collision method and F-wave analysis, nearly all fasciculations had an axonal origin.[105] These studies, however, do not necessarily rule out postsynaptic abnormality at the neuromuscular junction. In fact, this type of activity may appear transiently after administration of an anticholinesterase medication or a depolarizing neuromuscular blocker[102] and may sometimes persist despite distal nerve block.

Fasciculation potentials (Table 14-3), although typically associated with diseases of anterior horn cells, also occur in radiculopathy, entrapment neuropathy, and the muscular pain fasciculation syndrome (see Chapter 28-7). In patients with cervical spondylotic myelopathy, the same type of potentials may appear in the lower limbs, presumably secondary to loss of inhibition, vascular insufficiency, cord traction, or denervation. Although these hypotheses lack anatomic or physiologic evidence, spontaneous discharges do abate after cervical decompression.[66] The same spontaneous potentials also accompany some metabolic derangements such as tetany, thyrotoxicosis, and overdoses of anticholinesterase medication.[29] Simultaneous fasciculation potentials from multiple units, although frequently seen in amyotrophic lateral sclerosis (ALS) and progressive SMA, do not necessarily imply an ominous prognosis, as they also accompany other degenerative diseases such as poliomyelitis and syringomyelia. In double fasciculations, commonly seen in ALS, the second discharge may follow the first with a delay of 4-10 ms and 30–50 ms. These two types of paired discharge may represent a short interval reexcitation during supernormal period and a long interval F wave induced by antidromic invasion, respectively.[84] Synchronous discharges seen in muscles supplied by different nerves or in homologous muscles on opposite sides possibly suggest an intraspinal mechanism or a reflex origin via spindle afferent triggered by the arterial pulse.[107]

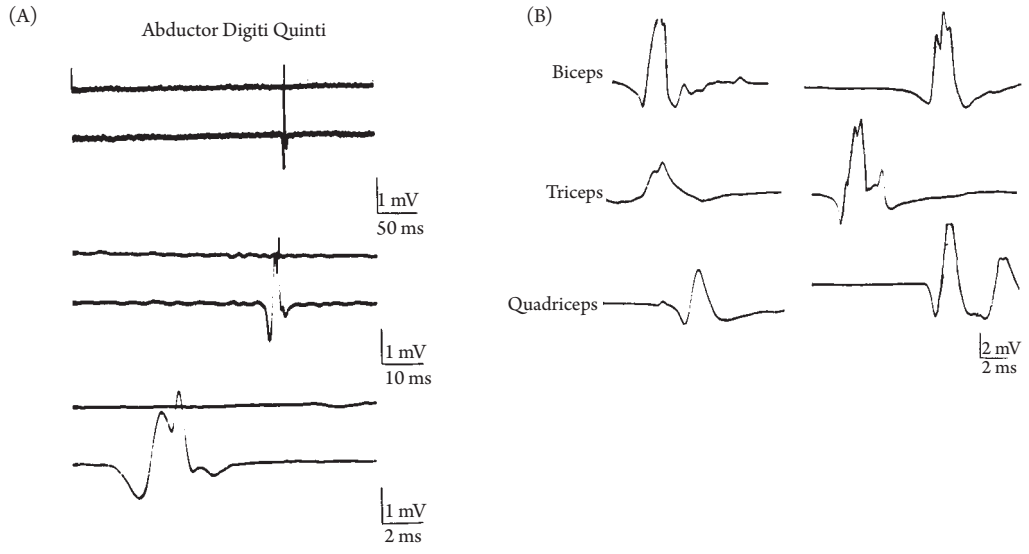

FIGURE 14-11 (*A*) A 59-year-old man with pain in the posterior calf following a fall from a ladder, landing on his feet. Electromyography showed fibrillation potentials and sharp positive waves in the abductor hallucis and only fasciculation potentials in the abductor digiti quinti. (From Kimura,[69] with permission.) (*B*) A 58-year-old man with muscular pain fasciculation syndrome of 1-year duration. He came to the hospital for evaluation of "muscle twitching," which began in the right arm but soon became generalized. Electromyography showed fasciculation potentials in most muscles tested, with no evidence of other spontaneous discharges such as fibrillation potentials or sharp positive waves. (Modified from Kimura.[69])

Fasciculations occur commonly in otherwise normal muscle[85] in many healthy subjects (although mostly recognized by medical students, anxious about ALS). Data obtained from a questionnaire survey of a group of 539 healthy medical personnel indicate that 70% have experienced some type of muscle twitch.[103] Long-term follow-up of 121 patients with benign fasciculations revealed no incidence of MND.[10] Because of the serious implications, a number of investigators have sought to differentiate this form of fasciculation potentials from those associated with MND, but in vain. No single method reliably distinguishes one type from the other on the basis of waveform characteristics, such as amplitude, duration, and number of phases. The frequency of discharge, however, may possibly separate the two categories: irregular firing at an average interval of 3.5 seconds in patients with MND compared with 0.8 seconds in asymptomatic individuals.[34] The discharges in ALS characteristically arise proximally early in the disease and distally in the later stages.[34] In my personal experience, waveform stability favors physiologic pattern as compared to unstable discharges, which tend to characterize ongoing pathology.

In summary, unlike fibrillation potentials and positive sharp waves, fasciculation potentials by themselves cannot provide absolute proof of abnormality. Excluding those seen in healthy subjects, fasciculation potentials suggest disease of the lower motoneuron with the origin at any level from the anterior horn cells to axon terminals. Electrophysiologic studies fail to offer reliable means of distinguishing between "benign" forms seen in otherwise normal muscle and "malignant" forms associated with MND except for the company they keep. Fasciculation potentials seen in conjunction with fibrillation potentials and positive sharp waves in the same or different muscles indicate, by association, abnormality of motor axons. Based on this notion, Awaji criteria for ALS advocate, in an appropriate clinical context, to equate fasciculation potentials with spontaneous single muscle fiber discharges when seen in a muscle showing the evidence of chronic denervation (see Chapter 22-2). To characterize a recorded discharge, the description should consist of its

amplitude, duration, firing pattern, frequency of occurrence, and, perhaps most important, waveform stability.

Myokymic and Neuromyotonic Discharges

In contrast to isolated discharges of one motor unit, more complex bursts of repetitive discharges cause vermicular movements of the skin, called myokymia (see Chapter 28-5). Repetitive firing of the same motor units usually occurs in bursts at regular intervals of 0.1–10 seconds, with 2 to 10 spikes discharging at 30–40 impulses per second in each burst (Fig. 14-12). These discharges may accompany neuromyotonia (see Chapter 28-6) characterized by repetitive firing usually exceeding 200 Hz.[25] Despite the common association, difference in discharge rate and duration readily distinguish the two.[55] Myokymic discharges commonly, though not specifically, involve facial muscles in patients with brainstem glioma or multiple sclerosis (MS). This type of discharge (Table 14-3) also favors certain chronic neuropathic processes, like the Guillain-Barré syndrome (GBS)[81] and radiation plexopathies.[1,2,32] The same discharges also appear in other conditions such as dermatomyositis in the presence of antibodies to voltage-gated potassium channels [94] and various axonal disorders, including ALS.[67,134] Hyperventilation induces hypocalcemia, which in turn amplifies axonal excitability and myokymic

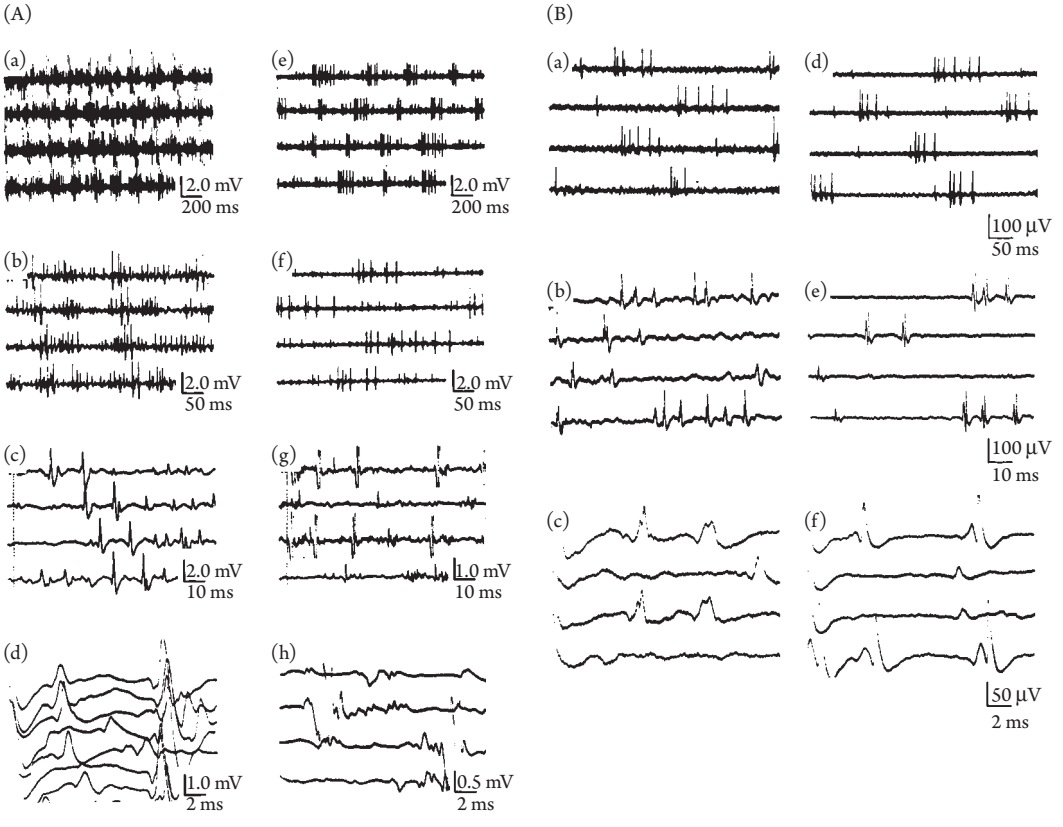

FIGURE 14-12 (*A*) Myokymic discharges in a 21-year-old woman with multiple sclerosis. The patient had visible undulating movement of the facial muscles on the right associated with characteristic bursts of spontaneous activity recorded from the orbicularis oris (a, b, c, d) and orbicularis oculi (e, f, g, h). In (d), each sweep, triggered by a recurring spontaneous potential, shows a repetitive but not exactly time-locked pattern of the waveform. (*B*) Myokymic discharges in a 57-year-old man with a 2-week history of the Guillain-Barré syndrome and a nearly complete peripheral facial palsy. Despite the absence of visible undulating movement, rhythmically recurring spontaneous discharges appeared in the upper (a, b, c) and lower (d, e, f) portions of the left orbicularis oris. In (c) and (f), each sweep triggered by a recurring spontaneous potential shows the repetitive pattern.

bursts, generated ectopically in demyelinated motor fibers.[13]

The descriptive term *neuromyotonia* or *neurotonia* serves best to denote the clinical conduction associated with sustained motor unit discharge of peripheral origin (Table 14-3).[52] Other names used include Isaacs' syndrome, quantal squander, generalized myokymia, pseudomyotonia, and normocalcemic tetany (see Chapter 28-6).[60,92] These syndromes probably constitute different diseases that vary in their clinical and electrophysiologic presentations despite the shared feature of continuous involuntary motor activity. The sites of generator responsible for different discharges vary from proximal segments of the nerve to the intramuscular nerve terminals.[5,106,127] Excess motor unit activity remains during sleep and after general or spinal anesthesia. Nerve block will effectively eliminate the discharges if they originate proximal to the injection site. Neuromuscular block totally abolishes the abnormal activity, confirming its neural origin.

Clinical examination shows undulating movements of the overlying skin and a delay of relaxation after muscle contraction. Needle studies demonstrate motor unit discharges with frequencies up to 300 Hz making a "pinging" sound. The firing MUP declines in amplitude slowly or rapidly as increasing numbers of muscle fibers fail to follow the high rate of repetitive pattern. This sometimes gives rise to sounds resembling myotonic discharge, thus the name *neuromyotonia*. Ischemia or electrical nerve stimulation, but usually not voluntary contraction, provokes the high-frequency discharge. Patients respond well to treatment with phenytoin or carbamazepine, which effectively reduces involuntary movements.

Continuous Muscle Fiber Activity

Continuous muscle fiber activity refers to diffuse, sustained spontaneous motor unit activity seen in a heterogeneous group.[43] Stiff-person syndrome represents a rare but well-recognized entity characterized by sustained involuntary discharges of central origin (see Chapter 28-11). A needle recording reveals a normal MUP that produces an interference pattern involving the agonists and antagonists simultaneously. These discharges abate with peripheral nerve or neuromuscular block, after spinal or generalized anesthesia, or during sleep. The administration of diazepam, but not phenytoin or carbamazepine, abolishes or attenuates the activity.

Cramps

Cramp constitutes the brief involuntary contraction of a muscle, either as a normal phenomenon or as a sign of abnormality in pathologic conditions (see Chapter 28-7). The responsible impulses originate in the peripheral nerve or anterior horn cells, but the exact underlying mechanism of cramping remains unknown. Some studies suggest it may result from mechanical excitation of motor nerve terminals during muscle shortening.[75,76,93] Peripheral nerve block often abolishes the activity, but spinal or general anesthesia has no effects. After severe cramps, pain may persist for days. During cramp episodes, needle recording consists of repetitive discharges of normal MUPs at a high frequency in the range of 200–300 Hz. Beginning with single potentials or doublets, the activity gradually spreads to involve other areas of a muscle. Several different active sites may evolve simultaneously or sequentially. The discharges wax and wane for several minutes, then abate spontaneously. Between the episodes of cramps, voluntary contraction recruits motor units normally, fairly commonly showing doublets and triplets.

Types of Spontaneous Discharges

Basic types of spontaneous activity (Table 14-2) comprise (1) those generated from denervated muscle fibers, including fibrillation potentials, positive sharp waves, and CRD, and (2) those originating from hyperexcitable motor axons, including fasciculation potentials, and myokymic and neuromyotonic discharges. Patients with the stiff-person syndrome and movement disorder also suffer from involuntary muscle contraction, although the responsible discharges originate in the central nervous system. Isolated visible muscle twitches over a localized area may accompany fasciculation potentials and CRD,

but not fibrillation potentials or positive sharp waves. Myokymic discharges seen in cramp syndromes cause sustained segmental contraction, or myokymia (see Chapter 28-5), whereas more generalized muscle spasms characterize the syndrome of neuromyotonia (see Chapter 28-6) and stiff-person syndrome (see Chapter 28-11).

Both fibrillation potentials and positive sharp waves represent spontaneous single muscle fiber action potentialsb.[40,73,90] In contrast, the CRD results from many muscle fibers rapidly firing in sequence, driven ephatically at a point of lateral contact.[122] A spontaneous discharge from a single muscle fiber, serving as a pacemaker, regulates the subsequent pattern by two different, usually independent, mechanisms: rate of rhythmic depolarization of the pacemaker and circus movements of currents among different muscle fibers.[64]

Fasciculation potentials result from isolated spontaneous discharges of a motor axon, whereas myokymic discharges represent repetitive firing of a motor unit, thus the name *grouped fasciculation*. Neuromyotonic discharges, so called because of its superficial resemblance to myotonic discharges, imply sustained spontaneous motor unit discharges with its origin in motor axons. In the syndrome of neuromyotonia (see Chapter 28-6), myokymic discharges also abound, giving some investigators a rationale to use the two terms synonymously, but their characteristic pattern of firing seems to indicate that they constitute related but two separate entities.

A numeric grading system serves to semiquantitate each of these spontaneous activities: +1, rare spontaneous potentials recordable at one or two sites only after some search, including insertional positive sharp waves, or a sustained run of positive discharges induced by moving the needle electrode; +2, occasional spontaneous potentials easily registered at two or more sites; +3, frequent spontaneous potentials recordable regardless of the position of the needle electrode; and +4, abundant spontaneous potentials nearly filling the screen of the oscilloscope.

Clinical Interpretation

Spontaneous single muscle fiber activity, if reproducible at two or more sites in the muscle, serves as an unequivocal sign of abnormality, which usually, though not always, suggests lower motoneuron disorders. Because of the latent period of 2–3 weeks, however, its absence does not rule out denervation during the first 2 weeks of nerve injury. The distribution of spontaneous potentials can aid in localizing lesions of the spinal cord, root, plexus, and peripheral nerve. Fibrillation potentials show progressive decline in amplitude and eventually disappear as muscle atrophy develops after nerve injury. In one study,[72] the maximum peak-to-peak amplitude measured in 69 subjects declined from 612 μV during the first two months after injury to 512 μV during the third and fourth months, 320 μV during the fifth and sixth months, and less than 100 μV after the first year. Spontaneous discharges also abate if reinnervation occurs in the denervated muscle.[58]

Fibrillation potentials and positive sharp waves develop not only in denervated muscles but also in a variety of myogenic conditions (Table 14-3) (see Chapter 27) such as muscular dystrophy and myositis and, less consistently, diseases of the neuromuscular junction. These include facioscapulohumeral (FSH) dystrophy, limb girdle (LG) dystrophy, oculopharyngeal dystrophy, myotubular or centronuclear myopathy, and trichinosis. Fibrillation potentials found in 25% of patients with progressive muscular dystrophy[22] result at least in part from denervation secondary to muscle necrosis.[35] Spontaneous discharges seen in myositis imply increased membrane irritability, inflammation of intramuscular nerve fibers, or focal degeneration separating a part of the muscle fiber from the endplate region. In support of postulated myogenic denervation, SFEMG and histochemical techniques reveal evidence of reinnervation in the terminal innervation pattern in myositis.[59]

Spontaneous discharges also occur, though not consistently, in otherwise uninvolved paretic limbs between 6 weeks and 3 months after the onset of acute upper motoneuron lesions.[65,79] In an experiment with cats,[23] fibrillation potentials seen below the level of spinal cord injury improved with neurotrophins and exercise. One study[70] reported spontaneous activity in 68% of the arms and 70% of the legs on the affected side in 50 hemiplegic patients without apparent plexus injury. In another study,[24] the amount of spontaneous activity seen in the lower limb muscles after cervical spinal

cord injury showed a positive correlation with the length of the axon and a negative correlation to the degree of spasticity. Some, however, argue that the positive sharp waves and fibrillation potentials seen in hemiplegic patients reflect secondary disease of the lower motoneurons.[26] As a rule, no spontaneous activity develops in disuse atrophy.

Spontaneous discharges can occur in the absence of clinical signs or symptoms, presumably reflecting a subclinical nerve injury. For example, 9 of 62 and 8 of 66 asymptomatic subjects had spontaneous discharges in cervical and lumbosacral paraspinal muscles.[28] Similarly, 7 of 21 asymptomatic subjects showed abnormalities in the extensor digitorum brevis or abductor hallucis muscles.[86] In another series of healthy subjects,[11] the abductor hallucis showed fibrillation potentials in 10% of those 60 years or younger and 30% of the remainder. These compared to 0% and 9% of incidence, respectively, found in the peroneus tertius, which, therefore, may be better suited for the evaluation of length-dependent neuropathy.[12] In our laboratory, we examine 2nd dorsal interosseus pedis with needle insertion in the web between 1st and 2nd metatarsal heads, which most patients tolerate well. Similarly, 4th dorsal interosseus pedis serves as a useful muscle for this purpose.[114] In either case, an isolated abnormality of intrinsic foot muscle provides no clear evidence of pathology, unless corroborated by other findings.

5. MOTOR UNIT POTENTIALS

The measures to define an MUP comprise amplitude, rise time, duration, phases, stability, and territory. A wide range of neuromuscular disorders alter the waveform in different but characteristic combinations.[119,120] Hence, such abnormalities help distinguish primary muscle diseases from disorders of neuromuscular junction and lower motoneurons. A decrease in spike duration and amplitude characterizes an MUP in myopathies associated with random loss of individual fibers. In contrast, larger than normal potentials appear in neuropathies or anterior horn cell diseases, where a loss of axons results in sprouting from surviving fibers. Some studies report MUP changes after stroke, suggesting functional loss reminiscent of axonal or neuronal lesions and collateral reinnervation.[56,79]

Types of Abnormalities

Taken together with abnormalities of insertional and spontaneous activities, changes in the MUP size and recruitment pattern play an essential role in the classification of weakness in diseases of the nerve and muscle.[45] In addition, their serial assessment helps monitor the disease process based on the established sequential physiologic changes, which correlate with histologic alteration of the motor unit.[117] The following discussion deals with the contrasting MUP features seen in myopathies and lower motoneuron disorders. Each type of change occurs as a common finding in a number of disease categories, as listed here and described in greater detail later from clinical points of view for individual entities (see Chapters 22 through 27). Thus, such abnormalities per se often fail to establish a specific diagnosis.

The recorded amplitude varies greatly with the position of the needle electrode relative to the discharging unit. Selecting an MUP with a short rise time of 500 μs or less guarantees its proximity to the recording surface. The number of single muscle fibers within the approximately 500 μm recording radius from the tip of the needle determines the size of the negative spike. The number of muscle fibers lying close to each other near the recording surface gives rise to a higher amplitude. Hence, in general, the amplitude aids in determining the muscle fiber density, not the motor unit territory. Distant units not contributing to the amplitude of the negative spike add to the motor unit duration, increasing the time of the initial and terminal positivity. Thus, the MUP duration serves as a measure of a larger part of the muscle fiber population lying within a 2.5 mm radius but still not the entire motor unit territory, which measures 1–2 cm. Meaningful assessment calls for comparison of the measured value with the normal range established in the same muscle for the same age group by the same technique.[16,39]

A diphasic or triphasic MUP abounds in normal muscles, with only 5% to 15% having four or more phases. The number of polyphasic units

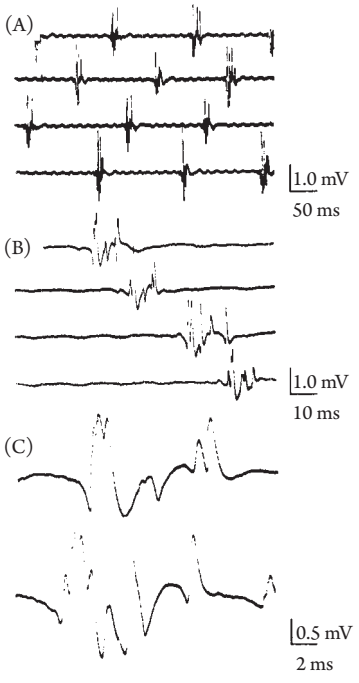

FIGURE 14-13 Polyphasic motor unit potentials from the anterior tibialis in a 52-year-old man with amyotrophic lateral sclerosis. Temporal variability of repetitive discharges in waveform suggests intermittent blocking of some axon terminals.

increases in myopathy, neuropathy, and motoneuron disease (Fig. 14-13). Polyphasia indicates temporal dispersion of muscle fiber potentials within a motor unit. Excessive temporal dispersion, in turn, results from differences in conduction time along the terminal branch of the nerve and over the muscle fiber membrane. Extra components clearly separated from the main unit constitute a satellite potential.[30,48,129] Its presence suggests neuropathy or myopathy, both showing a five times higher incidence [49] than normal muscles, which also occasionally show such outliers.[74] During neurapraxia or an acute stage of axonotmesis, an MUP, if recorded at all, shows normal waveforms, indicating the integrity of the surviving axons (Fig. 14-14).

Motor units normally discharge semirhythmically with successive potentials showing nearly identical configuration. Fatigue causes irregularity and reduction in the firing rate, without altering its waveform. In patients with defective NMT, the amplitude of a repetitively firing unit may fluctuate or diminish steadily. This finding suggests intermittent blocking of individual muscle fibers within the unit as recurring discharges deplete the store of immediately available ACh. Excessive jitters of the constituent single muscle fiber potentials also increase the waveform variability of an MUP.[97] Waveform variability of a repetitively firing MUP, termed *jiggle*, serves to document deficient NMT.[121] This method, like SFEMG, plays an important role, especially in muscles not accessible by conventional nerve-stimulation techniques (see Chapter 16-3). Such instability may imply a large group of disorders affecting the neuromuscular junction. These include myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), botulism, ALS, poliomyelitis and syringomyelia, as well as the early stages of reinnervation. In MG, a characteristic decline in amplitude of successive discharges typically recovers during continued contraction.

In another pattern, called doublets or triplets, a motor unit fires twice or three times at very short intervals. In doublets, or double discharges, two action potentials maintain the same relationship to one another at intervals of 2–20 ms. The term *paired discharges* describes a set of spikes with longer intervals, ranging from 20 to 80 ms. In triplets, the middle spike tends to discharge closer to the first than to the third, although both intervals range from 2 to 20 ms. The physiologic origin and clinical implication of multiple discharges remain unclear. Doublets may occur at the beginning and end of voluntary contraction in normal muscles.[96] More commonly, they accompany cramps, latent tetany, hyperventilation, and other metabolic states associated with hyperexcitability of the motoneuron pool. The disease entities associated with this type of hyperexcitability include poliomyelitis,[132] MND,[100] GBS,[104] radiculopathy, and myotonic dystrophy.[95]

A fraction of an MUP may fire repetitively, giving rise to a series of recurring late potentials. These generally comprise sustained or intermittently blocking high-frequency discharges of short-duration, low-amplitude potentials. A study using double stimulation technique revealed an ephaptic re-excitation of the axonal branch by a sprout rather than an ectopic focus as their

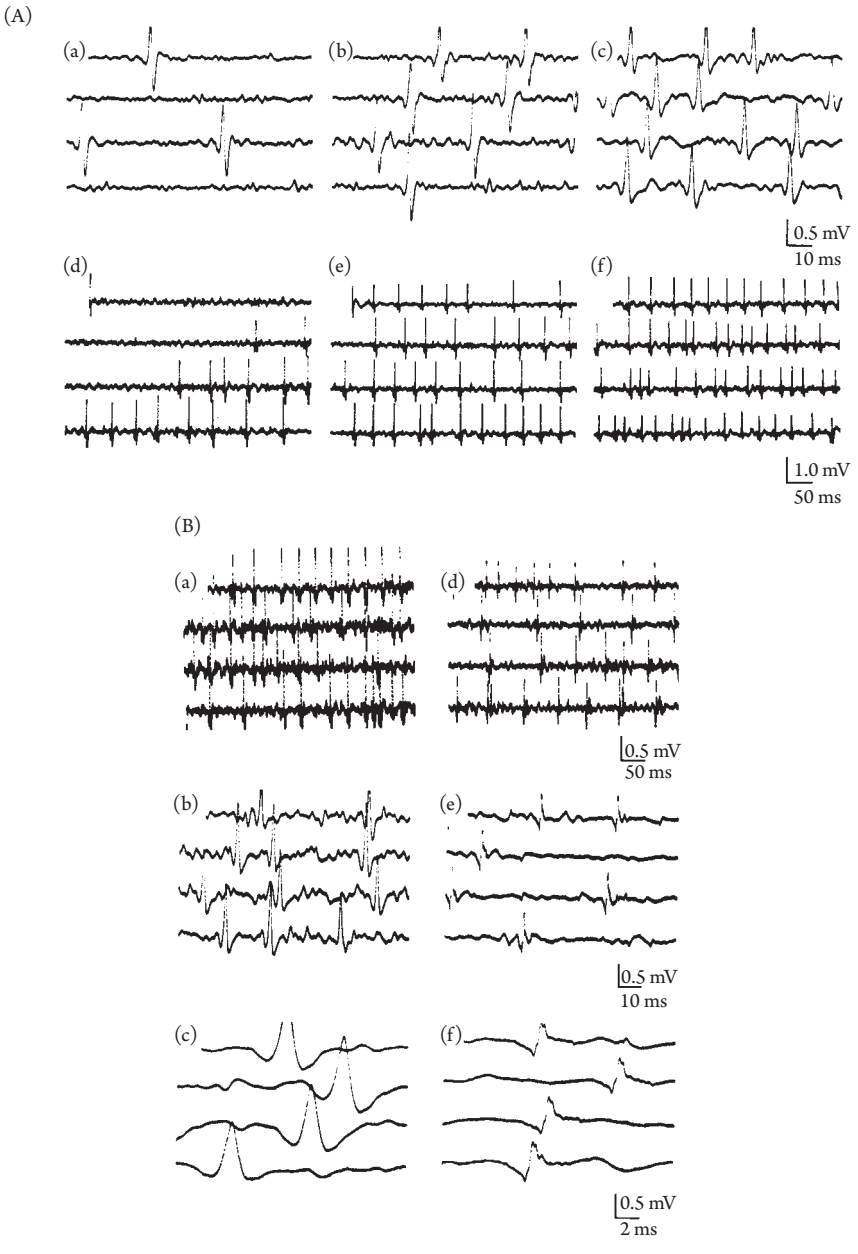

FIGURE 14-14 (*A*) Motor unit potentials from the extensor digitorum communis in a 20-year-old man with partial radial nerve palsy. Minimal (a, d), moderate (b, e), and maximal voluntary contraction (c, f) recruited only a single motor unit, which discharged at progressively higher rates. (*B*) Motor unit potentials from the extensor carpi ulnaris (a, b, c) and extensor carpi radialis longus (d, e, f) in the same subject. Maximal voluntary contraction recruited only a single motor unit firing at a high discharge rate.

origin.[115] The generation of ephaptic discharges suggests a hyperexcitable axon sprout typical of a heterogeneous group of chronic neurogenic disorders, which include neuromyotonia,[6] entrapment syndrome,[124] and the syndrome of familial ataxia and myokymia.[15]

Lower Motoneuron versus Myopathic Disorders

Increased amplitude and duration (Fig. 14-15) generally suggest disorders of the lower motoneuron, such as MND, myelitis, and syringo-

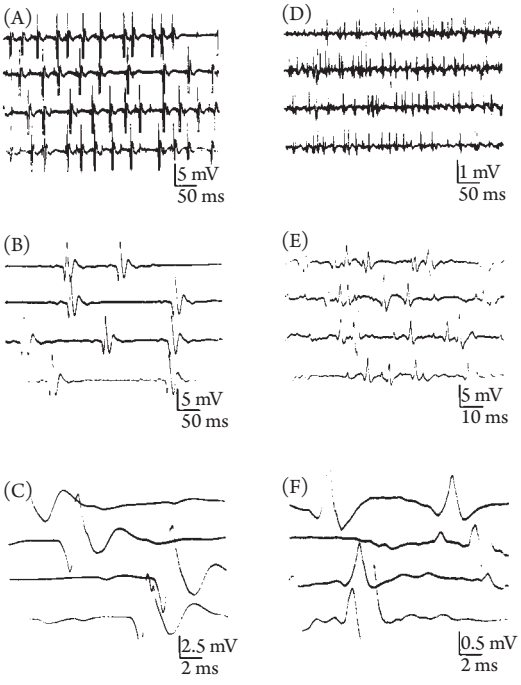

FIGURE 14-15 Large-amplitude, long-duration motor unit potentials from the first dorsal interosseus (*A, B, C*) compared with relatively normal unit from orbicularis oculi (*D, E, F*) in a patient with polyneuropathy. Note a discrete single unit interference pattern during maximal voluntary contraction (*A*).

Table 14-4 Types of Motor Unit Potentials

Brief Duration, Small Amplitude, Early Recruitment
Muscular Dystrophy
Congenital Myopathy
Metabolic Myopathy
Endocrine Myopathy
Myositis
Myasthenia Gravis
Myasthenic Syndrome
Long Duration, Large Amplitude, Late Recruitment
Motoneuron Disease
Radiculopathies
Plexopathies
Polyneuropathies
Mononeuropathies

myelia, or diseases of the peripheral nerve, such as chronic neuropathy and reinnervation after nerve injury (Table 14-4).[116] In these disorders, the increased MUP size indicates anatomic reorganization of denervated muscle fibers by means of reinnervation. Sprouting axon terminals usually remain within their own motor unit territory, failing to reach the denervated muscle fibers outside this boundary. Thus, with incorporation of denervated fibers, the consequences of reinnervation relate primarily to an increased number of muscle fibers, rather than an enlarged territory of the surviving axon (Fig. 14-1). Increased amplitude indicates a greater muscle fiber density, whereas an increased duration probably results from abnormal variability in length and conduction time of regenerating axon terminals, as might be predicted by computer simulation.[77,119,120,139] Alternatively, two or more motor units may discharge simultaneously with abnormal synchronization at the cord level or with ephaptic activation at the root level[27] or near the terminal axons.[108] Even then, a monopolar or concentric needle, inherently restricted by its small recording radius, fails to identify the enlarged territory covered by simultaneously firing multiple units. A macro study with much larger recoding radius serves better for delineating the size of discharging units.

Studies on the time course of reinnervations have revealed characteristic MUP change following traumatic nerve injury. After complete nerve transaction, very small nascent units appear first, signaling the beginning of reinnervation. These motor units typically show increased polyphasicity and temporal instability, with intermittent segmental conduction block of regenerating motor axons. The same does not apply after a partial nerve lesion, when surviving motor axons give rise to extensive collaterals for reinnervation of the denervated muscle fibers. A larger MUP often has late components, which, linked to the main unit, will substantially increase the total duration. These long-latency components, easily overlooked in free-running modes, become apparent if recorded with the use of an internal trigger. In this arrangement, a recurring MUP itself initiates the sweep, but a delay line allows display of the potential in its entirety (see Chapter 3-4).

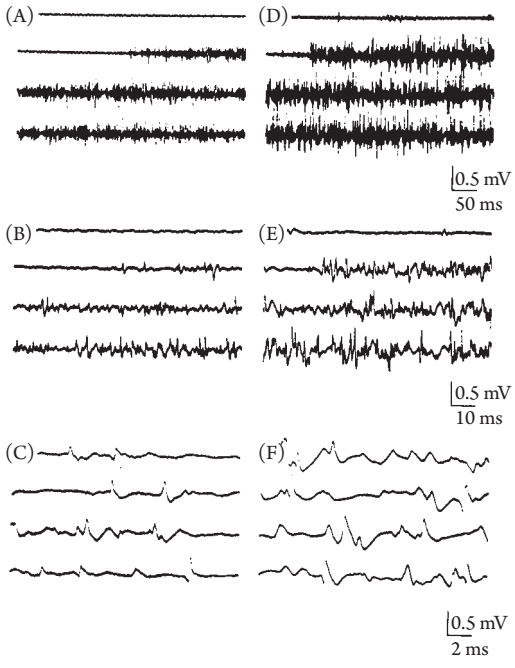

FIGURE 14-16 Low-amplitude, short-duration motor unit potentials from the biceps (*A, B, C*) and tibialis anterior (*D, E, F*) in a 7-year-old boy with Duchenne dystrophy (cf. Fig. 14-8e). Minimal voluntary contraction recruited an excessive number of motor units in both muscles.

In general, reduction in MUP amplitude and duration (Table 14-4, Fig. 14-16) suggests primary myopathic disorders such as muscular dystrophy, congenital and other myopathies, periodic paralysis, myositis, and disorders of NMT, such as MG, LEMS, and botulism. All these entities have in common the random loss of functional muscle fibers from each motor unit, caused by muscle degeneration, inflammation, metabolic changes, or failure of neuromuscular activation. A decrease in the number of muscle fibers leads to a lower fiber density, which in turn causes a reduction in amplitude and duration. In extreme cases, voluntary contraction activates only a single muscle fiber, displaying a waveform indistinguishable from a fibrillation potential. The short spikes, 1–2 ms in duration, produce a high-frequency sound over the loudspeaker, reminiscent of spontaneously discharging fibrillation potentials. Unlike some inherited disorders of muscle, metabolic or toxic myopathies may cause reversible changes. Mild metabolic and endocrine myopathies characteristically show little or no alteration in duration or amplitude.

Contrasting changes in MUP waveform generally help differentiate myopathies from lower motoneuron disorders (Table 14-4).[17,18] In fact, EMG and histochemical findings from muscle biopsies have an overall concordance of 90% or greater.[9,17,18,57] The distinction, however, may blur in some cases showing equivocal findings.[46] Sick axon terminals in distal neuropathy, for example, may result in random loss of muscle fibers within a motor unit. Similarly, during early reinnervation, immature motor units consist of only a few muscle fibers, giving rise to a low-amplitude, short-duration, polyphasic MUP. In either instance a neuropathic process will produce changes classically regarded as consistent with a myopathy.[89]

Conversely, an MUP may have a long duration in myopathies with regenerating muscle fibers causing an increased fiber density, erroneously suggesting a neuropathic process.[35] Complex potentials with normal or increased duration may also appear in myopathy, primarily reflecting increased variability of fiber diameter.[91] A remote element may occur quite distinct from the main unit, as indicated by the terms *satellite or parasite potentials*, now abandoned in favor of a more descriptive name, *late component*. These findings, usually, but not always (see Chapter 13-5), signal a restructured motor unit in either myopathic or neuropathic disorders, including intra-axial axonal transection, for example, in multiple sclerosis.[4] In one study of 41 patients with different myopathies,[131] quantitative analyses including and excluding the late potentials revealed a reduced mean duration in 64% and 95%, respectively. This observation confirms the need to exclude the late components in calculating the mean duration for diagnostic purposes.

Hence, the oversimplified dichotomy between myopathy and neuropathy may not necessarily hold in interpreting MUP abnormalities and correlating them with clinical diagnoses. Despite these uncertainties, the EMG studies allow division between myogenic and lower motoneuron involvements in most patients with definite weakness.[21] Template-operated MUP analyses also

demonstrated reasonable predictive value for diagnosis and exclusion of myopathy.[101] Findings often vary among different muscles in the same patient or even from one site to another within a given muscle. An adequate study comprises exploration of different parts of the limb, sampling each muscle in several areas. In some disease states, muscles with minimal dysfunction may show no abnormality, whereas very severely diseased muscles may reveal only nonspecific end-stage changes. Optimal evaluations, therefore, should include those moderately affected but not totally destroyed by the disease process. Quantitative and discriminant MUP analyses may improve diagnostic yields in distinguishing myopathic and neuropathic samples.[98]

6. RECRUITMENT PATTERN

Upper Motoneuron Disorders

In late recruitment caused by failure of descending impulses seen in upper motoneuron lesions, the activated motor units tend to discharge more slowly than expected for normal maximal contraction.[138] The same holds for hysterical weakness (Fig. 14-17). In one study of 15 stroke patients with paretic tibialis anterior, low-threshold motor units fired within the lower end of the normal range, whereas high-threshold motor units, if recruited at all, discharged below their normal range.[51] Patients with hemiparesis also showed a compressed range of motoneuron recruitment and a failure of high-frequency discharge despite maximal voluntary contraction of the paretic muscles.[53] Stroke patients have a selective functional loss of the large, high-threshold motor units, which therefore do not recruit at the high force unlike healthy subjects.[80] Other signs suggesting a central nervous system disorder include poor activation, poor relaxation, extensor plantar responses, and flexor spasms on needle EMG.[54] In an incomplete spinal cord injury, an increase in the surface EMG during biofeedback may depend on higher rates of firing of the already activated motor units rather than recruitment of previously unavailable motor units.[123]

Needle studies have value in quantitatively assessing paresis caused by upper motoneuron lesions. For example, it may reveal the presence of surviving fibers that traverse the injured portion of the spinal cord even in patients diagnosed as having a complete transection.[36] Conversely, it may detect changes caused by an upper motoneuron lesion, which alter single motor unit firing characteristics early, at a time when clinical examination shows no evidence of increased tone or spasticity.[112] Increased discharge variability in

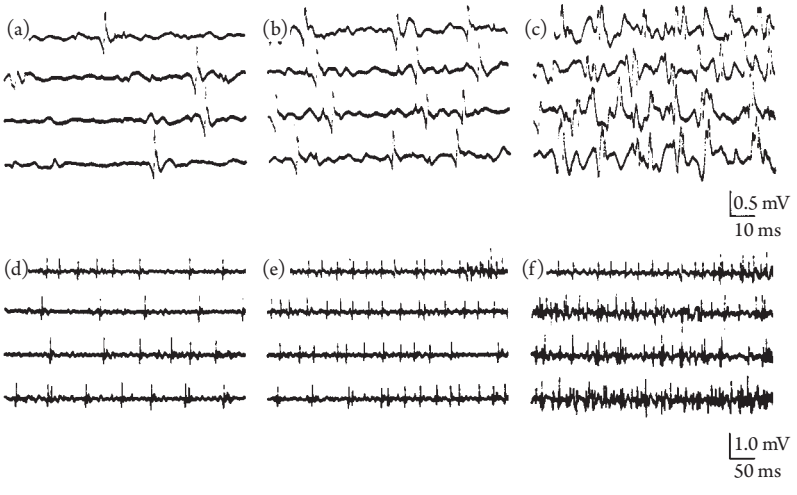

FIGURE 14-17 Reduced recruitment and incomplete interference pattern of the tibialis anterior in a 31-year-old woman with hysterical weakness. Minimal (*a*, *d*), moderate (*b*, *e*), and maximal (*c*, *f*) effort to contract the muscle altered neither the rate of firing nor the number of discharging motor units appreciably.

muscles just above the level of spinal cord injury also suggests that subtle effects extend beyond the clinically apparent segments of involvement.[136] Section of the spinal cord may result in a loss of short-term synchrony between pairs of motor units, probably reflecting the removal of synchronizing inputs or the reorganization of synaptic inputs.[33]

Lower Motoneuron Disorders

The number and the average force of functional motor units dictate the recruitment pattern. In disorders of the motoneuron, root or peripheral nerve, increased effort to contract the muscle produces limited recruitment, reflecting reduced numbers of excitable motor units. To maintain a certain force, surviving motoneurons must fire rapidly to compensate for the loss in number. In extreme instances, a single MUP may discharge at frequencies as high as 50 Hz, producing a discrete "picket fence" appearance of the interference pattern induced by maximal effort (Fig. 14-18).

Thus, a lower motoneuron weakness with a rapid rate of discharge stands in good contrast to an upper motoneuron or hysterical paralysis with a slow rate of discharge, even though both show a reduced interference pattern. In addition, hysterical weakness or poor cooperation often produce irregular, tremulous firing of motor units, not seen in a genuine paresis unless the patient also suffers from an essential or other type of tremor. Isokinetic measurements of muscle strength reveal increased variability of tonus in repeated tests and other signs of inconsistency and contradictory motor performance.

Myopathy

In this condition, an MUP, brief in duration and small in amplitude, shows polyphasic waveform probably reflecting an increase in muscle fiber diameter variability, rather than a loss in number of muscle fibers. If each unit contributes a smaller force than normal, many such units must discharge early to functionally compensate in quantity, hence the analogy to Boy Scouts for brief and small MUPs: many little guys trying to do a man's job (King Engel, personal communication). The number of units required to maintain a given force increases in proportion to the inefficiency of unit discharge. Thus, with slight voluntary effort, many axons begin to fire almost instantaneously in advanced myopathy

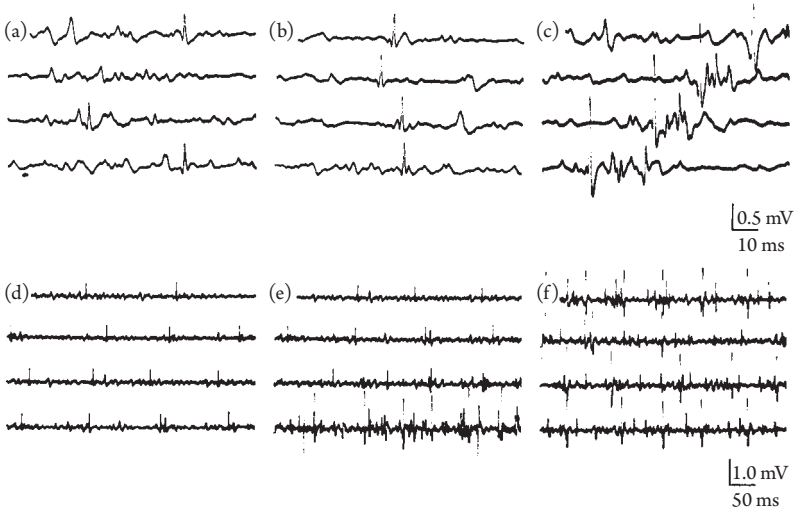

FIGURE 14-18 Reduced recruitment and incomplete interference pattern of the mildly paretic extensor carpi radialis in a 20-year-old man with partial radial nerve palsy. The rate of firing rather than the number of discharging motor units increased during minimal (*a*, *d*), moderate (*b*, *e*), and maximal voluntary contraction (*c*, *f*) (cf. Fig. 14-14).

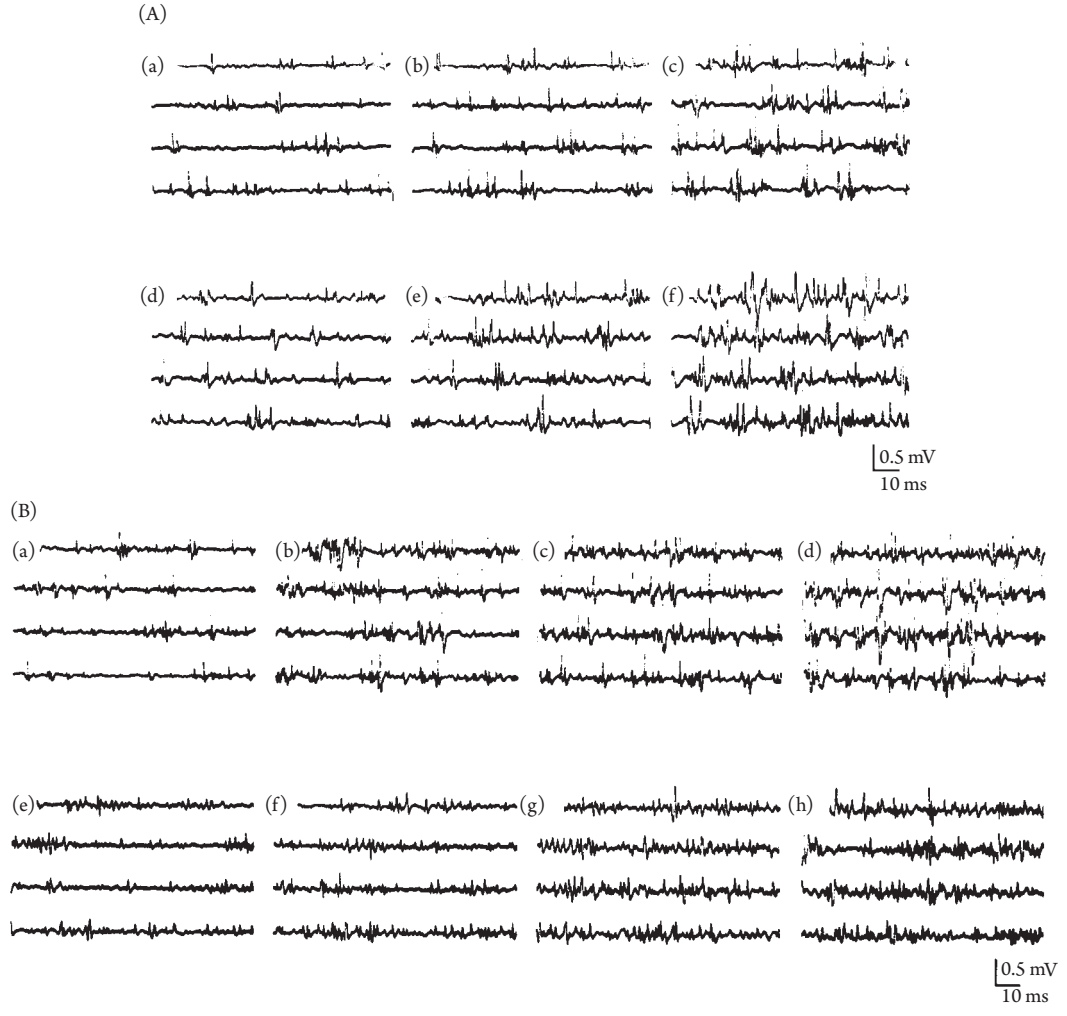

FIGURE 14-19 (*A*) Early recruitment of the deltoid (a, b, c) and tibialis anterior (d, e, f) in a 9-year-old boy with a 6-week history of dermatomyositis (cf. Fig. 14-8D). Note abundant motor units discharging with increasing effort from (a) through (c) and (d) through (f) during minimal muscle contraction. (*B*) Early recruitment of the biceps (a, b, c, d) and tibialis anterior (e, f, g, h) in a 7-year-old boy with Duchenne dystrophy (cf. Fig. 14-8E). An excessive number of motor unit potentials appeared during minimal (a, e), mild (b, f), moderate (c, g), and maximal contraction (d, h).

(Fig. 14-19). A full interference pattern develops at less than maximal contraction, although its amplitude remains low as an expression of a decreased fiber density. For the same reason, the motor units also show early recruitment, reaching full interference prematurely in diseases of NMT. This general rule may not apply in advanced myogenic disorders with loss of whole motor units instead of individual muscle fibers. Here a limited recruitment leads to an incomplete interference pattern as expected from a reduced number of motor units, mimicking a neuropathic change.

Involuntary Movement

Involuntary motor symptoms sometimes show EMG findings that may resemble changes seen in a lower motoneuron disease. Tremors show characteristic bursts of MUP repeating at a fairly constant rate (Fig. 14-20). Although many motor units fire in a group during each burst, no fixed temporal or spatial relationships emerge among them. Successive bursts characteristically vary in amplitude, duration, waveform, and number of simultaneously discharging motor units. A subclinical

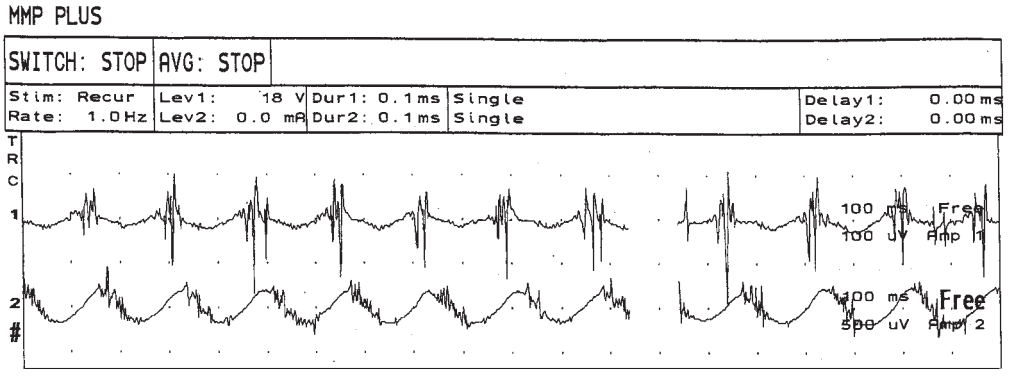

FIGURE 14-20 A 51-year-old woman with Parkinson's disease. Simultaneous needle recording from the wrist flexors (upper trace) and extensors (lower trace) documented 5 Hz alternate contraction of agonist and antagonist muscles, typical of resting tremors seen in this disorder.

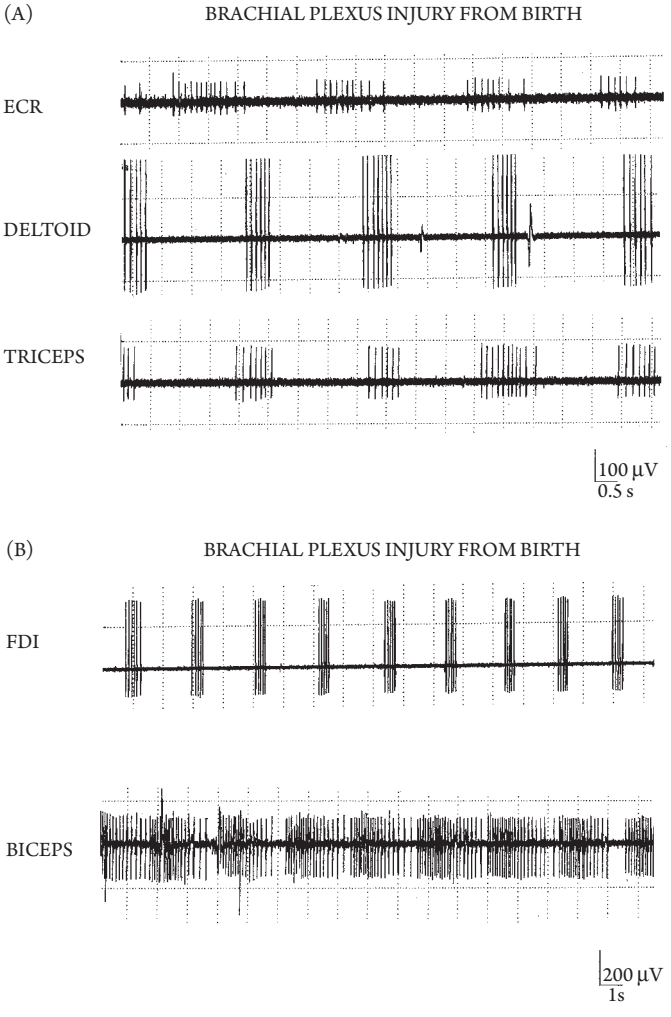

FIGURE 14-21 A 3-year-old girl, who 2.5 years earlier had a brachial plexus reconstruction surgery with satisfactory recovery of shoulder function. Electromyography revealed repetitive short trains of discharges, each lasting 0.5 second. Synchrony of this discharge with her respiration in all muscles tested indicates aberrant reinnervation from the phrenic nerve.

tremor burst could masquerade an unstable long-duration polyphasic MUP varying in appearance and rhythm. Careful EMG analyses help characterize different types of tremor on the basis of their rate, rhythm, and distribution.[113] Synkinesis seen in hemifacial spasm or other conditions with aberrant regeneration gives rise to unintended activation of motor units in the muscles not under voluntary control (see Chapter 8-6). Simultaneous recording from multiple muscles confirms the presence of time-locked aberrant discharge (Fig. 14-21), thus differentiating pathologic synkinetic discharges from voluntary co-contraction of two separate muscles.

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15

Examination of Nonlimb Muscles

Abbreviations: ALS—amyotrophic lateral sclerosis, CRD—complex repetitive discharge, EMG—electromyography, MG—myasthenia gravis, MND—motoneuron disease, MUP—motor unit potential

1. INTRODUCTION

Nonlimb muscles readily accessible to needle examination include the muscles of mastication, face, soft palate, and tongue. Studies of laryngeal muscles require the assistance of an otolaryngologist for proper placement of the needle electrode. Examination of the extraocular muscles also poses technical difficulty, but ophthalmologists with the special skill and knowledge can place the electrode safely in the intended muscles. These muscles have the same physiologic and pharmacologic properties as the peripheral skeletal muscles.

The same technique applies to the truncal musculature and the muscles of the limbs. The intercostal nerves derived from the anterior rami of the spinal nerve innervate the abdominal muscles, whereas the posterior rami supply the paraspinal muscles. The study of these muscles and the external anal sphincter requires no special instrumentation. Full evaluation of the paraurethral muscles depends to a great extent on cystometry and other urodynamic procedures, usually conducted by urologists with special expertise in this area.[65]

2. MUSCLES OF THE FACE, LARYNX, AND NECK

The ordinary techniques used for the skeletal muscles also apply in studies of most voluntary muscles innervated by the cranial nerves, with the exceptions of the laryngeal and extraocular muscles, as discussed later in this section. The most commonly tested muscles in the face and neck include the masseter, temporalis, orbicularis oculi, orbicularis oris, tongue, trapezius, and sternocleidomastoid. In studying these muscles,

holding their belly between the index finger and thumb for firm immobilization generally facilitates needle insertion.

Facial Muscles

Because of anatomic proximity, the needle electrode placed in the orbicularis oris or oculi may detect distant potentials generated in the masseter or temporalis muscle. To avoid this interference, the patient should open the mouth slightly and relax the jaw. In the mimetic muscles of the face, motor unit potentials (MUPs) show low amplitude and short duration with reported values ranging from 2.3 ± 0.3 ms (mean ± SD)[58] to 5 or 6 ms.[16] The orbicularis oris contains some muscle fibers crossing from one side to the other. In the case of unilateral denervation, therefore, activity of muscle fibers innervated by the normal facial nerve on the unaffected side may confuse the findings. Anesthetic block on the healthy side can establish a complete loss of innervation on the side of the lesion.[14]

After nerve injury, fibrillation potentials appear slightly earlier in the face than in the limb. Detection of spontaneous activity helps differentiate structural damage to the axon from demyelinative block in patients with peripheral facial palsy. In the face, a normal MUP, small in amplitude and brief in duration, can mimic fibrillation potentials in waveform (Fig. 15-1). Accurate assessment of spontaneous potentials, therefore, calls for complete relaxation of the muscle under study. As in the skeletal muscles, the appearance of nascent units precedes the clinical return of voluntary movement as the electrical evidence of reinnervation. The facial nerve, if degenerated from a proximal injury site, nearly always shows the signs of aberrant regeneration (see Fig. 8-15 in Chapter 8).[45] Random misdirection may involve two branches of the facial nerve or two distinct but anatomically close nerves, such as the facial

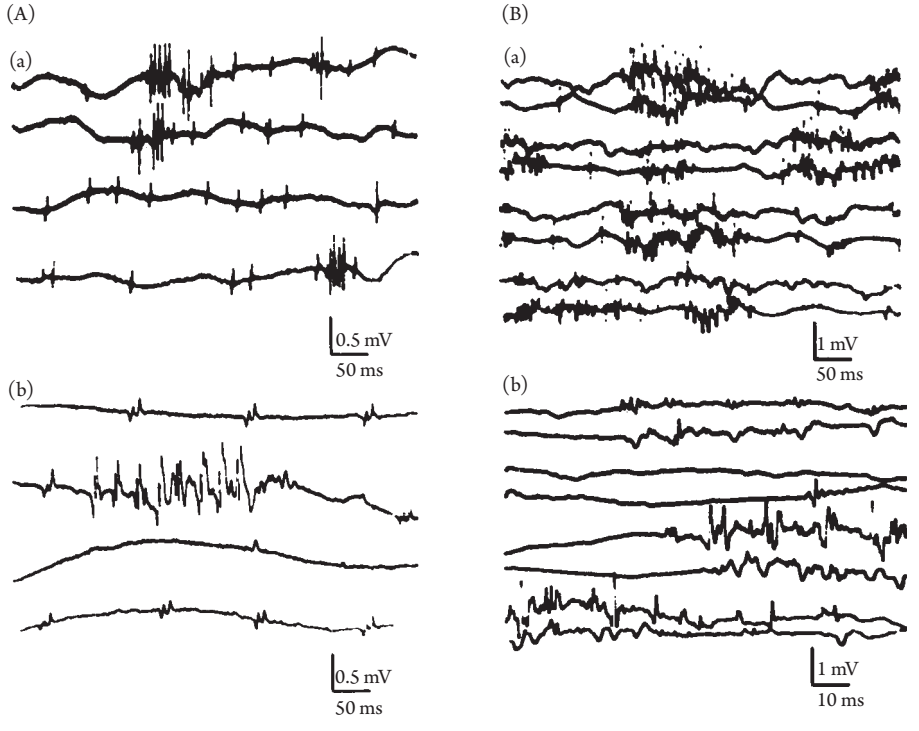

FIGURE 15-1 (*A*) Motor unit potentials recorded in a 54-year-old woman with hemifacial spasm. Recurrent spontaneous bursts of high-frequency discharges from the orbicularis oris shown at a slow (a) and fast sweep (b). (*B*) Simultaneous recording from the orbicularis oculi (top tracing in each pair) and oris (bottom). The patient blinked quickly several times to show synkinesis involving the two muscles.

and trigeminal nerves.[67] In these cases, simultaneous recording from the affected muscles substantiates the presence of synkinesis. In facial paralysis, reinnervation of midline muscles may result from the contralateral side along the nerve or muscle fibers crossing to the affected side.[33]

Laryngeal and Nuchal Muscles

The glossopharyngeal nerve and the recurrent branches of the vagal nerve subserve the same motor function in the larynx. Here, electromyography (EMG) can characterize the paralytic involvement of the vocal cord, palate, and pharyngeal and laryngeal muscles.[70,82] Similarly, EMG recording from thyroarytenoid and cricopharyngeus muscles helps identify a distinct swallowing pattern in patients with neurogenic dysphagia.[34] Pharyngeal and laryngeal EMG, though technically feasible,[27,46,64] lies outside the routine studies conducted in an ordinary EMG laboratory.[3,56] Studies of these anatomic structures may need a flexible wire electrode usually inserted with the help of an otolaryngologist. In contrast, submental surface electrodes suffice to monitor laryngeal movements.[2,28]

In one study with seven healthy subjects,[66] the vocalis muscle and cricothyroid showed a mean amplitude of 426 μV and 500 μV and mean duration of 3.5 ms and 4.4 ms, respectively. Like in skeletal muscles, EMG abnormalities of the pharyngeal and laryngeal muscles generally show better correlation with clinical findings of lower motoneuron than upper motoneuron involvement.[55] In patients with vocal cord paralysis, the absence or paucity of MUP indicates a poor outcome, although the reverse does not necessarily hold.[26]

For examination of the tongue, most investigators recommend inserting the needle from the bottom through the under surface of the mandible, 2 to 3 cm posterior to the tip of the chin in the midline rather than laterally to avoid blood vessels. With this technique, the needle passes through the genioglossus muscle before reaching the tongue itself. Abnormalities of either muscle implicate a lesion of the hypoglossal nerve on one side or the other, depending on the direction of needle insertion. To minimize anxiety, we usually tell the patient that we will check "a little muscle" under the chin without mentioning the tongue per se. An alternative method of placing the needle in the lateral portion of the protruded tongue causes more discomfort, often resulting in an unsatisfactory recording. To study spontaneous activity, the patient withdraws the tongue to the floor of the mouth with the electrode in place. Deviation of the tongue away from the needle activates and deviation toward the needle relaxes the muscle. Its protrusion in the midline requires simultaneous contraction on both sides. The innervation ratio of these muscles probably falls between those of the extraocular and limb muscles.

The spinal accessory nerve supplies two readily accessible muscles: the sternocleidomastoid and the trapezius (see Chapter 1-2). The sternocleidomastoid has unique ipsilateral supranuclear control, unlike most other muscles, which receive crossed input from the contralateral cerebral hemisphere.[5] Unilateral activation turns the head away from the contracting muscle. The muscle on the opposite side receives reciprocal inhibition in healthy subjects but not in patients with torticollis (Fig. 15-2). Bilateral contraction flexes the head forward. The activation of the trapezius causes the patient to shrug the shoulders upward toward the ears. The trapezius receives limited and inconsistent motor contribution directly from C2, C3, and C4 roots.[53]

Diaphragm

The sternal origin of the diaphragm arises from the xiphoid process. Here, the needle electrode inserted behind the bone slightly off midline to either side enters the muscle readily. An alternative, and generally preferred, approach uses needle placement in the costal insertion of the diaphragm at the anterior axillary line, distant from the major vessels, pleura, lungs, and abdominal viscera.[68] Insertion of the needle perpendicular to the skin between the 7th or 8th rib avoids the intercostal nerves and arteries, which run along the lower border of the respective ribs. The needle must pass the intercostal muscle to reach the thin diaphragm, which measures only 3–4 mm in thickness. Listening to rhythmical discharges synchronous with inspiration helps identify proper location of the needle tip. Technical difficulties[41]

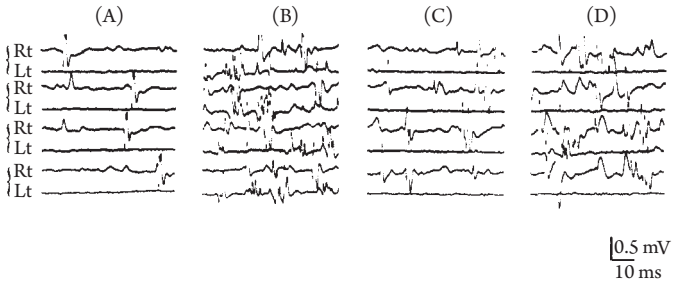

FIGURE 15-2 Torticollis on the right in a 30-year-old woman. Each pair of recordings shows muscle action potentials registered simultaneously from right (upper tracing) and left (lower tracing) sternocleidomastoid. During the sequential recordings, the patient either faced straight ahead (*A* and *C*) or turned the head to the right (*B*) or left (*D*). The muscle on the right continuously discharged regardless of the head position, whereas the muscle on the left fired only when the subject turned the head to the opposite direction (*B*).

usually relate to the proximity of the diaphragm to the overlying muscles, its shortening and lengthening with respiration, and the concern for a small risk of pneumothorax reported to occur in less than 0.2% of insertions.[9] An ultrasound-guided needle placement may enhance safety by avoiding accidental puncture of vital organs.[10]

Different types of neuromuscular diseases may involve the diaphragm, causing respiratory symptoms.[4,22,24,25,50] In addition to phrenic nerve conduction, needle study of the diaphragm provides great assistance in identifying the nature and site of the disorder.[9,18] Diaphragmatic studies depend heavily on the assessment of spontaneous discharges at rest and the interference pattern produced by respiration, because few patients can contract the muscle partially. In one study,[51] turns analysis demonstrated a substantial overlap between neuropathic and myopathic involvement. Continuous recording by laparoscopic implantation of diaphragm electrode provides a comprehensive analysis of respiratory function in an ALS patient.[43]

3. EXTRAOCULAR MUSCLES

Early work[7,12] provided detailed descriptions of EMG in the extraocular muscles and indicated its usefulness in differentiating causes of paralytic squint, such as denervation, ocular myopathy, and myasthenia gravis (MG). Ocular studies also help detect abnormalities of eye movements attributable to mechanical limitations, dislocation of the globe, anomalies in tendon attachment, presence of fascial bands connecting one muscle with another, and fibrous tissue partly replacing the extraocular muscles. Assessment of electrical activity of the extraocular muscles reveals no abnormality in most patients with mechanical strabismus. More recent studies have confirmed its diagnostic value, especially in diseases such as myositis, muscular dystrophy, and isolated peripheral nerve lesion.[30,31]

Recording Technique

Monopolar needle electrodes currently in use have an insulated shaft about 0.25 mm in diameter with a bare tip. Recording requires either an indifferent electrode placed on the tip of the nose or a blepharostat attached to the eyelid. Some investigators prefer a fine concentric electrode, 1–1.5 inches long and similar to a 30-gauge hypodermic needle in diameter. The needles come in different sizes, ranging from 0.25–0.5 mm in external diameter with a leading area varying from 0.005 to 0.015 mm^2. Simultaneous recording from a second needle electrode placed in an agonist or antagonist muscle allows studies of synergistic actions or reciprocal inhibition.

The patient lies supine on the examining table for placement of the needle electrodes through the skin of the lid after application of a topical anesthetic to the eye. To evaluate voluntary eye movements, the subject, awake during the examination, must cooperate fully. This requirement precludes the use of any form of general anesthesia. Electrical activity decreases during general,

retrobulbar, or local anesthesia as the level deepens, leading to complete electrical silence with the eyes assuming a position of divergence.

An ophthalmologist familiar with the extraocular muscles can easily reach the inferior oblique and, with some search, any of the remaining extraocular muscles. The study of the least accessible muscle, the superior oblique, requires a considerably longer needle. Monitoring the waveform and the sound of motor unit discharges helps adjust the position of the needle inserted subconjuctivally into the belly of a muscle along its long axis. Most patients tolerate the procedure well with minimal discomfort. Rare complications include ecchymoses of the conjunctiva, subcapsular hemorrhage, and exposure keratitis, all of which clear without sequelae. Inadvertent perforation of the globe can occur, especially in the presence of undetected glaucoma.

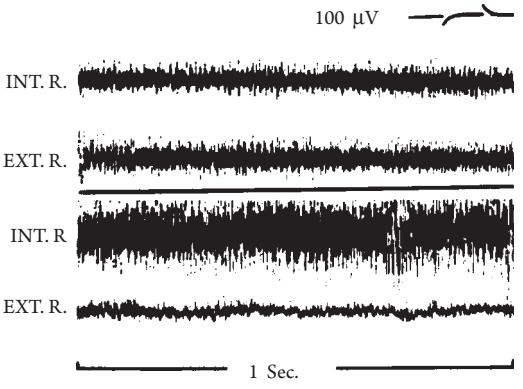

FIGURE 15-3 External and internal rectus of the left eye in a normal subject, recorded simultaneously for comparison. Upper tracing shows nearly equal and constant activity of normal amplitude in both muscles. Lower tracing, taken with the eye turned strongly into field of action of internal rectus, reveals increased motor unit activity of this muscle and corresponding reciprocal decrease in activity of external rectus. (Modified from Van Allen and Blodi,[78] with permission.)

Unique Properties of Extraocular Muscles

The eyes move rapidly and accurately. Complex coactivation of synergistic muscles and relaxation of the antagonists achieves precisely controlled movements of a constant load. Sherrington first described this principle of reciprocal inhibition based on studies of the extraocular muscles. In sharp contrast to the usual rates of firing of less than 50 impulses per second in the skeletal muscles, the eye muscles can discharge at a rate of up to 200 Hz.[7] Extraocular muscle fibers range from 10 to 50 μm in diameter.[11] The motor units consist of a small number of muscle fibers, averaging 23 in one study[20] and 6–12 in others.[74] These numbers fall considerably below the average value for the limb muscles, which varies from 100 to 2000.[15,71] The low innervation ratio and other physiologic characteristics of the fast twitch fibers permit rapid and very finely graded eye movements. Slow twitch fibers found near the surface layer of the extraocular muscle show characteristic monophasic, low-amplitude potential.[12]

Unlike the limb musculature, the extraocular muscles show tonic activity to maintain the eyes in the primary position during the alert state. With ocular movement, motor unit discharge increases in the contracting muscles and decreases in the others (Fig. 15-3). The antagonist develops complete electrical silence only through reciprocal inhibition during fast eye movements. The smaller diameter of the muscle fibers and lower innervation ratio make the MUP lower in amplitude and shorter in duration in the extraocular muscles than in the limb muscles. Reported normal values (mean ± SD) include amplitude of 108 ± 9.2 μV and a duration ranging from 1.60 ± 0.06 ms[7] to 2.8 ± 0.1 ms.[29] Another study[12] reported a normal amplitude of 20–600 μV with an average of 200 μV in the primary position, and a normal duration of 1–2 ms, with an average of 1.5 ms. As in the limb muscles, individual potentials mostly show triphasic waveforms, with occasional polyphasic activities. With maximal effort of contraction, they discharge at a rate of up to 200 Hz.[7] Spectral analysis also demonstrates a greater power in the higher frequency domain in the extraocular muscles as compared to the limb muscles.[44]

Neurogenic Extraocular Palsy

A neurogenic extraocular palsy results from lesions of the third, fourth, or sixth nerve. In principle, EMG reveals the same abnormalities as

those in denervated limb muscles. In the extraocular muscle, however, physiologic tonic discharge with the eyes in the primary position may obscure pathologic discharges. To compound the problem, a normally brief MUP resembles fibrillation potentials. Studies can still confirm denervation with certainty in a paretic muscle where spontaneous activities occur independent of any attempted contraction. Reinnervation results in a high-amplitude MUP of long duration with increased polyphasic activities, but to a lesser extent than in the skeletal muscles. A large MUP frequently accompanies aberrant regeneration of oculomotor nerves.[12]

Myopathy and Myasthenia Gravis

In ocular myopathy, unlike in neurogenic paralysis, EMG shows the preservation of a normal interference pattern with no evidence of denervation.[8] The abundance of a brief, low-amplitude MUP suggests random loss of individual muscle fibers without major change in the number of functional motor units. Except in advanced cases, myopathic features may escape detection because normal extraocular muscles show a similar pattern. In MG, which affects the ocular muscles early, causing diplopia and abnormal fatigue of eye movements, needle studies of the extraocular muscles may help establish the diagnosis. The MUP amplitude fluctuates or steadily declines during sustained contraction. A decreased number of discharging motor units results in a reduced interference pattern, which may return to normal immediately after injection of edrophonium (Tensilon). In patients with ptosis, studies of the levator palpebrae, though technically difficult to localize, may reveal abnormality.

4. TRUNCAL MUSCULATURE

Abdominal Muscles

The anterior rami of the cervical spinal nerves supply the upper-limb muscles and those of the lumbosacral spinal nerves, the lower-limb muscles (see Chapter 1-3). Similarly, 12 pairs of intercostal nerves derived from the anterior rami of the thoracic spinal nerves innervate intercostal and abdominal muscles. Involvement of the intercostal nerve results in segmental paralysis of the abdominal muscles and weak respiration. In this condition, the abdomen would protrude on coughing and the umbilicus would deviate to the unaffected side by unopposed action of the normal muscle. The various abdominal muscles have different and distinguishable actions on trunk movement, acting together in breathing.[35]

Studies of the abdominal muscles also help detect a lesion at the thoracic levels, which do not have appendicular representation in the limbs. For example, cutaneous herpes zoster in the area of the thoracic dermatomes may cause segmental denervation of the corresponding myotomes in addition to conduction abnormalities of the involved intercostal nerves.[37] Each segmental level receives at least two adjoining intercostal nerves in both thoracic and abdominal regions. The considerable overlap in segmental representation precludes the exact localization of the involved cord level.

The abdominal musculature just as easily accessible with a needle as the limb muscles includes the external oblique tested at the anterior axillary line 5 to 10 cm above the anterior superior spine of the iliac crest. The needle, if inserted obliquely, can sample the electrical activities along the course of the muscle fibers, which run medially and downward. The needle, if placed too deep, may reach the internal oblique or transverse abdominis (or the abdominal cavity). Even with the patient completely relaxed, the diaphragm and, to a much lesser extent, the intercostal muscles fire rhythmically with respiration. Volume-conducted potentials from this source may mimic spontaneous discharges, but the time relationship to the breathing cycle differentiates the two. For MUP analysis, the patient contracts the muscle by bending the upper trunk forward.

The abdominal rectus lies between the linea alba, which connects the xiphoid and umbilicus in the midline, and the linea semilunaris, which forms the lateral margin of the rectus. The needle insertion into the muscle must avoid the three transverse tendinous bands located at the xiphoid, the umbilicus, and halfway in between.[36] The patient bends forward against resistance to contract the muscle for MUP assessment.

Paraspinal Muscles

In contrast to the limb and abdominal musculature innervated by the anterior ramus of the spinal nerve, the posterior ramus supplies the paraspinal muscles at respective segmental levels. Documentation of EMG abnormalities in this region thus identifies a radicular lesion that affects the spinal nerve at a point proximal to its bifurcation into the posterior and anterior rami (see Fig. 1-7 in Chapter 1). A more distally located lesion at the level of the plexus or the peripheral nerve would entirely spare the paraspinal muscles innervated by the intact posterior rami. Hence, the examination of paraspinal muscles plays a critical role in the investigation of cervical or lumbar disc herniation.

The paraspinal musculature covers the muscles lying between the spinous and transverse processes of the vertebra. The erector spinae, its anatomical term, consists of three portions, iliocostalis muscle most laterally; short spinal muscles, or multifidus, originating from different spinous processes medially; and long spinal muscles, or longissimus dorsi in between. The short spinal muscles, located deep, immediately posterior to the transverse process, receive a fairly discrete segmental nerve supply from corresponding posterior rami.[17] A needle inserted deeply, just lateral to the spinal process, toward the transverse process reaches this portion of the muscle. The long spinal muscles, located more superficially, extend several centimeters to either side of the spinous process and ligamentum nuchae. Their nerve supply overlaps at least one to two segments caudally and rostrally.[47,80] A needle reaches this portion of the muscle quite superficially if inserted 2–3 cm lateral to the spinous process at either the cervical or the lumbar level.

Some authors advocate paraspinal mapping to quantify needle study, incorporating the concept of unisegmental innervation of medial multifidus muscles,[39] but its clinical utility awaits further documentation.[21] In one study,[40] cadaveric dissection confirmed accurate needle placement into specific fascicles for 91 of 112 injections into multifidus; 39 of 43 injection into longissimus; and 35 of 44 injections into iliocostalis. Another study, using percutaneous injection of colored latex into cadavers,[72] also confirmed the ability to make appropriate needle placement.

To achieve complete relaxation, the subject lies in the prone position with pillows under the neck and the abdomen for cervical and lumbar studies, respectively. The cervical paraspinal muscles usually relax if the patient bends the neck forward, pressing the forehead against the mattress or dropping the head from the end of the table, if necessary. For relaxation of the lumbar paraspinal muscles, the patient tries to raise the abdomen off the table, which seems to work nearly always. In some subjects, lung tissue extends above the clavicle with a distance from skin surface of approximately 3.3 cm.[42] Thus, unnecessarily deep insertion of the exploring needle below the apex of the lung could induce pneumothorax, especially in patients with a long neck. Directing the probe perpendicular to the spine or slightly upward just to the depth of the muscle minimizes the risk.

Patients in early stages of radiculopathy within 1 to 2 weeks after the onset may have electrical abnormalities limited to this region. Paraspinal studies help evaluate not only segmental pathology but also diffuse processes such as myopathy and motoneuron disease (MND). For example, vacuolar myopathies affect paraspinal muscles more than limb muscles.[59] In amyotrophic lateral sclerosis (ALS), detection of profuse spontaneous discharges in the thoracic paraspinal muscles confirms denervation unrelated to nerve entrapment. Some systemic disorders, most notably myositis, may also affect the paraspinal muscles preferentially and sometimes exclusively.[1,73] Relatively selective denervation in this region also develops in degenerative joint disease, arachnoiditis, diabetic polyradiculopathy, and rare local metastasis to the muscles. In one study,[21] up to 15% of asymptomatic subjects had positive sharp waves and fibrillation potentials in lumbosacral paraspinal muscles.

Patients generally have some difficulty in voluntarily activating the paraspinal muscles for MUP assessment, which is recommended by some[13] but not by others.[76] Quantitative measures of phases, turns, and other characteristics pose particular challenges.[6,75] In the cervical or lumbar region, a normal MUP, small in amplitude

and brief in duration, may mimic a fibrillation potential.

5. ANAL SPHINCTER

Indications and Technique

The anal sphincter receives the innervation of the pudendal nerve, which derives from the anterior division of S3, S4, and occasionally also S2 spinal nerves. Interdigitation of muscle fascicles across the midline results in substantial overlap of innervation between the two sides. This enables partial reinnervation from the contralateral side after unilateral pudendal neurectomy.[81] The anal sphincter, which normally operates under volitional control, shares similar physiologic properties with the skeletal muscles of the limbs. Surface EMG has long contributed to kinesiologic studies of the normal anal sphincter at rest and during defecation. Surface recordings from the sphincter have shown increased activity during coughing, speaking, and body movements of the trunk and decreased activity in sleep. Other kinesiologic studies used either a 25-μm wire electrode or steel pins to study reflex contraction induced by digital stretching of the sphincter. The conventional concentric or monopolar needle suffices for routine clinical use.

Needle studies quantitate sphincter dysfunction in neurologic disorders [38,48,60] particularly in patients with bladder-emptying difficulties and perineal sensory loss.[60] They help establish or rule out the possibility of agenesis of the striate sphincter in the preoperative assessment of the newborn with an imperforate anus. Electrical studies not only localize the sphincter precisely but also determine its functional capacity. The anal sphincter may sustain traumatic injury during parturition, prostatectomy, or rectal surgery for repair of an anal fistula or prolapse. Anal sphincter EMG also helps determine the extent of damage in such cases and aids in differential diagnosis of fecal incontinence.[19] The anal and external urethral sphincters share a common segmental derivation. Thus, confirming the integrity of the anal sphincter provides an important, albeit indirect, guide in ilioconduit surgery for prominent urologic dysfunction. Needle studies of the urethral sphincter should ideally involve the help of urologists working in a laboratory equipped with tools for urodynamic investigations.[65]

For studies of the anal sphincter, adults and older children usually prefer the lateral decubitus position. The patient may assume the knee-chest or modified lithotomy position, which allows the best examination in infants. After digital examination of the sphincter tone, a gloved finger, still in place, can guide the needle inserted through the perianal skin adjacent to the mucocutaneous junction. The tip of the electrode should enter perpendicular to the skin surface close to the anal orifice, 0.5 to 1 cm from the ring.[62] The ring of the anal orifice has four parts, anterior and posterior quadrants on both sides. A complete study consists of exploration of the four quadrants with the anal sphincter at rest and during voluntary or reflexive contraction.

Resting and Voluntary Activities

Unlike peripheral skeletal muscles, the anal sphincter maintains a certain tonus without volitional effort. Thus, the subject at rest maintains sustained MUP firing at a low rate with activity varying considerably by subject position. The discharge continues during sleep, although the rate drops substantially more than during wakefulness. Sphincter activity ceases completely only during attempted defecation. Conversely, volitional contraction of the anal sphincter inhibits rectal motility based on reciprocal innervation between the rectal musculature and the striated muscle of the anal sphincter. The presence of physiologic tonic activity at rest makes detection of abnormal spontaneous potentials difficult in a partially denervated muscle. In contrast, the paretic sphincter may reveal abundant fibrillation potentials, positive sharp waves, and complex repetitive discharges (CRDs), as in any denervated limb muscles

To test voluntary activity, the patient contracts the sphincter as though attempting to hold a bowel movement. In one study, MUP ranged from 5.5 to 7.5 ms in duration and 200 to 500 μV in amplitude.[57] In another study, an automated analysis showed a gradual progression of the MUP duration with advancing age.[23] Digital

examination of the anus reveals that coughing or crying elicits reflex activity of the sphincter. A full interference pattern should accompany a normal maximal contraction, whether induced voluntarily or reflexively. Reliability of grading the degree of such discharge, as in the skeletal muscles of the limb, depends on patient cooperation. Some subjects can neither relax nor contract the sphincter as instructed by the examiner during the test. In these cases, an appraisal of sphincteric tone by the interference pattern might erroneously suggest a central lesion. Experienced electromyographers, however, can usually correlate electrical activity and sphincter tone with reasonable accuracy.

Central versus Peripheral Paralysis

Paralysis of the striated sphincter may result from a pure central, pure peripheral, or mixed lesion. Central paralysis causes reduction in voluntary discharges with preservation of reflexive activation. A full effort induces an incomplete interference pattern, which, though normal in amplitude, discharges at low frequency. With a complete loss of voluntary activity, the low-frequency discharge normally seen at rest continues during maximal effort of contraction. Peripheral paralysis of the anal sphincter usually results from lesions in the cauda equina or in the sacral or pudendal plexus. In contrast to central paralysis, volitional effort recruits a few motor units that fire at a high frequency. In an incomplete paralysis, the surviving units show a polyphasic waveform and a long duration. In an acute cauda equina syndrome, the initial paralysis usually implies a functional block. Axonal degeneration, if present, gives rise to fibrillation potentials, positive sharp waves, and CRD (Fig. 15-4).

Patients often have a mixture of central and peripheral paresis in congenital malformation, vascular disease, traumatic injury of the conus medullaris, and spina bifida with meningomyelocele. In these cases, anal sphincter EMG reveals absent or markedly reduced voluntary activity. Reflexive contraction, if present, shows isolated high-frequency discharges of a few motor units. Complete damage to the sacral segment of the

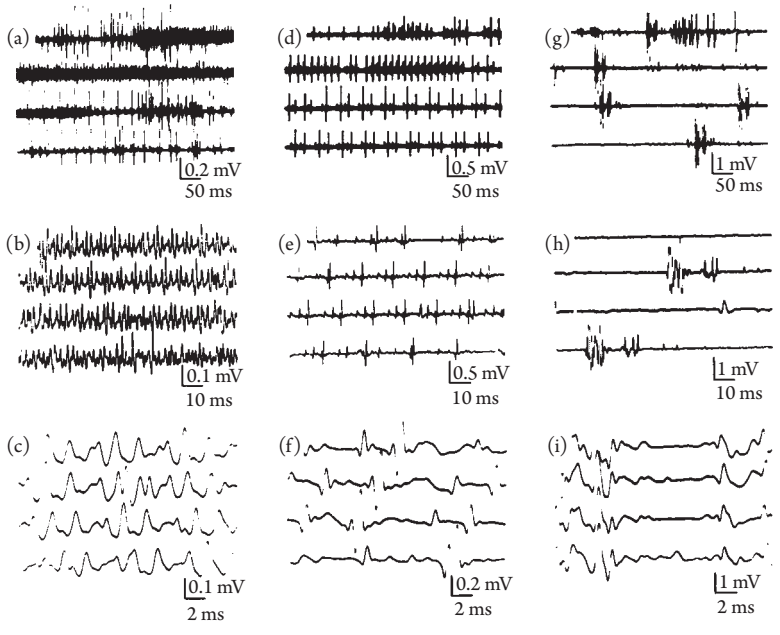

FIGURE 15-4 Recording from anal sphincter in a 16-year-old girl with incontinence. Tracings include continuous discharge at high frequency, resembling very prominent endplate noise (*a*, *b*, *c*), complex repetitive discharges (*d*, *e*, *f*), and very polyphasic fasciculation potentials (*g*, *h*, *i*), all recorded in a localized small area of the sphincter with the patient completely at rest. In (*i*), each sweep triggered by a recurring fasciculation potential shows a consistent late component following the main discharge.

conus medullaris abolishes both voluntary and reflexive sphincter response. Spontaneous potentials recorded in these cases indicate the involvement of the anterior horn cells.

Patients with ALS typically have normal sphincter activities, even when the limb muscles show the evidence of conspicuous denervation.[69] In contrast, abnormal spontaneous activity serves as a specific marker for neuronal degeneration of Onuf's nucleus in multiple system atrophy[63] and progressive supranuclear palsy.[77] In one series of 126 patients with suspected multiple system atrophy, 82% of those with definite diagnosis had abnormal sphincter studies.[54] This finding may [52,61,79] or may not[32,49] help differentiate this entity from Parkinson's disease.

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16

Single-Fiber and Macro Electromyography

Abbreviations: ACh—acetycholine, AChE—anticholinesterase, AChR—acetycholine receptor, ALS—amyotrophic lateral sclerosis, CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, CPEO—chronic progressive external ophthalmoplegia, DMD—Duchene muscular dystrophy, DMI—myotonic dystrophy Type 1, EMG—electromyography, EPP—endplate potential, FSHD—facioscapulohumeral dystrophy, HyperPP—hypokalemic periodic paralysis, IBM—inclusion body myositis, LEMS—Lambert-Eaton myasthenic syndrome, LGD—limb-girdle dystrophy, MC—myotonia congenita, MCD—mean value of consecutive differences, MG—myasthenia gravis, MMN—multifocal motor neuropathy, MND—motoneuron disease, MSD—mean sorted interval difference, MUP—motor unit potentials, MUSK—muscle-specific kinase, NMT—neuromuscular transmission, RNS—repetitive nerve stimulation, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy

1. INTRODUCTION

The concentric[2] and other bipolar or monopolar needles record from multiple single muscle fibers that constitute part of a single motor unit derived from a spinal motoneuron. As the smallest functional unit of muscle activation, a motor unit potential (MUP) represents different muscle fibers within a motor unit, all of which fire more or less synchronously. In contrast, the single-fiber needle[18] allows extracellular recording of individual muscle fiber action potentials during

voluntary contraction.[88,104,108] Termed single-fiber electromyography (SFEMG), this technique has contributed substantially to the understanding of muscle physiology and pathophysiology.[117] In the clinical domain, the SFEMG supplements conventional electromyography (EMG) by determining (1) fiber density, the number of single-fiber action potentials within the recording radius of the electrode, and (2) jitter, the variability of the interpotential interval between two or more single muscle fibers belonging to the same motor unit.[108,115]

2. RECORDING APPARATUS

Electrode Characteristics

A small leading-off surface of the single-fiber needle electrode lies close to fewer muscle fibers than the larger tip of the conventional needle that commands a wider territory. In addition, a smaller pickup area causes little shunting and consequently less distortion of the electrical field (Fig. 16-1). This type of needle, therefore, helps establish selective recording from the generator under study (see Chapter 3-2). Here, the action potential decreases almost exponentially as the recording electrode moves away from the origin. Thus, the recorded amplitude declines very steeply with increasing distance between the electrode and the source (see Fig. 13-6 in Chapter 13). This, in turn, results in sharp discrimination of single-fiber potentials with minimal interference from action potentials of neighboring muscle fibers.

A recording surface diameter in the range of 25–30 μm serves best for this purpose, considering the average muscle fiber diameter of 50 μm. Most SFEMG needles have an active recording surface located 3 mm from the needle tip along the side port. This arrangement minimizes the chance of recording from muscle fibers damaged by needle penetration. A system such as this allows an uptake area approximately 300 μm from the needle and consequently records signals from only one or two fibers. Bipolar derivation with two small electrodes separated by a short interelectrode distance further improves the selectivity of single-fiber recording, as opposed to a monopolar arrangement with a reference electrode outside

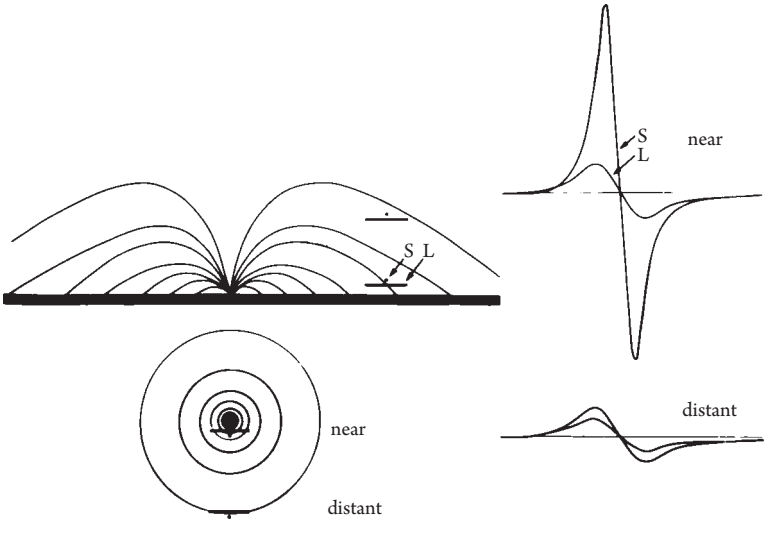

FIGURE 16-1 Electrical field around a muscle fiber recorded with a small (S) and a large (L) leading-off surface. The size of the recording area primarily determines the magnitude of shunting across the high-density isopotential lines near the generator source, but to a lesser degree further in the periphery. This, in turn, dictates the relationship between the amplitude recorded and the electrode distance from the source, that is, a much steeper decline in potential per unit radius with a smaller leading-off surface (cf. Fig. 13-6 in Chapter 13). (From Stålberg, Trontelj, and Sanders,[117] with permission.)

the muscle (see Fig. 3-1 in Chapter 3). The suggested interelectrode distance of 200 μm provides enough separation for optimal amplification of a single discharge but precludes recording from two independent sources.[117]

In comparison, the conventional needle electrode has a leading-off surface of about 150 by 600 μm, which records from an area within a 500 μm to 1 mm radius (see Fig. 3-1 in Chapter 3). This larger leading-off surface induces prominent shunting across the electrical fields that becomes disproportionately greater near the source, where the isopotential lines gather in high density (see Fig. 16-1). Thus, the ordinary electrode registers comparatively less amplitude near the potential generator. Farther from the source, the shunting effect diminishes with either type of electrode because the larger radius of the isopotential lines gives rise to a lower gradient of the electrical field. With large leading-off surfaces, therefore, the action potential does not decrease exponentially with increasing recording distance,[30] showing relatively little difference in amplitude between potentials derived from near and distant fibers.

Amplifier Settings

A single-fiber electrode with a small leading-off surface has a much higher electrical impedance than a conventional monopolar or concentric needle. Impedances range on the order of megohms (MΩ) at 1 KHz for a platinum needle but vary for different metals. To maintain a high signal-to-noise ratio, therefore, the amplifier must have a very high input impedance on the order of 100 MΩ (see Chapter 3-3). This helps maintain an adequate common mode rejection ratio or differential amplification between the signal and the interference potential.[117] The initial amplifier settings include a sensitivity of 0.2–1 mV/cm and a sweep speed of 0.5 to 1 ms/cm.

A short-duration, high-amplitude single-fiber action potential, recorded near the generator, consists mainly of high-frequency components. In contrast, distant potentials have a larger proportion of low-frequency discharges because the intervening muscle tissue tends to filter out high-frequency components. Thus, the use of a low-frequency cutoff of 500 Hz, for example, selectively attenuates volume-conducted background activity. The action potential from fibers close to the electrode also decreases by about 10%. This slight change in shape of the single-fiber potential barely affects the measurements of propagation velocity, fiber density, or jitter. In the analysis of waveforms, however, one must lower the high-pass (low-frequency) filter setting to about 2–10 Hz rather than 500 Hz, which eliminates many low-frequency components. A high-frequency cutoff of 35 KHz, though ideal, adds little in practice, because a low-pass (high-frequency) filter of 10 KHz can substantially maintain the amplitude and shape of the original spike.

3. SINGLE-FIBER POTENTIAL

An optimally placed single-fiber electrode registers a biphasic spike with a rise time of 75–200 μs and total duration of about 1 ms. The peak-to-peak amplitude varies widely, from a low of 200 μV to a high of 20 mV, but usually within the range of 1–7 mV. The recorded amplitude attenuates exponentially as the distance between the electrode and the discharging muscle fiber increases. With a time resolution of 5–10 μs, the shape of the potential remains nearly constant for successive discharges. The frequency spectrum ranges from 100 Hz to 10 KHz with a peak at 1.61 ± 0.30 KHz.[30]

Recording Procedures

Either electrical or voluntary activation can suitably generate an MUP for SFEMG. Surface stimulation of the motor fibers evokes many motor units simultaneously, making single-fiber recording difficult. In contrast, stimulation of an endplate zone with a bipolar needle electrode can excite only a few terminal twigs of a motoneuron. The activated terminal twigs conduct the action potential first antidromically to the branching point, then orthodromically to the remaining nerve twigs of the entire motor unit. This allows recording of SFEMG from a single motor unit firing in response to electrical stimulation. In cooperative subjects, slight, steady voluntary muscle contraction also reliably generates an isolated MUP, a preferred method of studying SFEMG.

The recommended recording procedure[117] calls for amplifier sensitivity of 0.2–1 mV and sweep of 0.5–1 ms/cm for initial exploration. For insertion of the needle, the subject, comfortably lying down or seated, slightly contracts the target muscle. Optimal acquisition of single-fiber potentials depends primarily on maintaining the needle at the critical area with a steady hand. Small shifts of needle position result in radical changes in the waveform and amplitude of the recorded response.[78] The clear, high-pitched sound of a single-fiber discharge, audible over the loudspeaker, indicates a suitable site for further study. Careful rotation and advancement or retraction of the needle then maximizes the potential on the oscilloscope. The trigger level set on the initial positive deflection of the action potential allows consecutive discharges to superimpose on a storage scope screen using a new sweep speed of 20 μs/cm. A constant waveform registered in successive tracings confirms a single muscle fiber discharge, whereas varying patterns indicate a composite action potential not suitable for analysis.

Recommended Criteria

The criteria for accepting a potential as generated by a single muscle fiber near the needle include peak-to-peak amplitude exceeding 200 μV; rise time from the positive to the negative peak of less than 300 μs; and successive discharges with a constant waveform, assessed with a time resolution of 10 μs or better. The amplitude of a single-fiber discharge decreases to less than 200 μV at a distance greater than 300 μm. Thus, counting the spike discharge fulfilling the aforementioned criteria reveals all the muscle fibers of a motor unit located within this radius. Commercially available SFEMG systems may provide different time resolution of the amplifier and other particulars, which dictate the accuracy of analysis. Each laboratory should ideally establish its own normal values.

The use of a high-pass filter set at 500 Hz eliminates most low-frequency responses that represent volume-conducted potentials from distant muscle fibers. In fact, even regular needle electrodes selectively register the activity from a few muscle fibers located nearby. Thus, the use of even greater low-frequency attenuation with a high-pass filter of 2–3 KHz helps record single-fiber potentials by a monopolar or concentric needle in lieu of single-fiber needle.[129] Although this type of recording does not always accurately distinguish single-fiber responses from summated potentials of more than one fiber, it often reveals abnormal complexity and instability of the motor unit not otherwise appreciated. This approach may bridge the gap between the SFEMG and conventional EMG.[9,22,75,89,117]

4. FIBER DENSITY

Definition and Clinical Significance

The single-fiber electrode randomly inserted into a slightly contracting normal muscle generally records activities derived from only one muscle fiber. The electrode may occasionally lie close to two or more muscle fibers of the same motor unit. The recorded activity then consists of multiple single-fiber potentials discharging synchronously within the recording radius of the single-fiber electrode (Fig. 16-2). Repeated counting of such spikes with amplitude greater than 200 μV determines the EMG fiber density defined as the mean number of associated single-fiber potentials that fire almost synchronously with the initially identified potential.[113] All potentials greater than 200 μV originate within a 300 μm radius of the recording surface in the normal adult.[115] Thus, the motor unit fiber density indicates the average number of single muscle fibers belonging to the same motor unit within this radius.

Fiber density provides a measure of muscle fiber clustering, rather than the total number of muscle fibers within a motor unit. Random loss of muscle fibers generally escapes detection by this technique because, by definition, the lowest possible value is 1.0. However, a local concentration of action potentials or an increase in fiber density usually indicates the presence of collateral sprouting.[111] Fiber density rivals histochemical fiber grouping in identifying rearrangements within the motor unit.[117] Studies have shown a slightly higher density in the frontalis and lower values in the biceps brachii. Table 16-1 summarizes normal

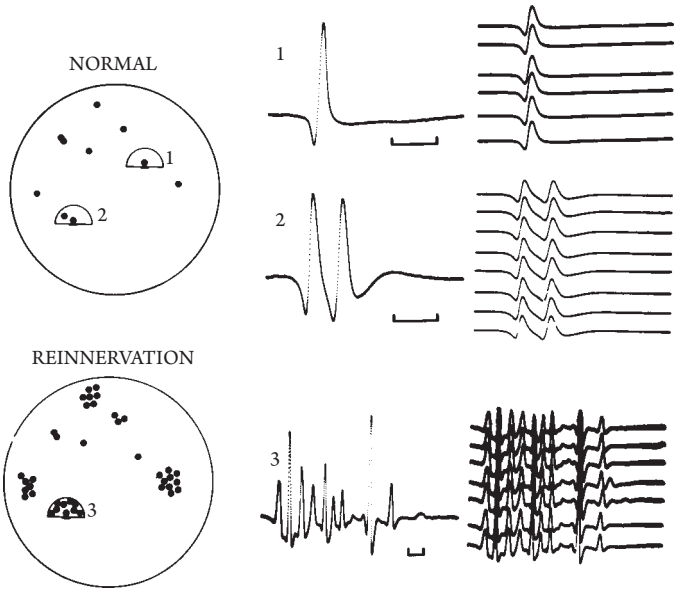

FIGURE 16-2 Fiber density in normal and reinnervated muscles. All muscle fibers belonging to one motor unit (small closed circles) discharge synchronously, but the recording radius of the single-fiber electrode (half circle) normally contains only one (1) or two (2) muscle fibers. Following reinnervation, however, a large number of fibers (3) cluster within the same radius, reflecting an increase in fiber density. Time calibration: 1 ms. (From Stalberg, Trontelj, and Sanders,[117] with permission.)

Table 16-1 Fiber Density in Normal Subjects*

MUSCLES	AGES					
	10–25 YEARS			26–50 YEARS		
	MEAN	SĐ	n	MEAN	SD	n
Frontalis	1.61	0.21	11	1.72	0.21	15
Deltoid	1.36	0.16	20	1.40	0.11	10
Biceps	1.25	0.09	20	1.33	0.07	17
Extensor digitorum communis	1.47	0.16	61	1.49	0.16	98
First dorsal interosseous	1.33	0.13	14	1.45	0.12	6
Rectus femoris	1.43	0.18	11	1.57	0.23	14
Tibialis anterior	1.57	0.22	18	1.56	0.22	21
Extensor digitorum brevis	2.07	0.42	16	2.62	0.30	11

*Fiber density in different muscles of normal subjects arranged in four age groups; *n*, number of subjects. Modified from Stalberg and Trontelj.[115]

values.[117] Subjects under the age of 10 and over the age of 60 years, in general, have slightly higher counts. Fiber density increases slowly during life, with faster progression after the age of 70 years, perhaps indicating degeneration of motoneurons with aging, compensated for by reinnervation.[113]

Determination of Fiber Density

Fiber density determination depends on recording a single-fiber potential with the leading-off surface of the electrode optimally positioned close to the identified fiber. In practice, moving the needle tip back and forth and rotating it will achieve the maximal amplitude of the identified potential with the trigger level of the oscilloscope set at 200 μV. Adequate stabilization of the first action potential facilitates counting the number of simultaneously firing single muscle fibers for a time interval of at least 5 ms after the triggering spike. For inclusions, an action potential must have an amplitude exceeding 200 μV and a rise time shorter than 300 μs with a high-pass filter set at 500 Hz. Advancing the needle to identify single muscle fiber potentials at 20 different sites allows calculation of the fiber density as the average number of simultaneously firing single muscle fibers within the recording radius. For example, isolated discharges of a single muscle fiber at 10 different recording sites and two fiber discharges at 10 other insertions would yield an average fiber density of 1.5.

In some disease states, a complex pattern of discharges may preclude counting the number of associated spikes. This situation calls for reporting the percentage of needle insertions that encounter only one single-fiber potential without associated spikes. Isolated discharges of one single fiber occur in 65%–70% of random insertions in the normal extensor digitorum communis muscle. Only two fibers discharge in the remaining 30%–35%, and triple potentials appear in 5% or less.[113]

Duration and Mean Interspike Intervals

The duration of the action potential complex, determined at each random insertion during the fiber density search, provides an additional means of characterizing the motor unit. This value, defined as the time difference between the first and last single-fiber potentials of the same motor unit, reflects the difference in nerve terminal conduction, neuromuscular transmission (NMT), and muscle fiber conduction times within the recording radius of the needle. In practice, each recording site provides a measure of the interval from the baseline intersection of the first potential to the return to the baseline of the last potential. The average of at least 20 such measurements normally yields a duration of 4 ms or less in over 95% of all multiple-potential recordings in the extensor digitorum communis. In contrast, values may reach as high as 40–50 ms in some pathologic conditions.

Dividing the total duration by the number of interspike intervals, or the number of spikes minus one, yields another index called the mean interspike interval. The normal values in the extensor digitorum communis range from 0.3 to 0.7 ms. This measure increases in muscular dystrophy, myositis, and early reinnervation.[117]

5. JITTER AND BLOCKING

Definition and Basic Physiology

A series of single-fiber potentials recorded after repetitive stimulation of the nerve show almost, but not exactly, the same latencies with each stimulus. This latency variability, on the order of tens of microseconds, represents the jitter that serves as a sensitive measure of NMT (Fig. 16-3). The term, previously used in the engineering literature, denotes instability of a time base generator.[19] Repetitive discharges of a single muscle fiber when evoked as H reflex has a greater latency variability than direct responses because of additional instability at the neural synapse between the Group IA afferent and the motoneuron.[46,123] The H-reflex jitter shows a correlation with age, motor unit size, and recruitment threshold.[1,44] Antidromic rather than reflexive activation of a single motoneuron results in F wave with jitter values less than H reflex but more than direct response, indicating a very narrow window that the recurrent discharges must clear (see Chapter 7-2).

Axonal micro-stimulation serves as a convenient way to study the jitter at the individual

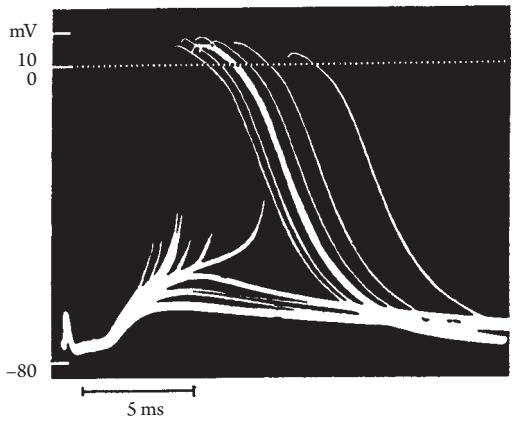

FIGURE 16-3 Endplate potentials (EPPs) and action potentials recorded intracellularly from the endplate region of a human muscle fiber. The inconsistency of neuromuscular transmission time (jitter) results primarily because amplitude and slope of EPP vary from one discharge to the next. (From Elmqvist, Hofmann, Kugelberg et al.,[21] with permission.)

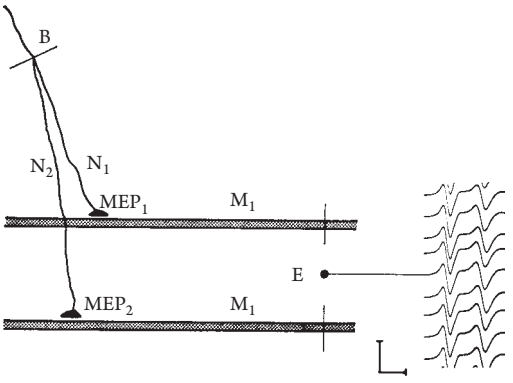

FIGURE 16-4 Determination of jitter by simultaneous recording from two muscle fibers, M1 and M2, within the same motor unit. The potential from M1 triggers the sweep, although the use of a delay line allows its display from the onset. The potential from M2 appears after a short interpotential interval determined by the difference in conduction time from the common branching point (B) to the recording electrode (E). The variability of the interpotential interval (jitter) occurs mainly at the motor endplates, with some contribution from changes in propagation time along the terminal axons and muscle fibers. Calibration in the strip recording: 2 mV and 500 μs. (From Dahlback, Ekstedt, and Stalberg,[15] with permission.)

motor endplates.[116,127] Some propose the use of surface stimulation to further simplify the method.[23] Compared to voluntary activation, the stimulation technique has the advantage of providing perfect control of the discharge rate for quantitative assessments,[5,116,130] although intrusion of F wave may occasionally interfere with jitter measurement.[11] It obviates the need to search for muscle fiber pairs and enables testing of young children and comatose or uncooperative patients, as well as those with impaired voluntary motor control.[127] Jitter values smaller than 4 μs usually indicate muscle rather than nerve activation, thus bypassing the intended NMT. Stimulation technique occasionally reveals abnormalities that otherwise escape detection. For example, bimodal latency distribution seen in patients with myasthenia gravis (MG) implies the presence of dual neuromuscular junction supplied either by a single or two different motoneurons.[127]

Routine jitter measurements in cooperative patients depend on the voluntary activation of muscle to isolate a pair of single-fiber potentials from two muscle fibers innervated by adjacent terminal branches of the same axon (Fig. 16-4). The patient slightly activates the muscle under study, and the examiner moves and rotates the needle until at least two time-locked single potentials appear. Skillful use of triggering mechanisms, coupled with delay lines, allows stable repetition of those discharges on the screen. The interpotential interval, then, represents the difference in conduction time from the common branching point to each fiber within the same motor unit.

In this type of recording, EMG jitter equals the degree of variability in the interval, or the combined variability of the two responses, measured with one of the two discharges taken as a time of reference. This stands in contrast to the jitter measured by stimulation of a single axon, representing the variability of only one response. Statistical analysis shows that the values obtained with voluntary contraction equals $\sqrt{2}$ times the stimulated single-fiber jitter.[116] Any factor influencing the conduction of any component will affect jitter. For example, jitter may result from variability in the conduction of impulses along the nerve and muscle fibers. These factors, however, contribute

little unless the paired potentials show an excessive interval or very rapid firing, as discussed later. Thus, the motor endplate constitutes the main source of jitter in normal muscles.[88] A slight change in the rising slope of the endplate potential (Fig. 16-3) and fluctuation in the threshold of the muscle membrane necessary for generation of an action potential probably account for most of the variability in NMT.[60]

When jitter increases excessively, the second potential fails. This phenomenon, referred to as "blocking," occurs more commonly in pathologic conductions such as MG but also, to a lesser extent, in normal subjects especially after age 50.[20]

Determination of Jitter

Jitter measurement with voluntary activation uses the same techniques as those described for fiber density assessments, except for the need to identify paired single-fiber potentials fulfilling the criteria. If the first of the paired responses triggers the oscilloscope sweep, then the changing delay of the second potential of the pair indicates the variability in the interpotential interval. Jitter may increase erroneously unless the examiner strictly adheres to the recommended criteria to analyze only potentials greater than 200 μV in amplitude with a rise time shorter than 300 μs. Other sources of error include use of an unstable or abnormal endplate[7] or a descending phase of the discharge as a trigger and accepting a potential pair separated by less than 150 μs, which usually results from variability in long muscle fibers doubly innervated at widely separated endplate.[57,58]

Most investigators express jitter as the mean value of consecutive differences (MCD),[17] rather than the standard deviation about the mean interpotential interval, which reflects not only the short-term random variability but also the slow fluctuation in muscle fiber propagation velocity. Superimposed slow latency shifts will cause an increase in the overall value, even though actual jitter between potentials on sequential firing remains the same. In contrast, the comparison of sequential discharges measures only the short-term variation. A series of consecutive differences has the additional advantage of easy computation. Jitter values expressed by this method remain the same during continuous activity lasting up to 1 hour.[17] Most digital instruments offer software for automatic analysis of jitter and display of the results by numeric or graphic means, which obviates manual determination of jitter using photographic superimposition of 50 sweeps in groups of 5 or 10 discharges with a sweep speed of 200 μs/cm or faster.

Muscle fiber propagation slows substantially upon rapid firing, because successive action potentials occur in the relative refractory period of the muscle. This delay may differentially affect the activation of two muscle fibers, depending on the lengths of their respective axon terminals. In general, rapid firing rates tend to increase jitter if the interpotential interval exceeds 4 ms, when physiologic slowing begins to influence two muscle fibers differently. A computer can sort the trials on the basis of firing rate or the interdischarge interval to calculate the corrected MCD, termed *mean sorted interval difference* (MSD).[128] If firing rate has not affected jitter, MCD/MSD = 1. If the ratio exceeds 1.25, one must use MSD instead of MCD because the firing rate has influenced jitter. Conversely, a ratio less than 0.8, indicating slow trends, favors the use of MCD, not MSD.

Normal and Abnormal Jitter Values

Different investigators have applied the technique to various conditions, including studies of laryngeal,[91] masseter,[49,80] orbicularis oculi,[53] frontalis,[6,130,131] and extensor digitorum communis.[52,96] Table 16-2[117] summarizes the jitter values. Jitter measurements may show a different range and higher mean value than those listed if recorded with less time resolution. They also depend on subjects' age, individual muscles tested, and the method of muscle fiber activation. For example, the orbicularis oculi shows a significantly lower jitter than the extensor digitorum communis muscle, with the upper limit of 30 μs for individual motor endplates and of 18 μs for the median of 20 motor endplates.[125] In general, stimulation technique yields a smaller jitter value and fewer percentages of abnormal fibers as expected from the measurement of one endplate rather than two endplates tested with voluntary contraction.

Table 16-2 Jitter in Normal Subjects*

MUSCLES	NUMBER OF POTENTIAL PAIRS	MCD		SD OF MD VALUES FROM INDIVIDUAL SUBJECTS		UPPER NORMAL LIMIT CLOSE TO MEAN + 3 SD
		MEAN	SD	MEAN	SD	
Frontalis	258	20.4	8.8	6.2	2.3	45
Biceps	125	15.6	5.9			35
Extensor digitorum communis	759	24.6	10.6	8.3	3.2	55
Rectus femoris	73	31.0	12.6			60**(65)
Tibialis anterior	153	32.1	15.0			60**(75)
Extensor digitorum brevis	29	85.3	68.6			None

*Jitter (MCD) measured with voluntary activation in normal subjects aged 10–70 years.

**Because of some extremely high values, the data deviate from a Gaussian distribution. None of the normal subjects showed more than one value exceeding 60 μs, which therefore constitutes a more appropriate upper normal limit. (Modified from Stalberg and Trontelj.[115])

Despite these variabilities, blocking in more than one fiber or jitter values exceeding 55 μs constitutes an abnormality in any muscle. Jitter remains relatively constant in the extensor digitorum communis but increases in the tibialis anterior around the age of 50, probably secondary to neurogenic change.[114] Normal muscles show the same jitter regardless of the innervation rates or the recording site relative to the endplate zone. Neuromuscular jitter may increase during continuous voluntary activation in patients with MG, spinal muscular atrophy (SMA), and motoneuron disease (MND), but not in normal subjects.[42]

In most recordings showing an interval of less than 4 ms, changes in conduction time by prior discharge largely cancel out between the two potentials. Thus, the jitters result primarily from variability in NMT. To support this view, nonparalytic doses of tubocurarine, known to block endplate depolarization, causes jitter to increase without changing the shape and amplitude of the single muscle fiber potentials.[19] In pathologic conductions, where the interval may reach many milliseconds, however, variability in the propagation velocity may contribute to the jitter. In fact, jitter changing with the firing rate may reflect the type of underlying pathology. In MG, characterized by postsynaptic defect, the rapid firing rate increases jitter, even with an interval of less than 4 ms. In presynaptic disorders such as Lambert-Eaton myasthenic syndrome (LEMS) and botulism, jitter increases at slow firing rates and decreases at fast rates.

Jitter increases 2–3 μs per degree Celsius as the temperature of the muscle falls from 36°C to 32°C, followed by a more rapid change of about 7.5 μs per degree Celsius thereafter.[107] Despite an increase in the jitter value, a train of stimuli shows a smaller decrement of the compound muscle action potentials (CMAPs) with cooling. A number of factors may contribute to this apparent paradox. Defective release of transmitters at low temperatures would explain the combination of an increased jitter and a smaller decrement; fewer quanta released by the first impulse leave more quanta available for subsequent release. This reduces the number of blocking fibers, which then contributes to increase jitter on one hand and reduces the loss of potentials on the other. Increases in temperature between 35°C and 38°C do not normally change the jitter value.

In normal muscles, jitter may increase during ischemia or following administration of curare. Conversely, cholinesterase inhibitors may mask the findings of increased jitter in patients with MG.[65] Abnormal jitter occurs not only in diseases of NMT but also in many other conditions associated with conduction defects of nerve and muscle. Chronic muscular activity also leads to increased jitter and other minor SFEMG abnormalities presumably caused by mild denervation and reinnervation of nerve terminals.[94] It may also reflect unusually low endplate potentials or a high threshold of the muscle fiber membrane. In general, an increase in jitter values, typically beyond 80–100 μs, accompanies a transmission block of single muscle fiber discharges, which induces a decrement of the CMAP with repetitive nerve stimulation (RNS).[32] Detecting an increase in jitter and impulse blocking helps identify NMT abnormalities earlier than surface recorded responses.[84]

6. USE OF CONCENTRIC NEEDLE FOR JITTER RECORDING

An increasing number of investigators now use a disposable concentric needle to measure neuromuscular jitter, in lieu of an expensive single-fiber needle electrode, which one must reuse to save cost. Signals recorded with concentric needle electrodes frequently represent the summation of many single-fiber action potentials, which will decrease the apparent jitter, making the reference data, a few microseconds lower compared to the traditional SFEMG values. Overall data show that this method, which will facilitate the use of jitter analysis, serves as a good alternative measure of NMT. If interpreted with caution, particularly in borderline cases, concentric needle provides the results acceptable for clinical use.[26,52,53,110, 117]

Recommendations for this technique include the use of the smallest electrode (facial electrode), filter setting of 1000 Hz to 10 KHz, and selection of only those spike components of the MUP with a fast rising slope, which remains unchanged at consecutive discharges. In addition, the time between the triggering peak and individual peaks used for jitter analysis must exceed 150 μs. A jitter value less than 5 μs indicates recording from either split muscle fibers or, less likely, summated rather than single spikes. Facial electrodes have a smaller leadoff surface than conventional concentric electrodes, although still considerably larger than the SFEMG electrode. The narrow filter setting helps exclude activities from remote muscle fibers and severe distortion of the signal. Concentric needle electrodes with a larger uptake radius cannot substitute SFEMG when measuring fiber density. Stimulated jitter recordings, more prone to artifacts with concentric than single-fiber electrodes, probably underestimate abnormality even more than voluntary activation studies. One must, therefore, interpret borderline findings with caution.

7. MACRO AND SCANNING ELECTROMYOGRAPHY

Compared with the single-fiber electrode that covers the radius of some 300 μm, the concentric or monopolar needle records action potentials from a much wider zone with a radius of about 500 μm to 1 mm. Motor unit territories, however, extend much further, varying in size from 5 to 15 mm. To capture the total electrical activity generated by a motor unit, the electrode must have a much greater recording surface. Such an electrode registers activities from a number of motor units because muscle fibers from different units intermingle within the recording zone. Macro EMG using a specially constructed needle circumvents this difficulty by means of an averaging technique (see Chapter 3-2).[101] Macro EMG signals give information about a greater part of the motor unit[105] in contrast to the regional electrical activity measured in conventional studies or the focal pickup recorded in SFEMG (Figs. 16-5 and 16-6). Macro EMG and a surface recorded MUP show a high positive correlation in area and in peak-to-peak amplitude.[79]

Macro potentials differ substantially from the ordinary MUP. A monopolar or concentric needle registers the activities generated by only a few muscle fibers within a 500 μm to 1 mm radius.

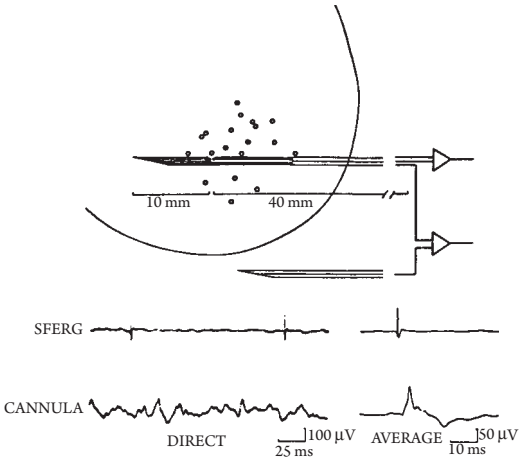

FIGURE 16-5 Principles for macro electromyography. Single-fiber action potentials recorded by a small leading-off surface provide triggers to average cannula activities time locked to the discharge from one muscle fiber. (From Stalberg,[100] with permission.)

In contrast, a macro EMG MUP receives contributions from many more muscle fibers located outside the range of the conventional recording, showing good short-term stability on repeated recording every 15 minutes during a 2-hour period.[38] Macro recording serves better in correlating the size of single motor units to their functional characteristics such as twitch properties.[132] For example, successively recruited motor units show a progressive increase in macro-potential and a decrease in firing frequency, confirming the size principle.[45] In juvenile myoclonic epilepsy, macro-recording shows an increase in MUP amplitude, suggesting an enlargement of motor units.[24] Macro studies show a similar sensitivity as concentric needle EMG in the detection of neuromuscular disorders.[28]

Table 16-3 summarizes the suggested normal data of macro MUP for different age groups. A macro MUP increased in size after the age of 60, in part reflecting reinnervation following physiologic loss of anterior horn cells with age.[16,109] The macro-potential has a 40%–50% smaller amplitude and area when triggered with concentric[43] as compared to single-fiber needle recording,[69] probably reflecting spatial orientation of the macro needle to the motor unit. With this technique, macro-recording showed a better correlation with the area than the amplitude of MUP recorded by a concentric needle both in normal subjects and in patients with myogenic or neurogenic disorders.[8,29]

A variant of macro-study serves to scan the motor unit territory by incrementally advancing the needle with a precision pressure device driven by a motor. The scanning method assesses spatial distribution of motor units and functional structure of the muscles.[35,68] This technique has verified the rearrangement of muscle fibers in disease state, showing the presence of long polyphasic sections as the most striking finding.[106] In one study,[36] most patients with myogenic disorders had a motor unit territory smaller than 4 mm, whereas those with neurogenic processes showed larger values. The sizes of the abnormal

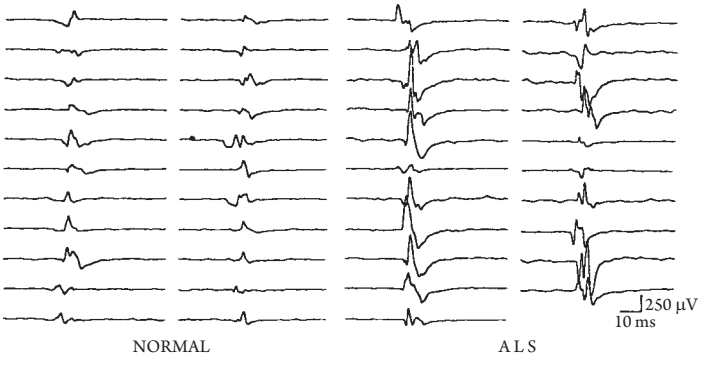

FIGURE 16-6 Examples of macro motor unit potentials recorded from normal muscle and amyotrophic lateral sclerosis. (Modified from Stalberg.[101])

Table 16-3 Macro Electromyography in Normal Subjects (μV)

AGE	BICEPS				VASTUS LATERALIS				TIBIALIS ANTERIOR			
	MEDIAN		INDIVIDUAL MACRO-MUP		MEDIAN		INDIVIDUAL MACRO-MUP		MEDIAN		INDIVIDUAL MACRO-MUP	
	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
10–19	65	100	30	350	70	150	20	350	65	200	30	350
20–29	65	140	30	350	70	240	20	525	65	250	30	450
30–39	65	180	30	400	70	240	20	550	65	260	30	450
40–49	65	180	30	500	70	250	20	575	65	330	30	575
50–59	65	180	30	500	70	260	20	575	65	375	40	700
60–69	65	250	30	650	80	370	20	1250	120	375	45	700
70–79	65	250	30	650	90	600	20	1250	120	620	65	800

(Modified from Stalberg.[101])

units, however, only occasionally exceeded the lower and upper limits of normal, ranging from 2 to 8 mm. In the process of reinnervation, for example, the terminal sprouts from a surviving motor unit respects its own territory, reaching only those denervated muscle fibers from another unit territorially overlapping with the sprouting unit, without extending beyond its own boundary. Thus, the size of the motor unit territory, which seems to remain the same, fails to provide a useful measure for detecting pathology.[106]

In summary, with a modified SFEMG electrode, single-fiber action potentials serve as the trigger for selective averaging of the intended MUP. Based on this principle, macro-technique extracts the contribution from most, if not all, muscle fibers belonging to a motor unit by recording the electrical activity obtained by the electrode shaft during voluntary muscle contraction.[100] During the reinnervation process, SFEMG reveals the dynamics, whereas macro EMG uncovers the topography.[103] The factors that determine the characteristics of macro EMG include number of fibers, fiber diameter, endplate scatter, pattern of nerve branching, motor unit territory, and electrode position.

8. CLINICAL VALUES AND LIMITATIONS

Table 16-4 summarizes the normative data, for various age groups ranging from 10 to 90 years.[12]

A computer-assisted method has rendered SFEMG simple enough to conduct as part of routine studies with a little extra training.[117] The method has clinical and research applications for disorders of nerve and muscle in general and of NMT in particular. It has proven most useful, from an electrodiagnostic point of view, as a test for MG and LEMS, and, to a lesser degree, for a variety of peripheral nervous system disorders, especially in assessing patterns of nerve regeneration.[102] Retrospective and prospective multicenter studies have provided collections of jitter and fiber density data for the purpose of defining reference values for many muscles and different ages.[31] Dynamic analysis suggests that normal NMT jitters result from intrinsic noise rather than from deterministic chaos.[33]

Motoneuron Disease

Disorders associated with abnormal SFEMG include degenerative processes affecting the

Table 16-4 Single-Fiber Electromyography Reference Values

MUSCLE	JITTER VALUES (μs): 95% UPPER CONFIDENCE LIMIT OF NORMAL MEAN CONSECUTIVE DIFFERENCE (MCD)/SINGLE-FIBER PAIRS								
	10 yr	20 yr	30 yr	40 yr	50 yr	60 yr	70 yr	80 yr	90 yr
Frontalis	33.6/49.7	33.9/50.1	34.4/51.3	35.5/53.5	37.3/57.5	40.0/63.9	43.8/74.1		
Obicularis oculi	39.8/54.6	39.8/54.7	40.0/54.7	40.4/54.8	40.9/55.0	41.8/55.3	43.0/55.8		
Obicularis oils	34.7/52.5	34.7/52.7	34.9/53.2	35.3/54.1	36.0/55.7	37.0/58.2	38.3/61.8	40.2/67.0	42.5/74.2
Tongue	32.8/48.6	33.0/49.0	33.6/50.2	34.8/52.5	36.8/56.3	39.8/62.0	44.0/70.0		
Stemocleidomastoid	29.1/45.4	29.3/45.8	29.8/46.8	30.8/48.8	32.5/52.4	34.9/58.2	38.4/62.3		
Deltoid	32.9/44.4	32.9/44.5	32.9/44.5	32.9/44.6	33.0/44.8	33.0/45.1	33.1/45.6	33.2/46.1	33.3/46.9
Biceps	29.5/45.2	29.6/45.2	29.6/45.4	29.8/45.7	30.1/46.2	30.5/46.9	31.0/48.0		
Extensor digitorum communis	34.9/50.0	34.9/50.1	35.1/50.5	35.4/51.3	35.9/52.5	36.6/54.4	37.7/57.2	39.1/61.1	40.9/66.5
Abductor digiti minimi	44.4/63.5	44.7/64.0	45.2/65.5	46.4/68.6	48.2/73.9	51.0/82.7	54.8/96.6		
Quadriceps	35.9/47.9	36.0/48.0	36.5/48.2	37.5/48.5	39.0/49.1	41.3/50.0	44.6/51.2		
Anterior tibialis	49.4/80.0	49.3/79.8	49.2/79.3	48.9/78.3	48.5/76.8	47.9/74.5	47.0/71.4	45.8/67.5	44.3/62.9

Recommended criteria: jitter is abnormal if (1) MCD of 20 fiber pairs is greater than the 95% upper confidence limit; or (2) jitter values exceed the 95% upper confidence limit in more than 10% of action potential pairs.

(*Continued*)

Table 16-4 (Continued)

MUSCLE	FIBER DENSITY VALUES: 95% UPPER CONFIDENCE LIMIT OF NORMAL FOR MEAN FIBER DENSITY								
	10 yr	20 yr	30 yr	40 yr	50 yr	60 yr	70 yr	80 yr	90 yr
Frontalis	1.67	1.67	1.68	1.69	1.70	1.73	1.76		
Tongue	1.78	1.78	1.78	1.78	1.78	1.79	1.79		
Stemocleidomastoid	1.89	1.89	1.90	1.92	1.96	2.01	2.08		
Deltoid	1.56	1.56	1.57	1.57	1.58	1.59	1.60	1.62	1.65
Biceps	1.52	1.52	1.53	1.54	1.57	1.60	1.65	1.72	1.80
Extensor digitorum communis	1.77	1.78	1.80	1.83	1.90	1.99	2.12	2.29	2.51
Abductor digiti minimi	1.99	2.00	2.03	2.08	2.16	2.28	2.46		
Quadriceps	1.93	1.94	1.96	1.99	2.05	2.14	2.26	2.43	
Anterior tibialis	1.94	1.94	1.96	1.98	2.02	2.07	2.15	2.26	
Soleus	1.56	1.56	1.56	1.57	1.59	1.62	1.66	1.71	

Fiber density is abnormal if mean value of 20 observations is greater than the 95% of upper confidence limit. (Modified from Bromberg, Scott, and AD HOC Committee of the AAEM Single Fiber Special Interest Group[12])

anterior horn cell[111] and tetanus.[27] The chronic processes with marked collateral sprouting, such as SMA, show the highest fiber density among MND. Clinical studies revealed an inverse relationship between muscle strength and fiber density.[120] The increased MUP duration found in this entity suggests a mixture of hypertrophic and atrophic fibers. In contrast, rapidly progressive diseases such as amyotrophic lateral sclerosis (ALS) show increased jitter and blocking. Studying the functional status of the motor unit by SFEMG may help establish the diagnosis and prognosis. Detecting abnormalities not apparent clinically or with conventional EMG provides early evidence of motoneuron involvement.

Peripheral Neuropathy

Disorders of the peripheral nerves also show increased jitter, occasional blocking, and increased fiber density. These findings become particularly prominent during the process of reinnervation, for example, up to 1 year after autogenous facial muscle transplants. Mean jitter values usually return to normal approximately 1 1/2 years after the onset of reinnervation, although some individual recordings may remain abnormal permanently.[135]

Polyneuropathies shown to have SFEMG abnormalities include alcoholic neuropathy,[121] diabetic neuropathy with or without clinical symptoms,[93] chronic renal failure,[51] chronic inflammatory demyelinating polyneuropathy (CIDP),[70] critical-illness polyneuropathy,[90] multifocal motor neuropathy (MMN) with persistent conduction block,[56] and idiopathic fecal incontinence.[95] In addition, single-fiber conduction velocity test may allow earlier detection of abnormalities in patients with diabetes melitis.[73]

Macro EMG studies in CIDP revealed an increase in average amplitude probably indicating the loss of smaller motor units rather than reinnervation.[55] Other entities studied by macro EMG include poliomyelitis[82] and diabetic neuropathy,[4] showing a greater increase in amplitude of macro MUP and fiber density in patients with weakness as compared to those with normal strength. These findings indicate incomplete reinnervation characterized by macro abnormality as the cause of the functional loss similar to the post polio syndrome.

Disorders of Neuromuscular Transmission

Normal muscles show increased jitter in 1 of 20 recorded pairs of potentials.[107] Thus, increased jitter or blocking, if found in 2 or more of 20 pairs of potentials, indicates defective NMT. A patient with MG may have normal or increased jitter values within any one muscle, although the facial muscles tend to show more abnormalities. Jitter exceeding 100 μs usually leads to intermittent blocking.[118] In generalized MG, more than 30% of recorded potential pairs show abnormalities in the extensor digitorum communis. Patients with ocular myasthenia may have such findings only in the facial muscles and not necessarily in the limb muscles.[66,74] About 25% of patients with MG have a slightly increased fiber density above the normal range. In one study of 15 myasthenic patients, voluntary activation demonstrated a greater increase in jitter value and proportion of blocking than stimulation technique probably because of different sampling bias between the two methods.[67] Approximately 40% of patients with anti-acetycholine receptor (AChR) antibody-negative MG have muscle-specific kinase (MUSK) antibodies. In one study, more than 70% of 12 MG patients with AChR antibodies had abnormal jitter in both extensor digitorum communis and orbicularis oculi, but the majority of 13 myasthenic patients with MUSK antibodies showing similar clinical scores had abnormal jitter only in orbicularis oculi.[25]

The SFEMG can detect disturbances of NMT before the appearance of clinical symptoms. Thus, normal jitter in a clinically weak muscle tends to exclude the diagnosis of MG.[85] In one series,[118] SFEMG showed an increased jitter or blocking in the hypothenar muscles in all 40 patients with mild to moderate, generalized MG, even though the RNS technique revealed equivocal results in 40% of these patients. In another series,[86] 127 of 131 patients demonstrated defective NMT by

SFEMG, whereas less than 50% of these patients had an abnormality by RNS. Studies of the extensor digitorum communis showed SFEMG abnormalities in 8 of 24 first-degree relatives of 12 patients with juvenile MG. In this asymptomatic group, increased jitter occurred, on the average, in 5 of 20 potential pairs. Hence, only 25% of all recordings showed abnormalities in contrast to 75% in clinically symptomatic patients.[118] In a study of 17 patients with pure ocular myasthenia,[48] SFEMG showed abnormalities in all superior rectus and levator palpebralis and in 62% of orbicularis oculi muscles.[76] In patients with restricted extraocular muscle weakness, 58% developed generalized symptoms if the extensor digitorum communis showed increased jitter initially as compared to 18% of those without such abnormalities.[133]

In general, SFEMG abnormalities correlate well with the clinical course in serial studies of individual patients.[64,84] Administration of edrophonium (Tensilon) usually shortens abnormal jitter and decreases the incidence of blocking, without affecting the initially normal jitters. A therapeutic dosage of AChR medication may also correct jitter in myasthenia. In some cases, however, recovery from blocking in a number of fibers may give an apparent increase in jitter values after treatment. In a healthy subject, anticholinesterase (AChE) has no effect on the jitter value. Indeed, the jitter value remained normal in a patient who had received the medication for years with an incorrect diagnosis of MG.[115] The study may occasionally return to normal during spontaneous remission or after thymectomy, but most of these patients still have increased jitter without blocking.[115]

In the LEMS, a slight increase in fiber density probably results from Type II fiber grouping.[115] In this syndrome, blocking tends to occur at greater jitter values than in MG. In fact, jitter may reach as high as 500 μs, with the interval between the first and last of the second potentials reaching 2 ms for 50 discharges. Other conditions with SFEMG abnormalities include congenital myasthenia.[122] Some patients also have dissociation between jitter values and blocking. In a Japanese case with endplate AChE deficiency,[50] relatively strong first dorsal interosseous muscle showed a low blocking rate (6.2 ± 7.4%) despite markedly increased jitter (227 ± 147 μs) (Fig. 16-7). In-vitro microelectrode study and computer simulation suggested that a reduced endplate potential (EPP) amplitude with an abnormally prolonged delay time constant account for this discrepancy (Fig. 16-3).

In presynaptic disorders such as LEMS, Jjitter values usually improve at high rate of stimulation[13,77] and worsen after rest.[14,83] These findings,though rarely seen in patients with MG, do not necessarily imply a presynaptic abnormality.[126] Serial studies show a corresponding change with remission or after therapy, providing a quantitative measure of the ongoing clinical status.[71,81]

In human botulism,[72] SFEMG may yield a different pattern of abnormality depending on the type of toxin and stage of illness. In two patients with wound botulism, for example, stimulation SFEMG showed increased jitter at a high shock frequency,[61] countering the general principle expected in disorders of ACh release. In four patients given therapeutic botulinum toxin as therapy for blepharospasm, SFEMG demonstrated abnormal NMT in the arm muscles.[87] The time course, as well as the inverse relationship between jitter and the firing rate in the affected muscle, indicated that the toxin spread remotely from the site of injection.

Myopathy

Dystrophic muscles in general have an increased fiber density and jitter, although some recordings may also show a decreased jitter. Macro EMG studies indicate a normal diameter of motor units with no signs of abnormal volume conduction. These findings suggest a remodeling of the motor unit as the result of fiber loss, fiber regeneration, and reinnervation. The increased fiber density probably reflects a localized abnormality in the distribution of muscle fibers within each motor unit. Fiber density may change after reinnervation of a portion of the muscle fiber separated from the endplate by transverse lesions, as shown in Duchenne dystrophy. Alternatively, fiber density may reflect new innervation of regenerating muscle fibers or splitting of muscle fibers.[97]

In one series,[99] patients with Duchenne muscular dystrophy (DMD) had a markedly increased fiber density, averaging 3.5 initially and less in the late stage, although still above the normal value of 1.45. Another series showed increased jitter in about 30% of the recordings in each muscle and occasional blocking in 10% of the recordings.[112] Interestingly, some pairs had jitter values below the normal range, suggesting the potential originating from split muscle fibers, which share a common innervation zone.[41] In support of this view, pairs with reduced jitter always block simultaneously when subjected to tubocurarine or other agents that inhibit NMT. Ordinary potential pairs would show clear dissociation with this type of inhibition. Fiber density also increases in limb-girdle dystrophy (LGD), but to a lesser degree than in DMD. In one series,[98] studies of clinically weak muscles showed increased jitter in 54% of the recordings and blocking in less than 10%. In another series of 20 patients,[92] SFEMG confirmed the original diagnosis in 16 unequivocal cases and helped differentiate 4 indeterminate cases into myopathic and neurogenic categories. Patients with facioscapulohumeral dystrophy (FSHD)[98] and chronic progressive external ophthalmoplegia (CPEO)[54] had findings similar to those reported in LGD.

In another study of 56 patients, SFEMG and histochemistry revealed a slightly increased fiber density in the majority of patients with acid maltase deficiency, LGD, and myositis and in nearly half of those with mitochondrial myopathy.[10] In contrast, patients younger than 40 with muscle phosphorylase deficiency, myotonia congenita (MC), or hypokalemic periodic paralysis

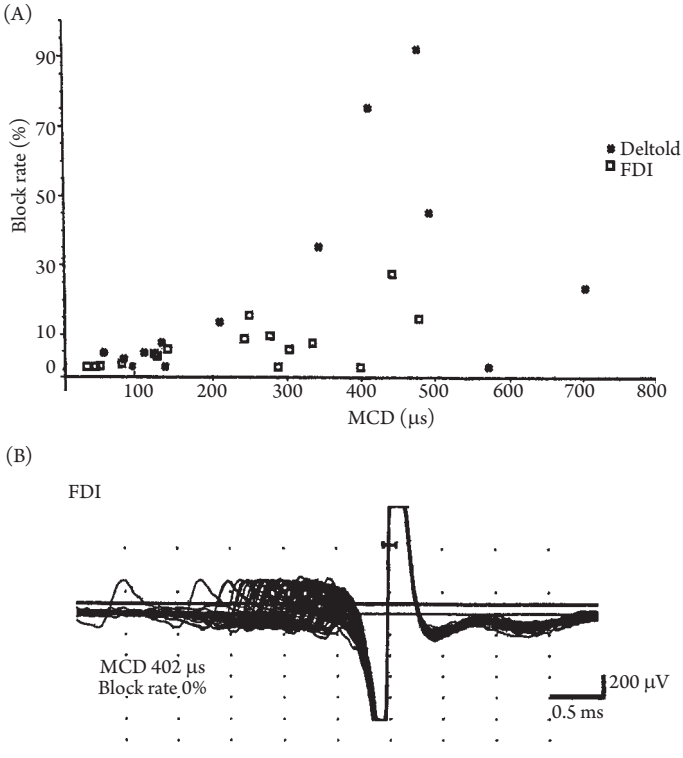

FIGURE 16-7 Single-fiber electromyography (SFEMG) showing dissociation between jitter values and blocking. (*A*) Deltoid (shown by X) revealed markedly increased jitter with high blocking rate, whereas FDI (open squares) with equal jitter had a significantly lower blocking rate. Several pairs showed little blocking despite the extremely large MCD jitter. (*B*) An example of SFEMG recorded from the FDI, showing extremely large jitter (402 μV) without blocking. (Modified from Kohara, Lin, Fukudome, et al.[50])

(HyperPP) had no abnormality. In myositis, a segmental degeneration separates a portion of the affected muscle fiber from its motor endplate. Collateral sprouts then reinnervate the denervated portion of the muscle fiber. This probably accounts for the presence of fibrillation potentials, increased fiber density, and increased jitter and blocking.[40] In myotonic dystrophy (DMI), high-frequency discharges recorded in SFEMG show a progressive decrease in amplitude and increase in rise time. In one series,[63] fiber density and jitter exceeded the normal range in 84% and 20% of the measurements. Other conditions associated with SFEMG abnormalities include inclusion body myopathy (IBM).[39]

Other Disorders

Other disorders not overtly associated with neuromuscular disorders also show SFEMG abnormalities, possibly implicating subclinical disturbance of muscle fibers. These include idiopathic scoliosis,[124] post-viral fatigue syndrome,[47] multiple sclerosis (MS),[134] acute quadriplegia,[62] migraine,[3,120] mitochondrial cytopathy,[34] and healthy muscle following a period of disuse.[37]

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PART V

Neuromuscular Transmission and Muscle Excitability

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17

Anatomy and Physiology of the Neuromuscular Junction

Abbreviations: ACh—acetycholine, AChE—acetylcholinesterase, AChR—acetycholine receptor, AChR-Ab—acetycholine receptor antibodies, CMAP—compound muscle action potential, CMS —congenital myasthenic syndrome, ECC—excitation-contraction coupling, EMG—electromyography, EPP—endplate potential, EPSP—excitatory postsynaptic potential, LEMS—Lambert-Eaton myasthenic syndrome, MEPP—miniature endplate potential, MG—myasthenia gravis, MuSK —muscle-specific tyrosine kinase, NMT—neuromuscular transmission

1. INTRODUCTION

The neuromuscular junction, a synaptic structure, consists of the motor nerve terminal, junctional cleft, and muscle endplate. Its chemical mode of transmission has fundamentally different properties from the electrical propagation of impulses along the nerve and muscle.[48] For example, the release of acetylcholine (ACh) ensures unidirectional conduction from the axon terminal to the muscle endplate. The same basic principle applies to synaptic transmission in a sequence of neurons and neuromuscular junction.[35] In contrast, an impulse conducts bidirectionally along the nerve axons from the point of stimulus unless it originates at the cell body or axon terminal as expected for any physiologic activation. The muscle fibers also show bidirectional propagation of impulse initiated at the motor point. Other characteristics common to nerve synapse and neuromuscular junction include a synaptic delay of a fraction of a millisecond and the nonpropagating nature of endplate potentials (EPPs). These local deporalizations cause no refractoriness, unlike the all-or-none response of nerve or muscle action potentials. The graded responses summate temporally as well as spatially after subliminal stimuli, thereby providing greater flexibility and adaptability. As in a synapse, the mobilization store must continuously replenish the liberated transmitters. Otherwise, the neuromuscular junction would fail with depletion of immediately available molecules.

This section provides a simplified overview of neuromuscular transmission (NMT) in preparation for a subsequent, more detailed clinical discussion (see Chapter 26). The presynaptic ending contains many minute vesicles, each with up to 10,000 ACh molecules. At rest, these vesicles randomly migrate into the junctional cleft, binding to and opening the ACh receptor (AChR). This allows an entry of cations into the postsynaptic membrane producing small depolarizations of the muscle fiber. These miniature EPPs (MEPPs) do not attain the critical level for generation of a muscle action potential. Activation of the nerve voluntarily or by electrical stimulation leads to the following sequence of events for muscle contraction. Depolarization of the presynaptic ending at the axon terminal triggers an influx of calcium, initiating the calcium-dependent release of immediately available vesicles into the junctional cleft. The greatly enhanced and synchronized ACh activity gives rise to a nonpropagated EPP from summation of multiple MEPPs. When the EPP exceeds the excitability threshold of the muscle cell, opening of the voltage-dependent sodium channels causes the generation of an action potential. Propagation of the muscle potential activates the contractile elements through excitation contraction coupling (ECC).

2. ANATOMY OF THE NEUROMUSCULAR JUNCTION

Endplate

Nerve and muscle become dependent on each other during the course of embryogenesis. The formation of the neuromuscular junction follows differentiation of the presynaptic nerve terminals, innervation of the postsynaptic components, and elimination of the remaining multiple axons.[84] The name *motor endplate* originally implied the specialized efferent endings that terminate on a striated muscle, as a whole. Most authors, however, now use the term to describe the postsynaptic membrane of the muscle alone. Each muscle fiber usually has only one endplate, and each branch of a motor axon innervates one endplate. The motor nerve fiber loses the myelin sheath at the nerve terminals, which, therefore, have only the Schwann cells separating them from the surrounding tissue. Thus, the neuromuscular junction consists of the motor nerve ending, Schwann cell, and muscle endplate (Fig. 17-1). At the junctional region, the nerve ending also loses the Schwann cells, forming a flattened plate lying within a surface depression of the endplate. This indentation of the muscle fiber, called a synaptic gutter or a primary synaptic cleft, measures about 200–500 Å deep. The thickened postsynaptic membrane in this region has narrow infoldings, called junctional folds or secondary clefts. A large number of mitochondria, nuclei, and small granules accumulate close to the secondary clefts. Many mitochondria and synaptic vesicles also lie in the axon terminals just proximal to the presynaptic membrane.

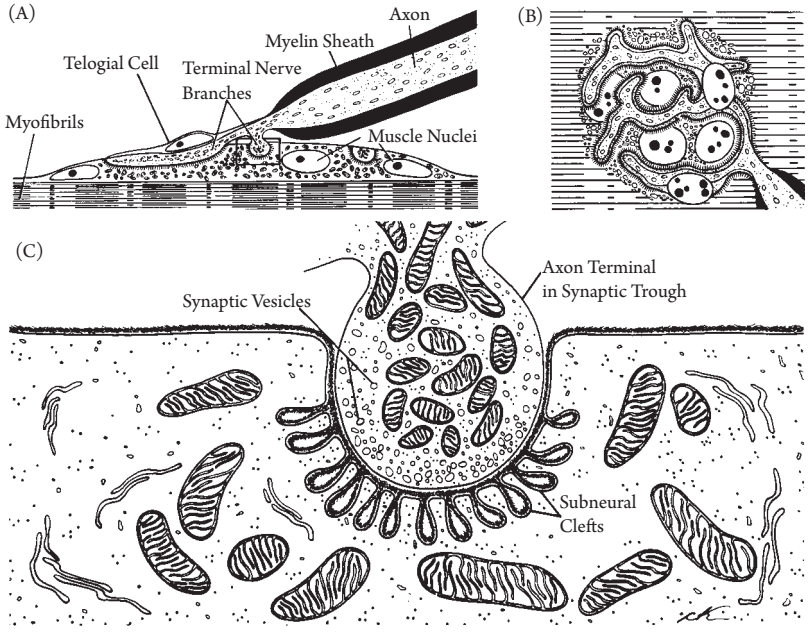

FIGURE 17-1 Motor endplate as seen in histologic sections in the long axis of the muscle fiber (*A*) and in surface view under the light microscope (B), and a section through the motor endplate under the electron microscope (*C*) (area in the rectangle in A). The myelin sheath ends at the junction where the axon terminal fits into the synaptic cleft. The Schwann (teloglia) cells cover the remaining portion without extending into the primary cleft. The plasma membrane of the axon (axolemma) forms the presynaptic membrane and that of the muscle fiber (sarcolemma), the postsynaptic membrane of the endplate. Interdigitation of the sarcolemma gives rise to the subneural or secondary clefts. The axon terminal contains synaptic vesicles and mitochondria. (From Bloom and Fawcett,[10] with permission.)

Electron microscopic studies have delineated the ultrastructural features of the endplates in human external intercostal muscles.[30] The presynaptic nerve terminal contains clear, round synaptic vesicles. They lie mostly clustered in the regions called active zones identified as the site of ACh release into the synaptic cleft. On average, a nerve terminal that occupies an area close to 4 μm^2 contains approximately 50 synaptic vesicles per square micrometer. The synaptic basal lamina interposed between the nerve terminal and muscle cell has special molecular composition containing, among other molecules, acetylcholinesterase (AChE).[69] The postsynaptic membrane, 10 times longer than the presynaptic membrane, forms elaborate invaginations, or junctional folds, containing a concentration of AChR.[82] The postsynaptic folds cover an area about two and a half times that of the terminal itself. Diseases of neuromuscular transmission alter the endplate profile (Fig. 17-2). In myasthenia gravis (MG), the terminal occupies less area with a simplified appearance of the postsynaptic folds. In contrast, the terminal seen in the Lambert-Eaton myasthenic syndrome (LEMS),[59] though normal in area, contains an elongated and sometimes markedly hypertrophic postsynaptic membrane. Neither disease shows alteration in the mean synaptic vesicle diameter nor mean synaptic vesicle count per unit nerve terminal area. Ultrastructural studies of clinically unaffected limb muscles may reveal characteristic abnormalities of the motor endplate in patients with ocular myasthenia gravis.[89]

Synaptic Vesicles

Minute intracellular structures, 300–500 Å in diameter, encapsulate ACh molecules inside the presynaptic axoplasm. In addition to the synaptic vesicles, the nerve endings contain high concentrations of choline acetyltransferase, which

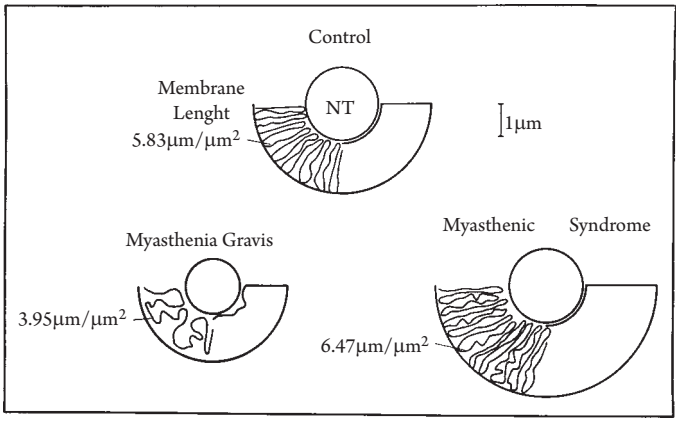

FIGURE 17-2 Schematic representation of the motor endplates in control, myasthenia gravis, and myasthenic syndrome drawn to the scale of the mean figure. The diagram shows an oversimplification of the postsynaptic membrane in myasthenia gravis and marked hypertrophy in myasthenic syndrome. (From Engel and Santa,[29] with permission.)

synthesizes ACh, and AChE, which hydrolyzes ACh. The proximal portions of neurons, though to a much lesser extent, also process the neurotransmitter and the two enzymes. This finding suggests that enzymatic synthesis takes place in the cell body before its transport to the nerve terminals. Each vesicle contains 5000–10,000 molecules of ACh or a quantum.[47] Some quanta (about 1000) located adjacent to the cell membrane form an immediately available store for release. Many more (10,000), contained in the mobilization store, move toward the membrane to continuously replace liberated ACh. The remaining and largest portion of quanta (300,000), or the main store, supplies the mobilization store as a reserve.

Acetylcholine Receptors

The nicotinic AChR, a transmembrane glycoprotein, comprises five subunits, two α (alpha) and one β (beta), γ (gamma), and δ (delta) each in the fetus, and two α and one β, ε (epsilon), and δ each in the adult, forming an ion channel. Binding of two ACh molecules to two specific sites of α subunits opens the ACh channel, allowing cations to flow through the postsynaptic membrane, with the net result of depolarization.[65] Patch-clamp studies have shown bursts of ACh channel activation, alternating open intervals and brief closures.[14] Synaptic maturation with switching from γ to ε subunit results in change of channel open time and consequently conductance. Studies of the kinetic properties of the normal AChR[70] help elucidate pathologic alterations seen in some congenital myasthenic syndromes (CMSs).[31]

3. ELECTRICAL ACTIVITY AT THE ENDPLATE

Miniature Endplate Potential

Many resting muscle fibers show a spontaneous subliminal electrical activity, the MEPP. It represents a small depolarization of the postsynaptic membrane induced by sustained but random release of a single quantum of ACh from the nerve terminal.[34] An ordinary needle electrode placed near the endplate of the muscle fibers can record MEPP as endplate noise (see Chapter 13-4). A microelectrode inserted directly into the endplate region achieves a higher resolution for quantitative analysis. Each ACh quantum liberated from the nerve terminal contains a nearly equal number of ACh molecules, irrespective of external factors such as temperature or ionic concentration. In contrast, the MEPP frequency varies over a wide range, increasing with elevated temperatures and upon depolarization of the motor nerve terminals. It decreases with deficiency of calcium, the ion known to enhance quantal release by increasing fusion of the ACh vesicles with the nerve terminal membrane.

The factors that dictate the MEPP amplitude, or quantum size, include the number of ACh molecules in a vesicle, diffusion properties of the liberated molecules, structural characteristics of the endplate, and AChR sensitivity. In normal human intercostal muscles, an MEPP recurs roughly every 5 seconds, measuring approximately 1 mV in amplitude when recorded intracellularly.[21] Hence, the MEPP falls far short of the excitability threshold of the muscle fiber, averaging about 2%–4% of the EPP generated by a volley of nerve impulses. A small dose of curare greatly reduces the MEPP amplitude, whereas an equivalent dose of neostigmine (Prostigmin) shows a reverse effect. The same MEPP, when recorded extracellularly with an electromyography (EMG) needle, gives rise to an endplate noise measuring about 50 μV (see Chapter 13-4). The MEPP ceases after denervation or nerve anesthesia. In MG, AChR insensitivity results in reduced MEPP amplitude, despite normal discharge frequency. Conversely, defective release of ACh reduces the rate of firing in the LEMS and botulism, although the MEPP remains normal in amplitude (see Chapter 26-2 through 5).

Events Related to Muscle Action Potential

In the resting state, the interior of the muscle fibers registers approximately 90 mV negativity relative to the exterior. This transmembrane potential primarily results from an unequal distribution of inorganic ions across the membrane with a high concentration of potassium intracellularly and of sodium and chloride extracellularly (see Chapter 2-2). It also depends on differential permeability across the muscle membrane with a high conductance for potassium and chloride and low conductance for sodium. The energy-dependent sodium-potassium pump counters a slight inward movement of sodium and outward movement of potassium at steady state to maintain the electrochemical potential equilibrium (see Fig. 2-1 in Chapter 2).

As mentioned earlier, spontaneous release of a single quantum of ACh induces an MEPP that falls far below the critical level necessary for generation of a muscle action potential. With the arrival of a nerve impulse, depolarization of the motor nerve ending initiates an influx of calcium into the motor axons. The increased amount of calcium accelerates fusion of the vesicle membrane with the nerve terminal membrane, thereby producing a large increase in the rate of quantal release. Massive synchronized release of ACh triggered by the arrival of a nerve action potential results in summation of MEPP, giving rise to a localized EPP. The number of immediately available ACh quanta and the concentration of calcium within the axon terminal together determine the size of the EPP. The number of quanta emitted per nerve impulse, or quantum content, averages 20–25, based on the amplitude ratio, EPP/MEPP.

Endplate Potential

Like an MEPP, an EPP results from depolarization of the motor endplate by ACh. The opening of AChR by the synaptic transmitter increases the conductance of various positively charged ions, principally those of sodium and potassium. Therefore, these ions move freely down their electrochemical gradients, resulting in the net effect of depolarization of the motor endplate. The rise time, amplitude, and duration characterize this nonpropagated local response, which declines rapidly with distance. It normally begins about 0.5 ms after the release of ACh, reaches its peak in about 0.8 ms, and decreases exponentially with a half decay time of about 3.0 ms. The EPP, a graded, as compared to all-or-none response, increases in proportion to the number of ACh quanta liberated from the nerve terminal. The sensitivity of the endplate to the depolarizing action of ACh also affects the degree of depolarization. Like the excitatory postsynaptic potential (EPSP), two or more subthreshold changes generated in near synchrony could summate to cause a larger EPP, which may exceed the critical level for generation of an action potential.

4. EXCITATION-CONTRACTION COUPLING

Generation of Muscle Action Potential

When the EPP exceeds the threshold or the critical level of depolarization to open the sodium channel, it generates an all-or-none muscle action

potential. A molecular change of the depolarized membrane results in selective increase of sodium conductance, followed by an increase of potassium conductance. As long as depolarization reaches the critical value, this phenomenon, inherent in the muscle membrane, occurs irrespective of the nature of the stimulus. The all-or-none characteristic that dictates the amplitude based on sodium channel kinetics does not apply to the latency of the action potential, which varies depending on the speed of depolarization. This variability forms the source of jitter in single-fiber studies (see Chapter 16-5), which serves as a sensitive measure of subtle alteration of the endplate. For example, even healthy muscle shows reversible changes of NMT after a period of disuse.[41] Once generated at the endplate, the action potential propagates bidirectionally to the remaining parts of the fiber. The impulse conducts only in the range of 3 to 5 m/s along the muscle membrane, compared with 50 to 60 m/s over the nerve (see Chapter 13-8). A neuromuscular block results when the EPP fails to reach the critical level with insufficient liberation of ACh from the axon terminal or reduced sensitivity of the muscle endplate. Although each muscle fiber generates a muscle action potential in an all-or-none fashion, the CMAP shows a graded response in proportion to the number of activated muscle fibers.

Transverse and Longitudinal Tubules and Triad

The spread of action potential from the motor endplate to the transverse tubules initiates muscle contraction. This process, called ECC, links electrical activity to mechanical force.[76] Simultaneous recording of the CMAP and the onset of movement allows calculation of ECC time by the latency difference between the two as shown in abductor pollicis brevis[58,72] and masseter muscle.[88] A delayed ECC time of the masseter muscle documented in MG patients showed a correlation with the bite force, possibly contributing to muscle weakness (see Chapter 26-2).[88]

Electrical activity of a muscle fiber consists of two temporally separate components attributable to different structures within the fiber.[15] The first portion originates at the motor endplate and spreads along the outer surface of the muscle fiber. The second part occurs within a complex tubular system that surrounds and interpenetrates the muscle fiber. This network, called the transverse tubules because of its orientation relative to the axis of the muscle fiber, lies at the junctions of the A and I bands in humans (see Fig. 12-1 in Chapter 12). These tridimensional tubules, though structurally internal to the cell, contain extracellular fluid, rendering the inside of the tubule electropositive relative to the outside surrounded by intracellular fluid. Muscle action potentials propagate along the tubules into the depth of the muscle.

A second tubular system, called the longitudinal tubule or sarcoplasmic reticulum, surrounds the myofibrils of a muscle fiber (Fig. 17-3). These tubules have longitudinal orientation with respect to the myofibrillar axis and, unlike transverse tubules, form a closed system devoid of continuity with either extracellular fluids or sarcoplasm. They appear as fenestrated sacs surrounding the myofibrils. The longitudinal tubules expand to form bulbous terminal cisterns on both sides of the transverse tubules, where they come into close contact. The two terminal cisterns and one interposed transverse tubule form a triad in longitudinal sections of the muscle.

Role of Calcium Ions

Propagated action potentials invade the muscle fibers along the transverse tubules to come into contact with the terminal cisterns of the longitudinal tubules at the triad. This coupling process to the sarcoplasmic reticulum gives rise to a small electrical potential referred to as an intramembranous charge movement.[13] The action potential crossing the terminal cistern initiates the release of calcium from the longitudinal tubules into the sarcoplasm that surrounds the myofilaments. The presence of calcium here in turn triggers a chemical interaction that leads to the formation of bridges between thin and thick filaments. Sliding of thin filaments against thick filaments results in contraction of the myofibril (see Chapter 12-2). At the end of the muscle action potential, rapid resequestering of calcium into the longitudinal tubules lowers its concentration

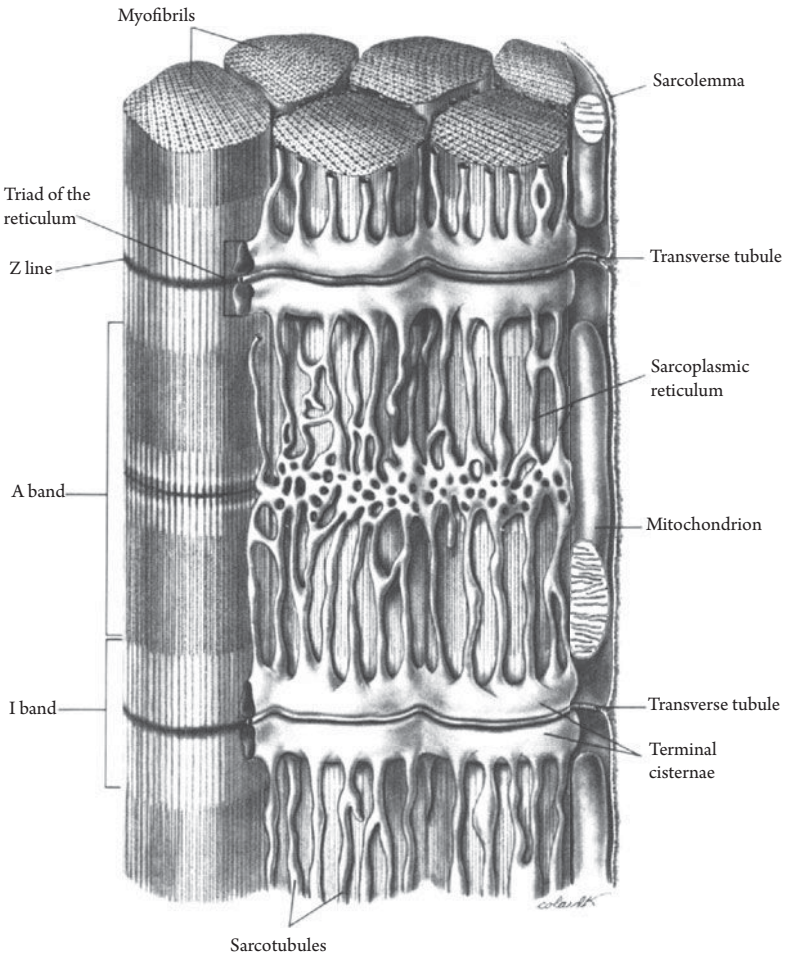

FIGURE 17-3 Anatomic relationship between the perpendicularly oriented longitudinal and transverse tubules. Propagating muscle action potentials initiate electromechanical coupling at the triad of the reticulum, which consists of two terminal cisterns of the longitudinal tubules and one transverse tubule between them. (From Bloom and Fawcett,[10] with permission.)

in the sarcoplasm. The myofibers relax as adenosine triphosphate breaks the existing bridges between filaments.

5. ABNORMALITIES OF NEUROMUSCULAR TRANSMISSION

Postsynaptic Defect in Myasthenia Gravis

In MG (see Chapter 26-2), intracellular recordings from the intercostal muscles have revealed reduced amplitude of MEPP or small quantum size but normal or nearly normal discharge frequency.[21] Consequently, EPP elicited by a nerve impulse also shows a reduced amplitude, despite a normal number of ACh vesicles liberated by a single volley, or quantum content. On repetitive stimulation, the number of quanta released falls gradually, as it does in normal muscle, causing a further decrease in the amplitude of the initially small EPP. With successive stimuli, the EPP becomes insufficient to bring the membrane potential to the critical level in a progressively greater number of fibers, thus causing reduction in CMAP amplitude. Neuromuscular transmission fails first in small motor units, perhaps

because they have a lower margin of safety than the large motor units.

Reduction in MEPP amplitude suggests (1) decreased numbers of ACh molecules per vesicle, (2) diffusion loss of ACh within the synaptic cleft, or (3) reduced sensitivity of the AChR. Early studies suggested normal postsynaptic sensitivity to carbachol and decamethonium added to the bath solution.[22] A presynaptic abnormality proposed on the basis of this finding, however, has subsequently received neither morphologic nor electrophysiologic confirmation. Indeed, micro iontophoretic application of ACh at the endplate region has since disclosed impaired postsynaptic sensitivity.[1] The observed electrophysiologic changes may also imply diffusional ACh loss resulting from alterations in postsynaptic membrane structure.

Ultrastructural histometric studies in myasthenic intercostal muscles have shown a distinct endplate profile, indicating postsynaptic membrane abnormalities.[30] Another experiment has revealed three types of neuromuscular junctions in the surface fibers of internal and external intercostal muscles of MG patients.[1] One group with mild morphologic alterations had an EPP of sufficiently large amplitude to trigger an action potential. A second group with a grossly altered postjunctional membrane showed marked reduction not only in amplitude but also in MEPP frequency and EPP amplitude. The last group had the totally degenerated endplates showing neither MEPP nor EPP.

Not every myasthenic endplate shows morphologic alterations, despite diminished MEPP amplitude demonstrated uniformly. Therefore, changes in endplate geometry per se may not totally explain the physiologic defect. Myasthenic muscles have a decreased number of functional receptor sites detected by radioactively labeled alpha-bungarotoxin, a snake venom that binds to the AChR.[33] Further, the number of functional AChR, when counted by this technique, shows a positive correlation with the mean amplitude of MEPP.[50] These findings indicate the presence of an AChR abnormality in MG. To support this view, partial blocking of the AChR with curare produces a similar physiologic defect. Thus, the auto antibody against nicotinic AChR must play an important role impairing NMT in MG and experimental autoimmune MG.[40,97] Indeed, intercostal muscle biopsies show reduced number of AChR and binding of antibodies to many of the remaining receptors in patients with MG.

Antibodies mediate obstruction of the AChR, presumably by binding with complement to the receptor zone of the postsynaptic membrane.[26] Studies using plasma exchange have revealed an inverse relationship between clinical muscle strength and antibody titers. Cytokines produced by $CD4^+$ and $CD8^+$ T helper cells mediate the production of anti-AChR antibodies (AChR-Ab),[96] sometimes induced by an external stimulus.[6] Other autoantibodies include those against muscle-specific receptor tyrosine kinase (MuSK), reported in 20%–40% of patients with AChR-Ab negative MG.[32,62,68,85] Patients with thymoma often have striational antibodies in addition to anti-AChR-Ab.[51] This may interfere with calcium release from the sarcoplasmic reticulum, resulting in a defect of ECC and contractility reported in myasthenic muscles.[75]

Experimental Models in Animal

Experimental autoimmune MG shares the morphologic and physiologic abnormalities with human disease.[20,37,44,61,80] Studies in rats showed a reduction in receptor content and an increase in receptor-bound antibody. Thus, defective neuromuscular transmission seems to result from a reduced number of fully active receptors. Typical histologic and electrophysiologic myasthenic features develop in mice after passive transfer of human serum fractions obtained from patients with MG.[87]

Intracellular recordings from muscle endplates of immunized rabbits show reduced MEPP amplitude but a normal number of ACh quanta released per nerve impulse.[23] Rats with chronic experimental myasthenia have the same MEPP changes despite normal ACh output at rest and during stimulation.[54] With passive transfer of human MG serum to rats, this abnormality develops after the first 24 hours rather than immediately, reaching minimum levels by 6 days.[46] The delayed development of this nature suggests a more complex mechanism by IgG antibodies[46] than a simple block of AChR like that caused by curare.

Similarly, despite a precipitous drop of antibody titers, electrophysiologic findings in MG patients usually show an improvement with a delay of at least 7 days from the start of plasmapheresis.[12]

Presynaptic Defect in Lambert-Eaton Myasthenic Syndrome

In the LEMS (see Chapter 26-3), myasthenia of skeletal muscles and autonomic symptoms result from an autoimmune mechanism against the voltage-gated calcium channel located in motor nerve terminal[60,73,77,83] and parasympathetic nerve.[45,92,93] In contrast to the receptor insensitivity of MG, defective release of ACh quanta characterizes the LEMS. Microelectrode recordings from excised intercostal muscles reveal no abnormality in MEPP amplitude or in quantum size, indicating normal sensitivity of the muscle endplate to ACh. The MEPP discharge frequency, however, does not increase as expected in response to depolarization of the motor nerve terminal.[59] Thus, a single nerve impulse releases a smaller number of ACh quanta than normal. A decreased quantum content gives rise to a reduced EPP, which fails to trigger an action potential in many muscle fibers, leading to a drastic reduction in CMAP amplitude.

The defect improves immediately with various maneuvers to prime the nerve terminals. For example, the EPP augments progressively with repetitive stimulation of the nerve. This postexercise augmentation lasts longer after cooling, which reduces the rate of calcium removal from the nerve terminal.[64] An increase of external calcium or the addition of quinidine also enhances the EPP. These findings suggest a normal number of quanta available in the presynaptic store despite a low probability of quantum release at the nerve terminal. Indeed, ultrastructural studies have revealed no alteration in the mean nerve terminal area or in the synaptic vesicle count per unit.[30]

Pathophysiology of Congenital Myasthenic Syndromes

Various types of CMS result from different types of presynaptic or postsynaptic mechanisms caused by one or more specific genetic abnormalities (see Chapter 26-4).[7,28,39,53,81] They comprise a number of myasthenic disorders not associated with detectable anti AChR-Ab. These entities, presenting at birth or in early life, have distinct etiologies identified by physiologic, ultrastructural, and cytochemical studies but share many common clinical characteristics. Typical patients have such features as deficient muscle AChE, decreased frequency but normal MEPP amplitude, decreased number of quanta liberated per nerve impulse, small nerve terminals, and focal degeneration of the postsynaptic membrane. In some types, a low number of quanta released per EPP primarily reflect a reduced store of ACh vesicles rather than a low probability of release seen in a classic LEMS. A congenital defect in the molecular assembly of AChE or its attachment to the postsynaptic membrane also represents a basic abnormality. A familial CMS shows deficient synthesis of ACh.[43]

The syndromes adequately characterized to date include AChR deficiency,[24,49] defective resynthesis or vesicular packaging of ACh,[71] AChR deficiency such as congenital paucity of secondary synaptic clefts,[95] kinetic dysfunction of AChR such as slow channel syndrome,[38] high-conductance, fast channel syndrome[31] and other abnormalities of interaction with ACh,[90] and familial limb-girdle myasthenia with tubular aggregates.[36]

Effect of Toxins and Chemicals

A number of other conditions show abnormalities of ACh release, which reduces the EPP. This includes a neuromuscular block by botulinum toxin (see Chapter 26-5),[66,79] which results neither from blockage of calcium entry into the nerve nor from reduced storage of ACh vesicles. The toxin interferes with the ACh release process itself by blocking exocytosis at the release sites, for example, by cleaving synaptic protein 25. Thus, reduced frequency of the MEPP, not affected by the addition of calcium, recovers after the administration of spider venom, which is known to neutralize the toxin.

High concentrations of magnesium block neuromuscular transmission.[11,86] Lowering the temperature increases transmitter release and reactivates previously paralyzed muscle with

botulinum toxin but not in normal muscle blocked by high magnesium concentration.[63] Experimental evidence indicates an inhibitory effect of manganese on transmitter release at the neuromuscular junction.[4] The long-term use of various nondepolarizing neuromuscular blocking agents can also cause prolonged muscle weakness.[5]

Aminoglycoside antibiotics such as neomycin and kanamycin not only interfere with ACh release directly[3,55] but also inhibit the transmission by postsynaptic block.[17] Other drugs associated with dysfunction of NMT include cocaine,[8,16] HIV protease inhibitor, ritonavir,[78] and D-penicillamine used to treat rheumatoid arthritis[19] and Wilson's disease.[2] In addition, β-blockers[52] and calcium channel blockers[94] may aggravate MG or induce a myasthenic syndrome.

6. TIME COURSE OF NEUROMUSCULAR TRANSMISSION

Repetitive Discharges after Single Stimulation

The size of immediately available store and calcium concentration at the nerve terminal determine the number of ACh molecules released by a nerve action potential. Single nerve shocks may excite muscle fibers twice or, rarely, three times or more if enough ACh molecules remain after the first discharge, as in CMS with AChE deficiency (see Chapter 26-4). Excess amount of ACh may result from the use of anticholinesterase as therapy for MG[25] or after organophosphate poisoning.[9] Reactivation of muscle response results despite normal amount of ACh molecules in the slow channel syndrome with prolonged depolarization.[27,74] In this entity, as in organophosphate poisoning and AChE deficiency (see Figs. 18-10 and 18-11 in Chapter 18), repetitive stimulation of the nerve shows a rate-dependent decrement of all muscle potentials, although secondary responses diminish first.[42,57,91]

Effects of Paired or Repetitive Stimulation

Repetitive stimulation affects the release of ACh and EPP in two opposing manners. On the one hand, the first shock utilizes a portion of the store, partially depleting the amount of ACh available for subsequent stimuli until the mobilization store has refilled the loss. On the other hand, calcium accumulates in the nerve terminal after each shock, enhancing ACh release. These two competing phenomena, though initiated by the same stimulus, follow different time courses.

Influx of calcium into the terminal axons takes place immediately after depolarization of the nerve, but the ion diffuses out of the axon over the next 200 ms. Hence, paired or repetitive stimulation with a shorter interstimulus interval causes accumulation of calcium. Such fast rates of stimulation, therefore, tend to facilitate release of ACh, despite concomitant reduction of its immediately available store. In contrast, slower rates of repetition result in suppression with loss of ACh stores, which negligible accumulation of calcium cannot counter (see Chapter 18-5). The dichotomy between the fast and slow rates of stimulation, however, does not always hold. For example, even at high rates of stimulation, ACh depletion far exceeding its mobilization store will lead to reduced release of the transmitter. The partially depleted ACh store recovers exponentially in 5–10 seconds through slow reloading of ACh at the ejection sites.

Neuromuscular Depression and Facilitation

A physiologic reduction in the number of ACh quanta released by the second shock given more than 200 ms later results in a smaller EPP, which fails to activate the muscle fibers with insensitive Ach receptors. The loss of these fibers makes the second CMAP smaller than the first response. Conversely, a physiologic increase in the number of ACh quanta released by the second shock given less than 200 ms later induces a larger EPP based on the neurosecretory potentiation. This results in a larger CMAP through recruitment of muscle fibers not activated initially, if any, because of deficient ACh release. The greater amplitude and area under the waveform in recruitment usually implies the discharge of additional muscle fibers. An increased amplitude may also result from two other physiologic mechanisms: summed EPP

elicited by paired shocks with a very short interstimulus interval[17] and synchronization of different muscle fibers. In the latter phenomenon, called pseudofacilitation, the area under the waveform, which approximates the number of active muscle fibers, shows no major changes. Increased activation of the electrogenic sodium-potassium pump triggered by preceding shocks results in hyperpolarization, which makes the amplitude of the subsequent single action potentials greater, thus enlarging the CMAP.[67]

Normal Recovery Cycle by Paired Stimuli

Studies of the recovery cycle consist of recording the muscle action potentials after delivering paired stimuli to the nerve at various interstimulus intervals. A second shock applied a few milliseconds after the first falls in the refractory periods of the muscle and nerve (Fig. 17-4). For the intervals of 10–15 ms, an overlap between the first and second muscle responses precludes accurate measurement of the individual potentials. Thereafter, the second CMAP remains the same in size as the first in the normal muscle. This finding, however, does not imply that the first and second stimuli elicit the same EPP . At interstimulus intervals of 100 to 200 ms, the second shock normally evokes a greater EPP than the first through neurosecretory potentiation. If the EPP by the first stimulus exceeds the threshold of excitation in all muscle fibers, however, enhanced EPP by the second stimulus recruits

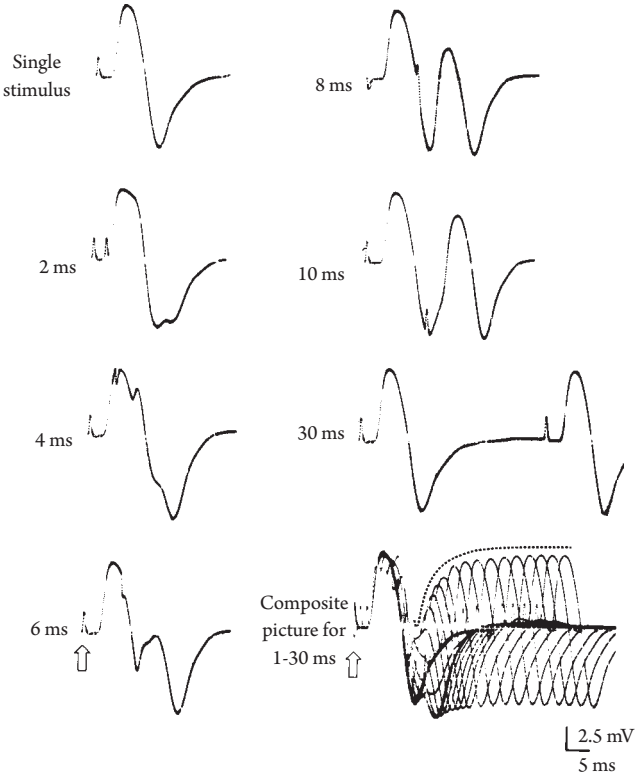

FIGURE 17-4 Compound muscle action potentials from the thenar muscles elicited by paired shocks delivered to the median nerve at the wrist. Time intervals ranged from 2 to 30 ms between conditioning (arrow) and test stimuli. The top tracing on the left shows a response to a single stimulus and the bottom tracing on the right, a composite picture superimposing 20 paired responses. The conditioning response of each pair appeared in the same spot on the photo, whereas the test responses shifted to the right in proportion to the interstimulus interval. An imaginary line connecting the peaks of the sequential test responses represents the time course of neuromuscular excitability change following the conditioning stimulus. (Modified from Kimura.[56])

no additional fibers. A second shock given at an interstimulus internal exceeding 200 ms releases a smaller number of ACh quanta even in normal muscles. Because of a large margin of safety, however, the decreased amount of ACh suffices to cause an EPP well above the critical level of excitation in all muscle fibers. In normal muscles, therefore, changes in the amount of ACh do not alter the size of CMAP elicited by the second or subsequent stimuli.

Effects of Disease States

Partially curarized mammalian muscle, with a reduced margin of safety, serves as a good model for studying the recovery cycle of the EPP.[18] With paired stimuli, the second muscle response equals or exceeds the first for the interstimulus intervals of 100–200 ms (Fig.17-5) that accompany calcium-dependent neurosecretory facilitation.[18] With longer intervals (Fig. 17-6), the second response falls below the first, because depleted stores of available ACh quanta can no longer overcome the receptor insensitivity. A slow recovery follows the maximal depression at interstimulus intervals ranging from 300 to 600 ms. Full return to the control value in about 10 seconds implies restoration of releasable ACh through replenishment of the stores. In MG, a reduced amount of ACh also fails to activate some muscle fibers with receptor insensitivity. Hence, the recovery cycle of the muscle action potential shows a great resemblance to that of curarized muscle. In either case, the maximal depression results from repetitive stimulation at 2–3 Hz, the rate fast enough for the depletion

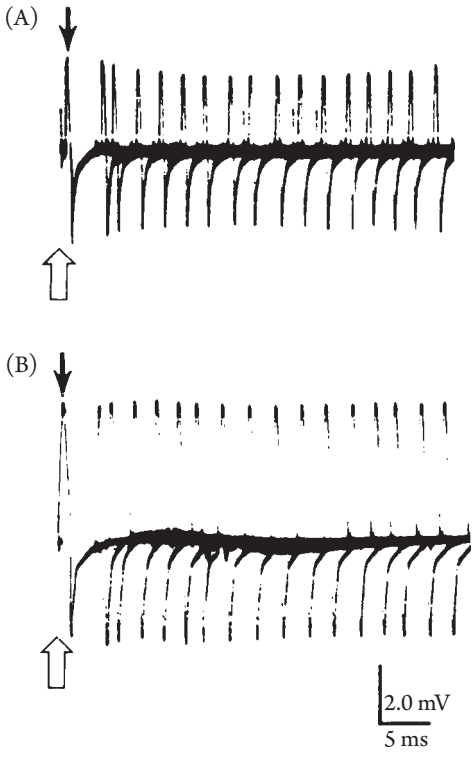

FIGURE 17-6 Composite pictures of 16 paired responses from the thenar muscles arranged in the same manner as in Figure 17-5. The interstimulus intervals of paired shocks ranged from 30 to 400 ms. The conditioning response of each pair appeared in the same spot of each tracing (arrows pointing down), whereas the test responses shifted to the right successively. The test response showed a mild but definite reduction in amplitude at the interstimulus intervals of 150–250 ms in the myasthenic muscle (*A*) but not in the normal muscle (*B*).

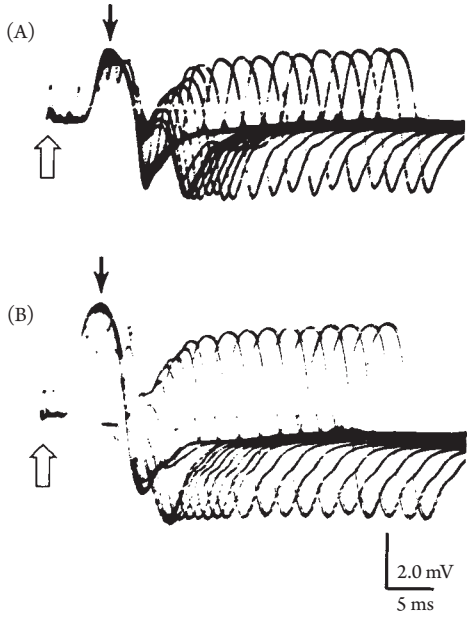

FIGURE 17-5 Composite pictures superimposing 20 paired responses from the thenar muscles (cf. bottom tracing on right in Figure 17-4). A patient with myasthenia gravis (*A*) and a normal control (*B*) showed the same recovery course for the interstimulus intervals ranging from 1 to 30 ms.

of ACh but slow enough for the diffusion of calcium out of the axon.

In LEMS, characterized by a defective release of ACh, the EPP elicited by a single stimulus falls short of activating many muscle fibers. With the second stimulus given in less than 10 ms, the summated EPP will recruit additional muscle fibers. With stimuli delivered at a longer interval of 100–200 ms, the EPP no longer summates, but the electrosecretory facilitation partially overcomes the defective release of ACh (Fig. 17-7). An increased EPP will in turn recruit some of the muscle fibers not activated by the first stimulus, which leads to an increase in amplitude of the second CMAP. This finding, though characteristic of this entity, constitutes a nonspecific increment seen whenever the first stimulus evokes less than the maximal response, for example, in some cases of MG or neuromyotonia (see Fig. 18-9 in Chapter 18). At a slower rate separated by more than 200 ms, the second EPP diminishes because calcium no longer accumulates to compensate for the depletion of available ACh stores. Defective release of ACh by the first stimulus, however, causes only limited depletion, not enough to show a major decrement of CMAP even at a slower rate of stimulation in most patients.

Defective release of ACh also underlines the electrophysiologic abnormality in botulism. With paired stimuli, summation of EPP augments the second response at intervals of less than 10 ms. Increased number of quanta released by the second impulse also causes facilitation at interstimulus intervals of 100 to 200 ms. As expected, paired shocks of longer intervals usually cause depression of the second response, though not as consistently as in MG. Figure 17-8 summarizes typical changes in quantum size and quantum content for MG and LEMS and contrasting CMAP changes induced by repetitive nerve stimulation in the two disorders (see Chapter 18).

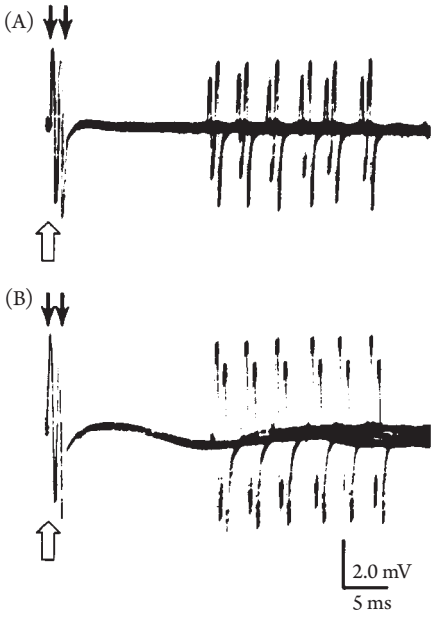

FIGURE 17-7 Composite pictures similar to those shown in Figures 17-5 and 17-6. Unlike the previous tracings, both conditioning and test stimuli consist of paired shocks with interstimulus intervals of 10 ms. The paired test stimuli followed the paired conditioning stimuli (open arrow) by the interval of 200–400 ms. The double peaked conditioning responses appeared in the same spot of each tracing (paired arrows). In myasthenia gravis (*A*), depletion of acetylcholine (ACh) by the conditioning stimuli reduced the first peak of each test response. The second peak of each test response, elicited 10 ms after the first, recovered to a normal level indicating the summation of the two endplate potentials (EPP). In a healthy control (*B*), the second peak of the pair, though displaced downward, had the same amplitude as the first. In each test response of the normal muscle, the maximal size of the first peak precluded any amplitude increase of the second peak.

Posttetanic Potentiation and Exhaustion

With prolonged repetitive stimulation, or after a sustained voluntary muscle contraction, the immediately available store of ACh may increase as a result of a greater mobilization rate. This increase of Ach storage, coupled with the accumulation of calcium in the axon, enhances the release of ACh and consequently the EPP for 1–2 minutes, causing posttetanic potentiation. Subsequent stimuli release fewer ACh quanta for up to 15 minutes, probably because of metabolic changes in the nerve terminal, leading to posttetanic exhaustion. These findings resemble the experimentally induced block by hemicholinium, which interferes with ACh synthesis.[18]

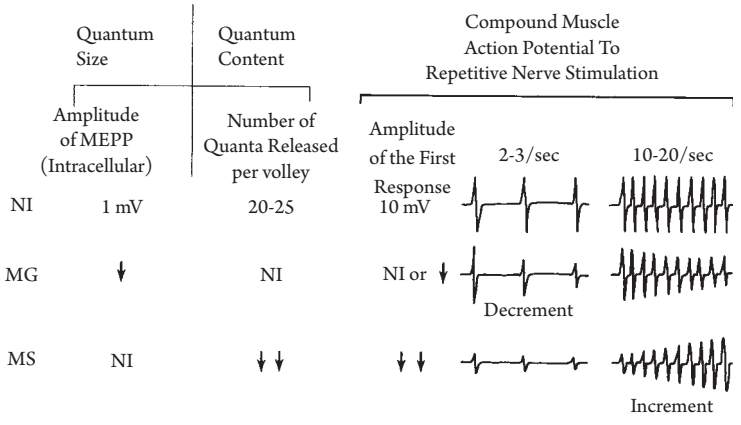

FIGURE 17-8 *Left:* Intracellular recordings reaveal a reduced quantum size, or the miniature endplate potential (MEPP), in myasthenia gravis (MG), reflecting insensitivity of acetylcholine receptors; and decreased quantum content, or the number of quanta released per volley, in the Lambert Eaton myasthenic syndrome (LEMS), indicating defective release of acetylcholine. *Right:* On repetitive nerve stimulation at a slow rate (2–3 Hz) to avoid superimposed neurosecretory facilitation, the quantum content falls gradually in MG, as it does in normal muscles. The physiologic decrement of endplate potential (EPP) leads to a progressive decrese in amplitude of compound muscle action potentials (CMAP) with dropout of individual muscle fibers in MG. Normal muscles show no change as a reduced EPP still suffices to activate all individual muscle fibers because of the margin of safety. On repetitive nerve stimulation at a fast rate (10–20 Hz), the quantum content rises gradually in LEMS, as it does in normal muscles. The physiologic increment of EPP leads to a progressive increase in amplitude of CMAP with recruitment of previously inactive muscle fibers. Normal muscles show no change as the initially maximal CMAP has no room to improve.

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18

Repetitive Nerve Stimulation and Exercise Tests

Abbreviations: AChE—anticholinesterase, AChR—acetycholine receptor, ALS—amyotrophic lateral sclerosis, CMAP—compound muscle action potential, CMS—congenital myasthenic syndrome, DMI—myotonic dystrophy Type I, DMII—myotonic dystrophy Type II, E1—active electrode, E2—reference electrode, EPP—endplate potential, HyperPP—hyperkalemic periodic paralysis, HypoPP—hypokalemic periodic paralysis, LEMS—Lambert Eaton myasthenic syndrome, MC—myotonia congenita, MG—myasthenia gravis, MND—motoneuron disease, MS—multiple sclerosis, NMT—neuromuscular transmission, PMC—paramyotonia congenita

1. INTRODUCTION

Nerve stimulation techniques as tests for neuromuscular transmission began with Jolly,[43] who applied faradic current repeatedly at short intervals. His equipment consisted of a double-coil stimulator capable of eliciting only submaximal responses and a mechanical, rather than electrical, recorder. Using a kymographic recording and visual inspection of skin displacement, he found that the size of the muscle response deteriorated rapidly in patients with myasthenia gravis (MG)

during the faradization. Faradic current also failed to elicit a response in the volitionally fatigued muscle prior to testing. Conversely, after faradization, muscle responded poorly to subsequent volitional contraction. Based on these findings, Jolly concluded that the myasthenics had motor failure of the peripheral, rather than central, nervous system, a remarkable insight, considering the technical limitations at the time.

The use of supramaximal stimulation and the recording of the muscle action potential have increased the reliability and sensitivity of nerve stimulation techniques considerably. In 1941, Harvey and Masland[35] noted that, in myasthenia, a single muscle response induced a prolonged depression, with a second maximal motor nerve stimulus exciting a reduced number of muscle fibers. A train of impulses resulted in a progressive decline in amplitude of the compound muscle action potential (CMAP). Later studies have established optimal frequency of stimulation, proper control of temperature, appropriate selection of muscles, and various activation procedures to enhance an equivocal block of neuromuscular transmission (NMT).[24]

Microelectrode studies provide direct recording of endplate potentials from muscle in vitro. All other electrophysiologic methods assess the neuromuscular junction only indirectly. Nonetheless, such an approach allows quantitation of the motor response to paired stimuli, tetanic contraction, and repetitive stimulation at slow or fast rates.[84] Transmission defects affect a variety of disease states, such as MG, Lambert-Eaton myasthenic syndromes (LEMS), botulism, amyotrophic lateral sclerosis (ALS), poliomyelitis, and multiple sclerosis (MS). This chapter deals with the physiologic techniques for elucidating decremental or incremental responses in the differential diagnosis of NMT disorders (see Chapter 26).[1,2]

2. METHODS AND TECHNICAL FACTORS

Belly-Tendon Recording

Belly-tendon recording consists of stimulating the nerve with supramaximal intensity and recording the CMAP with the active electrode (E1) placed over the motor point and the reference electrode (E2), on the tendon. The initially negative potential thus recorded represents the summated electrical activity from the entire muscle fiber population, discharging relatively synchronously. The area under the negative phase changes primarily with the number of activated muscle fibers. The magnitude of the unit discharge from individual muscle fibers also alters the CMAP size, especially in myogenic disorders. In clinical studies, area measurement provides more stable results,[5,95] although amplitude comparison suffices if a train of responses show the same duration and waveform.

Movement-Induced Artifacts

Movement-related artifacts abound during repetitive stimulation of the nerve. The recording electrode may gradually slide away from the muscle belly, or the stimulating electrodes may slip from the nerve, causing subthreshold activation. In either case, progressively smaller amplitude of the train mimics a decremental response. Shortening the muscle length passively or with voluntary contraction tends to synchronize muscle fiber conduction, thus increasing the amplitude and decreasing the duration of CMAP (Fig. 18-1).[36] Repositioning the limb also alters the shape of the volume conductor and the spatial relationship of muscle to the recording electrodes, leading to misleading waveform changes of the recorded response. Firm immobilization of the limb and the muscle under study minimizes the movement-induced variability.

In most instances, technical problems cause abrupt, irregular changes in the amplitude or shape of the evoked response. Some movement artifacts, however, induce a smooth, progressive alteration of amplitude that mimics the myasthenic response. Nevertheless, close scrutiny often discloses accompanying changes in duration or other aspects of waveform, usually attributable to an alteration in the length of the muscle or the shape of the volume conductor. In our experience, even gradually changing waveforms represent artifacts if repetitive stimulation induces excessive movement. Visual inspection helps detect movement-related artifacts. Repeated trials to

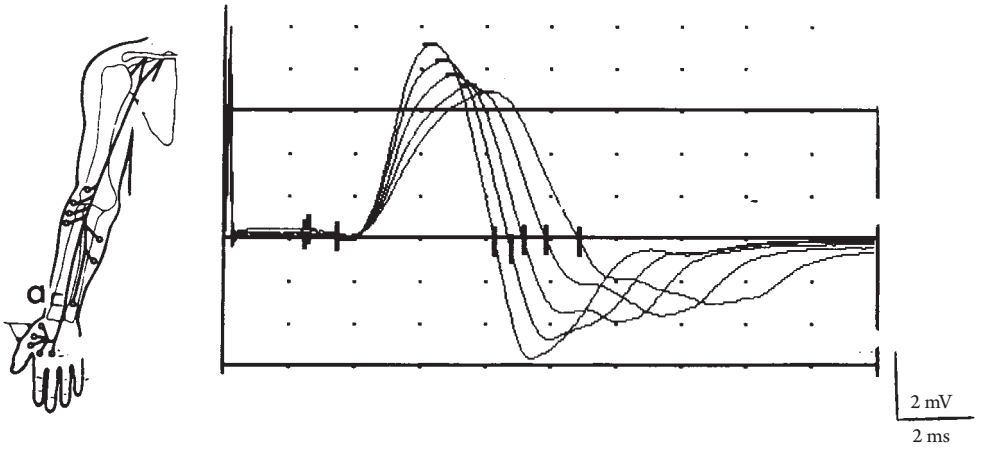


FIGURE 18-1 A train of responses recorded from the thenar muscle with stimuli delivered at 1 Hz to the median nerve at the wrist in a healthy subject. Intentional stepwise alteration in thumb position from abduction to adduction after each shock gave rise to a smooth reduction in amplitude with concomitant increase in duration of successive potentials. The area under the waveform showed relatively little change from the first to the fifth response.

verify reproducibility improve the reliability of the study. Intertrial intervals should exceed 30 seconds to avoid subnormality of NMT, which lasts for a few seconds after a single stimulus and a greater time period after repetitive impulses.

Temperature and Other Factors

Exposure to warm sunlight may precipitate ptosis and diplopia in patients with MG. Similarly, electrophysiologic abnormalities of weak muscles may appear only after local warming. Elevated body temperature up to 42°C causes no abnormality in healthy subjects, but it enhances the decrement on repetitive nerve stimulation in patients.[79] Conversely, cooling reduces the decrement to repetitive nerve stimulation (Fig. 18-2). Paradoxically, brief stimulation at high rates may produce a decremental response in normal muscles cooled below 32°C.[50] Patients with LEMS also experience distinct improvement after cooling,[96] as do those with ALS,[23] botulism,[97] and tick paralysis.[20] Lowering the intramuscular temperature from 35°C to 28°C increases the amplitude of the CMAP and enhances the force of the isometric twitch and tetanic contraction.[11]

Physiologic mechanisms that account for the improved NMT with cooling include (1) facilitated transmitter replacement in the presynaptic terminal[39]; (2) reduced amount of transmitter release at the neuromuscular junction by the first of a train of impulses, leaving more quanta available for subsequent stimuli[22]; (3) decreased hydrolysis of acetylcholine (ACh) by acetylcholinesterase (AChE), allowing sustained action of the transmitter already released from the axon terminal[78]; (4) increased postsynaptic receptor sensitivity to ACh[32]; and (5) reduced rate of removal of calcium ions from the nerve terminal following stimulation.[57]

Prior immersion of the limb in warm water or the use of an infrared heat lamp helps maintain the skin temperature over the tested muscle above 32°C as recommended in most laboratories for diagnostic application. Administration of AChE drugs within a few hours before the test reduces the probability of obtaining a decremental response. Discontinuance of the short-acting medication for several hours improves the sensitivity of the test. The patient must withhold a long-acting medication for a longer period, if clinically feasible. With an overdose of this type of drugs, a single nerve impulse may cause a repetitive muscle response, and a train of stimuli at a high rate gives rise to a decremental response (see Chapter 17-6).

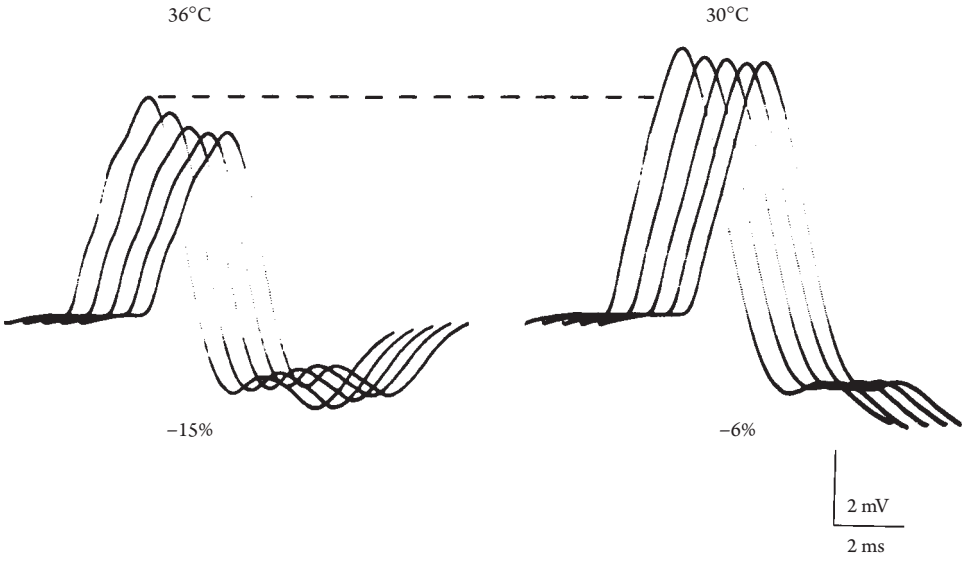


FIGURE 18-2 Decremental response of the hypothenar muscle with stimulation of the ulnar nerve at 2 Hz in a patient with myasthenia gravis, at 36°C on the left, and after cooling of the hand to 30°C on the right. Note a reduction in the decrement from 15% to 6%, associated with an increase in amplitude after cooling. (Modified from Denys.[22])

3. COMMONLY USED NERVES AND MUSCLES

Distal Versus Proximal Muscle

Patients with MG rarely have a decremental response in clinically unaffected muscle. Thus, isolated bulbar or respiratory muscle weakness may pose a diagnostic challenge.[58] Weak proximal or facial muscles show a higher incidence of electrical abnormality than stronger distal muscles.[63,88] Electrical and mechanical responses to repetitive stimuli show a substantially greater decrement and posttetanic potentiation in the platysma than in the adductor pollicis.[47] Also, the trapezius has proven more sensitive than the distal hypothenar muscles in detecting abnormalities of NMT in ALS.[45] Similarly, electrophysiologic findings in botulism may involve only weak muscles of the clinically affected limbs. In contrast, patients with the LEMS usually have prominent abnormalities in the proximal and, to a lesser degree, distal muscles.

In principle, the method consists of applying repetitive stimulation to a motor or mixed nerve and recording a train of responses from the innervated muscle. Although less sensitive than proximal muscles, distal musculature provides technically more reliable results for serial studies. A negative result with distal muscles should prompt examination of the proximal muscles such as the deltoid, biceps, and upper trapezius. Stimulation of the ulnar nerve at the elbow allows simultaneous recordings from one proximal muscle, the flexor carpi ulnaris, and three distal muscles, abductor digiti quinti, first dorsal interosseous, and adductor pollicis. Stimulation of the brachial plexus at the supraclavicular fossa tends to activate many muscles simultaneously. In contrast, stimulation of the accessory nerve yields a selective activation of the trapezius without contamination from other muscles. Stimulation of the facial nerve activates all the mimetic muscles, including nasalis, a preferred site of recording.[80,98] Studies of the lower limb pose a greater technical difficulty, yielding a wider normal range compared to the upper limb.[64] Wise choice of the nerve and muscle based on distribution of weakness increases the test sensitivity.

Upper Limb and Shoulder Girdle

HYPOTHENAR MUSCLES

Stimulate the ulnar nerve at the wrist and record from the abductor digiti quinti with E1 and E2 placed on the belly and the tendon. Binding the four fingers together with a bandage or Velcro strap prevents movement interference. A restraining metal bar also helps hold the hand flat, palm down, on the examining table. The patient exercises by abducting the little finger against the restraint.

THENAR MUSCLES

Stimulate the median nerve at the wrist and record from the abductor pollicis brevis with E1 and E2 placed on the belly and the tendon. The hand, held by a restraining metal bar, lies flat on the board, palm up and the thumb adducted. The patient exercises the muscle by abducting the thumb against the bar.

ANCONEUS

Stimulate the distal branch of the radial nerve 4 cm above the elbow on the line bisecting the distance between the olecranon and lateral epicondyle, and record with E1 placed 4 cm below the elbow on the same line and E2 placed 2 cm further distally. The patient, upright in a chair, holds on to the handle mounted on the side table with the arm flexed approximately 90 degrees and exercises the muscle by extending the elbow.

BICEPS

Stimulate the musculocutaneous nerve at the axilla and record from the biceps, with E1 and E2 placed on the belly and the tendon. The position of the arm depends on the type of mechanical board available. A handlebar attached under a solid table can serve as an excellent restraint. The patient, upright in a chair, holds on to the handle from below with the arm flexed approximately 45 degrees in the adducted and supinated position. Pulling up against the handlebar with flexion at the elbow exercises the muscle.

DELTOID

Stimulate the brachial plexus at Erb's point and record from the deltoid with E1 and E2 placed on the belly and the acromion. The patient sits upright with the arm adducted, flexed at the elbow and internally rotated to place the hand in front of abdomen and exercises by abducting the arm against the resistance of self-restraint by the opposite hand. Weak or uncooperative patients do better with a Velcro strap or sheet wrapped firmly around the trunk, holding both arms adducted at the side.

TRAPEZIUS

Stimulate the spinal accessory nerve with cathode and anode placed along the posterior border of the sternocleidomastoid muscle, and record from the upper trapezius muscle with E1 and E2 placed on the belly at the angle of neck and shoulder and the tendon near the acromion process. The patient, upright in a chair, with the arms adducted and extended, holds on to the bottom of the chair and exercises by shrugging the shoulders.

Lower Limb

TIBIALIS ANTERIOR

Stimulate the peroneal nerve at the fibular head and record from the tibialis anterior muscle with E1 placed on the belly in the middle of the leg and E2 placed a few centimeters distally. The patient sits in a chair with the foot held firmly on a restraining board by Velcro straps and exercises by dorsiflexing the foot against the restraint.

QUADRICEPS FEMORIS

Stimulate the femoral nerve at the groin just lateral to the femoral artery and record from the rectus femoris with E1 and E2 placed on the belly and the patellar tendon. The patient sits in a chair with the thigh and the leg fastened to the chair with Velcro straps and exercises by extending the leg against the restraint. The patient may also lie supine with the thigh bound to the bed and exercise by lifting the leg off the bed against a Velcro strap.

Facial Muscles

ORBICULARIS OCULI, ORBICULARIS ORIS, AND NASALIS

Stimulate a branch of the facial nerve distally for relatively selective activation of the target muscle and record from the orbicularis oculi innervated by temporal and upper zygomatic branch, nasalis supplied by lower zygomatic and buccal branch or orbicularis oris innervated by buccal branch with E1 placed on the target muscle and E2 placed on the opposite side or on the bridge of the nose (see Fig. 1-3 in Chapter 1 and Figs. 8-2 and 8-3 in Chapter 8).[63] The patient, lying supine, exercises by contracting the muscle.

Others Muscles

Less commonly used recording sites include tongue,[54] extensor indicis,[68] diaphragm,[99] serratus anterior,[53] and masseter.[74]

4. RECOVERY CURVES BY PAIRED STIMULATION

Short Interstimulus Intervals

Paired stimuli applied at various interstimulus intervals reveal the time course of recovery of NMT (see Chapter 17–6). In normal muscles, the first supramaximal stimulus activates the entire group of muscle fibers. A second stimulus delivered within a few milliseconds evokes a smaller response, indicating refractoriness of the nerve and muscle (see Fig. 17-4 in Chapter 17). With increasing interstimulus intervals, the second potential shows a progressive recovery despite some overlap with the first response at intervals of less than 15 ms.

In typical cases of MG, the first stimulus elicits a maximal or near-maximal response. The recovery curve also follows a normal pattern for short interstimulus intervals up to 15 ms. The curve deviates from normal in the LEMS, where the first stimulus elicits a submaximal response; second shock given at very short interstimulus intervals evokes a larger response with the amplitude one and a half to two times that of the first. The increment, based on summation of two endplate potentials (EPPs), represents recruitment of those fibers activated only subliminally by the first stimulus. Most patients with botulism (Fig. 18-3)[17] and occasional patients with MG who have less than a maximal initial response also show the same phenomenon.

Long Interstimulus Intervals

At greater interstimulus intervals exceeding 15 ms, two EPPs no longer summate. Potentiation of the second response here represents true facilitation, resulting from an increased number of quanta liberated by the second stimulus after accumulation of calcium in response to the first stimulus. Despite the release of a greater amount of ACh, the second muscle potential normally shows no increment from the already maximal first response. Most patients with MG or botulism also have minimal change at this interstimulus range. In contrast, LEMS patients, with a small initial response, show an increment at interstimulus intervals ranging from 15 to 100 ms. This simply represents the room for second and subsequent responses to increase up to the normal range.

The decremental response in MG begins at intervals of about 20 ms but becomes more definite at intervals between 100 and 700 ms. The response reaches the trough at an interstimulus interval of about 300–500 ms (see Fig. 17-6 in Chapter 17). At shorter intervals, concomitant facilitation attributable to the electrosecretory mechanism of calcium accumulation obscures the depression. The response slowly returns to the baseline in about 10 seconds. The results of paired stimuli predict that a train of stimuli produces the maximal decrement at the rate of 2–3 Hz.

5. DECREMENT AT SLOW RATES OF STIMULATION

Normal Muscles

Repetitive stimulation at a rate of 1–5 Hz depletes the immediately available ACh store, without superimposed facilitation from neurosecretory mechanisms (see Fig. 17-8 in Chapter 17).

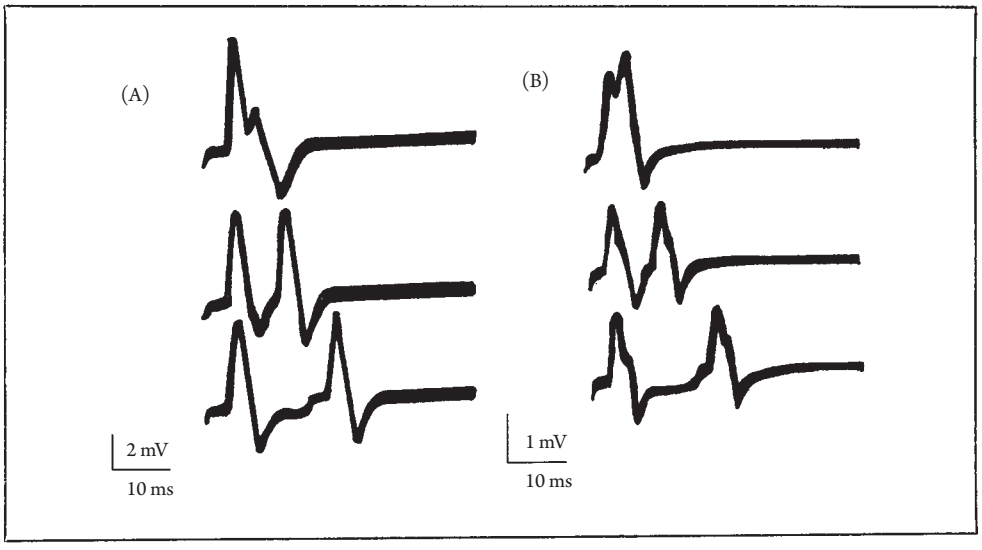


FIGURE 18-3 The effect of paired shocks given at interstimulus intervals of 2.5 ms (top), 15 ms (middle), and 25 ms (bottom). On the top tracings, the reduced test response in a healthy subject (*A*) indicates the effect of the refractory period, whereas the increased test response in a patient with botulism (*B*) suggests summation of two closely elicited endplate potentials discharging muscle fibers subliminary excited by the conditioning stimulus. (Modified from Cherington.[15])

Slow rates of stimulation induce relatively little movement-related artifacts because the muscle returns close to its original relaxed position before the next stimulus. Most patients tolerate a train at faster rates poorly. Moreover, continuous muscle contraction alters the muscle length and the geometry of the volume conductor, which in turn affect the waveform of the successive responses. As discussed earlier, movement artifacts, which ordinarily cause irregular variations, may also produce smooth, reproducible changes, erroneously suggesting an abnormality (Chapter 18-1). Careful evaluation of the waveform and close visual inspection of the contracting muscle usually disclose the source of artifacts.

Most modem equipment automatically calculates the percentage reduction for the smallest of the initial fourth to sixth responses, compared with the first in the same train. Accepting the computed results without verification of the waveform may lead to misdiagnosis. In normal muscles, decrement at stimulation of 2–3 Hz, if present, does not exceed 5%–8%. In fact, an optimal train comprises practically identical responses from the first to the last. Thus, the presence of any reproducible decrement should raise suspicion in a tracing free of any technical problems.

Myasthenia Gravis

In MG, the amplitude drops maximally between the first and second responses of a train, followed by a further but lesser decline up to the fourth or fifth potential (Fig. 18-4). Subsequent responses in the series then level off or, more typically, reverse the course by regaining some of the lost amplitude. Occasionally, the recovery may even exceed the original value by 10%–20%, especially after several seconds of repetitive stimulation. More characteristically, continued stimulation induces a long, slow decline after a transient increment. To avoid a false-positive result, most electromyographers use a conservative criterion of abnormality: a reproducible decrement of 10% or more between the first response and the smallest of the next fourth to sixth responses.[41] In addition to the changes in amplitude, the latency may progressively increase in some myasthenic muscles.

In equivocal cases, sampling several muscles improves the chance of documenting localized

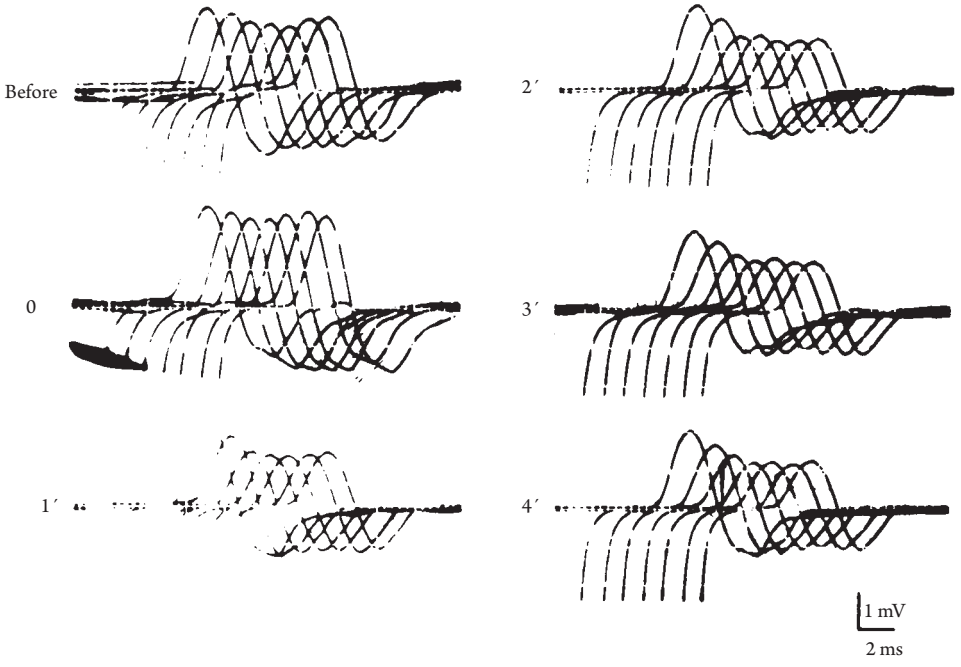


FIGURE 18-4 Thenar muscle potentials elicited by a train of stimuli at 3 Hz to the median nerve before and after 1 minute of exercise in a patient with generalized myasthenia gravis. Amplitude comparison between the first and fifth responses revealed a decrement of 25% at rest, 12% immediately after exercise, and 50% 4 minutes later.

myasthenic weakness. In particular, a negative result in the distal limb muscles should prompt further studies for possible electrical abnormalities detectable in the proximal or facial musculature (Fig. 18-5). The administration of edrophonium (Tensilon) or neostigmine (Prostigmin) helps further delineate the characteristics of defective NMT. These agents potentiate the action of ACh by blocking AChE in patients with postjunctional abnormalities. Therefore, a partial or complete reversal of the decrement by AChE agents tends to confirm the diagnosis of MG. Intrinsic hand muscles, though insensitive to confirm the diagnosis, serve better for sequential studies of unequivocal abnormalities (Fig. 18-6).

Other Neuromuscular Disorders

A train of stimuli at a slow rate causes decrementing responses not only in MG but also in a number of other conditions with reduced margins of safety. These include the LEMS (Figs. 18-7 and 18-8), congenital myasthenic syndromes (CMS), botulism, MS, motoneuron disease (MND),[38,45] X-linked spinobulbar muscular atrophy[40] and regenerating nerve.[29] A partially curarized muscle will develop a similar decrement to a train of stimuli. In patients with the LEMS or botulism, single stimuli typically elicit very small muscle action potentials. A decremental tendency with a slow rate of repetitive stimulation, though present in most cases, does not constitute an essential feature of these disorders characterized by defective release of ACh. A slow rate of stimulation may also induce similar decrement in other conditions with no apparent defect in NMT, for example, neuromyotonia, probably on the basis of abnormal axonal excitability (Fig. 18-9).

Slow-channel CMS and AChE deficiency syndrome resemble cholinergic crisis seen in overmedicated patients with MG and in those with organophosphate poisoning.[7,9] In these disorders, a markedly prolonged EPP outlasts the refractory period of NMT. Thus, single stimuli of the motor nerve typically elicit more than one CMAP, an initial main response followed by one or more

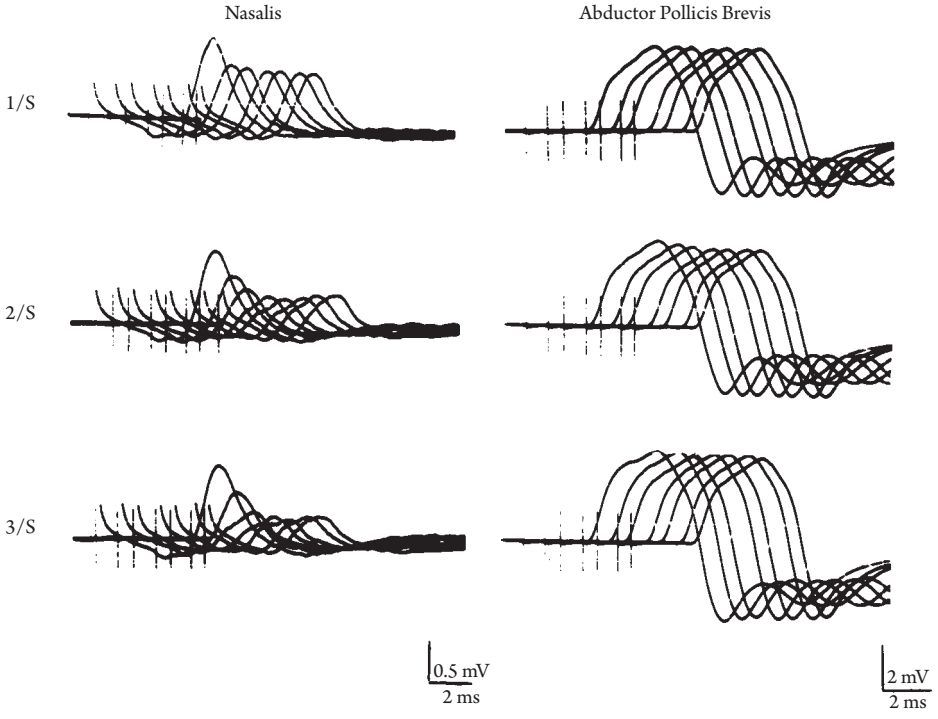


FIGURE 18-5 A 25-year-old woman with double vision of l.5 month duration. A train of shocks at 1, 2, and 3 Hz to the median nerve revealed no detectable abnormalities in the abductor pollicis brevis. Stimulation of the facial nerve elicited decrementing responses in the nasalis. Note greater change within the train as the rate of stimulation increased from 1 to 3 Hz. (Modified from Kimura.[46])

smaller recurrent responses, which appear at 3–7 ms intervals.[30,94] With repetitive stimulation both responses show a rate-dependent decrement based on depolarizing block, although the recurrent potentials diminish more rapidly and disappear after brief exercise (Figs. 18-10 and 18-11). Quinidine sulfate therapy reverses this abnormality concomitant with clinical improvement.[31] A low dose of pancuronium, an acetycholine receptor (AChR) antagonist, repairs the decrement seen in organophosphate intoxication, countering the prolonged depolarization at the endplate.[8]

6. INCREMENT AT FAST RATES OF STIMULATION

Normal Muscles

The recruitment of muscle fibers not activated by the first stimulus accounts for the incremental tendency seen in the LEMS, botulism, and some cases of MG. In normal subjects, supramaximal stimulation activates all muscle fibers innervated by the nerve, evoking a maximal CMAP. This leaves no room for further increment despite greater amounts of ACh released by subsequent stimuli. In normal adults, muscle action potentials remain stable during repetitive stimulation at a rate of up to 20–30 Hz.[67] Some healthy infants, however, may show a progressive decline in amplitude at this rate.[18] In adults, trains of 50 Hz may cause apparent decremental or incremental responses. Conversely, muscles stimulated repetitively at a high rate tend to discharge with increased synchrony without recruitment of additional muscle fibers. This phenomenon, called pseudofacilitation, characteristically shows increased amplitude without much change in area under the waveform of the CMAP. At such a fast rate, however, inherent movement artifacts render the measurement unreliable.

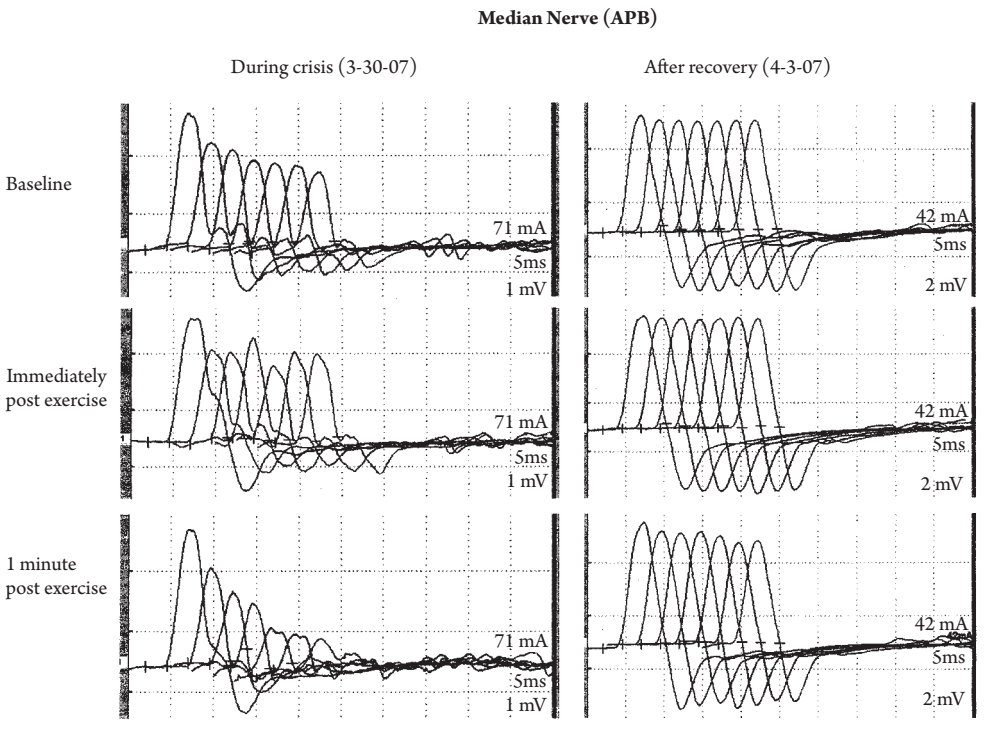


FIGURE 18-6 A 68-year-old man for myasthenia gravis taking mestinon 180 mg twice daily developed nausea, vomiting, abdominal pain, diarrhea, and generalized weakness 1 week before the admission. Note a profound decrement during myasthenic crisis, showing a repair immediately after exercise and exhaustion 1 minute later (left column) and nearly complete recovery after appropriate treatment (right column).

Myasthenic Syndrome and Botulism

In the LEMS, single stimuli typically elicit a strikingly small CMAP (Fig. 18-12). In view of a wide range of amplitude variability among different subjects, a decrease by as much as 50% in some individuals may still remain above the lower limit of normal of the average population. An apparent lack of reduction in amplitude, therefore, does not necessarily rule out the syndrome. A marked potentiation following a brief voluntary exercise would disclose the subnormality of the initial amplitude and confirm the diagnosis. A slow rate of sustained stimulation also facilitates the response if superimposed on voluntary contraction.[55]

Repetitive stimulation given at 20–50 Hz induces a remarkable increment of successive muscle action potentials to a normal or near-normal level (Figs. 18-7 and 18-8). A slight initial decrement may precede the increment, but the last response of a train at the end of 1 minute usually exceeds the first response several times.[51] Most patients tolerate the discomfort of the procedure poorly. Besides, voluntary contraction usually produces greater potentiation[92] than a train of stimulation at high rates, which, therefore, has seen only limited clinical application.[66] The electrophysiologic abnormalities often improve in parallel to the clinical course after the administration of guanidine[65] or 3,4-diaminopyridine.[85]

Patients with botulism may have entirely normal electrical responses in early stages of the illness or have a small muscle potential in response to a single stimulus.[16] An initially small response usually potentiates after voluntary exercise or with a train of stimuli (Fig. 18-13). Incrementing responses, though smaller in range, resemble those found in the LEMS.[59,87] Tetanic and posttetanic facilitation, the most characteristic abnormality

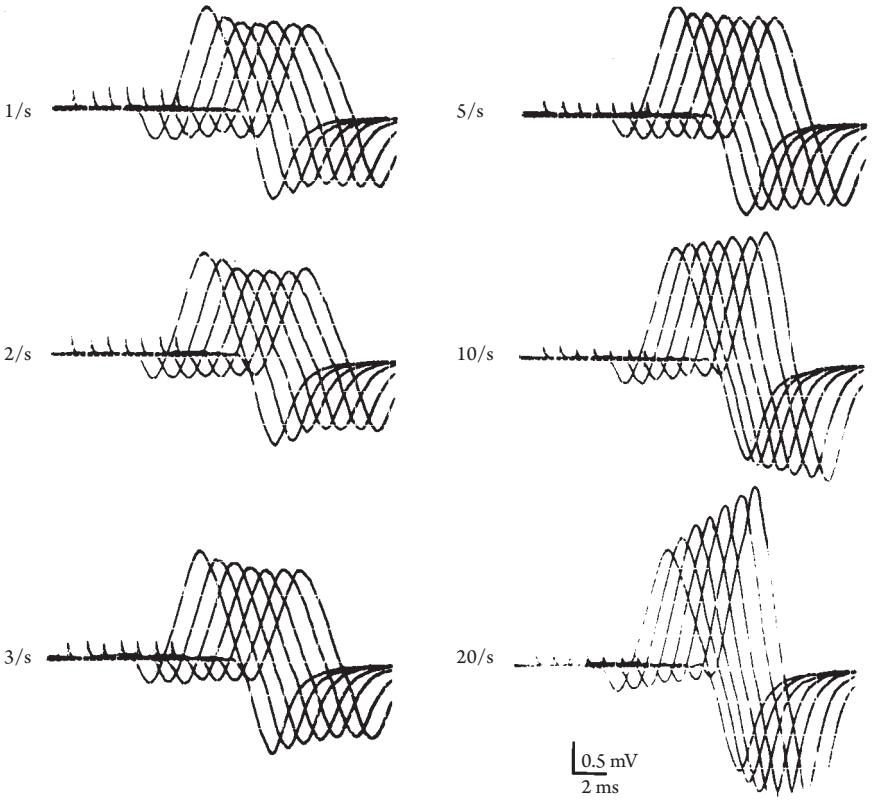


FIGURE 18-7 Thenar muscle potential elicited by a train of stimuli given at 1 through 20 Hz to the median nerve in a patient with myasthenic syndrome. Note decremental responses to slow rates of stimulation up to 5 Hz and incremental responses to faster rates of stimulation at 10 Hz and to a much greater degrees at 20 Hz.

of infantile botulism, persists for a number of minutes.[21,83]

Other Neuromuscular Disorders

An incremental response, though characteristic of the LEMS and botulism, by no means excludes other disorders of the NMT (see Chapter 26-6). Patients with MG not infrequently show such a pattern, either during a progressive phase of the disease or during steroid therapy.[86] In contrast to the marked potentiation in LEMS, however, changes in MG rarely exceed the initial value by more than 40% at the end of 1 minute. Other disorders associated with depressed NMT and incremental tendency by a train of stimuli include antibiotic toxicity,[69] hypocalcemia, hypermagnesemia,[90] and snake poisoning.[44] Again, these conditions show only a limited degree of potentiation in contrast to the multifold increase characteristic of LEMS. When the initial shock evokes a very small response, then, the subsequent stimuli tend to induce a greater change regardless of the type of abnormalities, simply reflecting greater room for potentiation (Fig. 18-9).

7. EFFECT OF TETANIC CONTRACTION

Use of Sustained Stimulation

Prolonged stimulation at a rapid rate adds diagnostic information in the evaluation of infantile botulism. Otherwise, clinical yields seldom justify subjecting the patient to this painful procedure. Further, sustained muscle contraction causes excessive movement artifacts that often interfere with accurate assessments of the waveform.

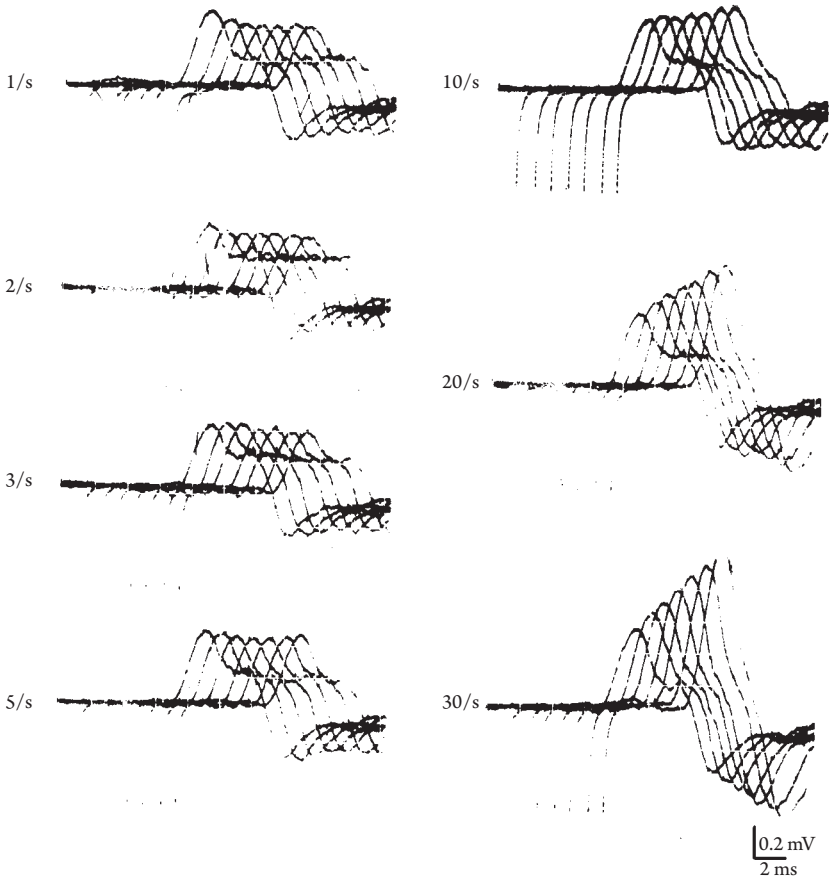


FIGURE 18-8 A repeat study in the same patient as in Figure 18-7 using the same recording arrangements. Note further diminution in amplitude of the compound muscle action potentials compared with an earlier study, slight decrement at slow rates of stimulation up to 5 Hz, and progressively more prominent increment at faster rates from 10 to 30 Hz.

As a research tool, a long train helps elucidate the time course of the mechanical force of contraction. The force of muscle twitch increases during prolonged stimulation in healthy subjects, but not in patients with MG. This phenomenon, called a positive staircase, has no diagnostic specificity as a clinical test.[25] Whatever the purpose, clinicians must resort to a train of rapid stimulation judiciously to avoid inflicting the patient with unnecessary discomfort.

Tetany develops after a 20–30 second train of electrical stimulation at 50 Hz or a continuous run for a few minutes at 3 Hz. Most subjects tolerate these procedures poorly. Fortunately, voluntary muscle contraction accomplishes the same effect, discharging motor fibers up to 50 Hz during maximal effort. A typical postactivation cycle following voluntary or stimulus-induced tetanic contraction consists of two phases: posttetanic potentiation, lasting for about 2 minutes, and posttetanic exhaustion, lasting up to 15 minutes.

Posttetanic Potentiation

Tetanic contraction not only causes calcium to accumulate inside the axon but also mobilizes ACh vesicles from the main store. Subsequent nerve stimulation gives rise to a larger CMAP in LEMS or related disorders with defective release of ACh by recruiting additional muscle fibers not previously activated (Figs. 18-14 and 18-15). In physiologic experiments of single

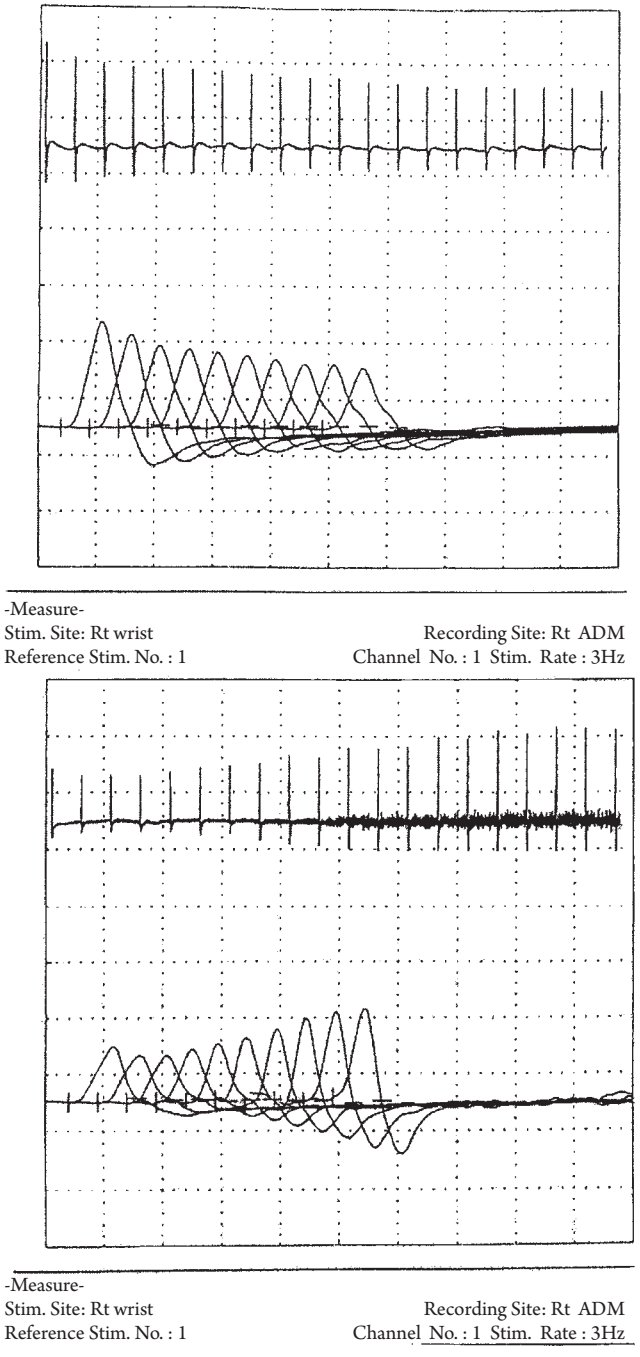


FIGURE 18-9 A 29-year-old man with potassium-channel antibody positive neuromyotonia showing muscle cramps and hypertrophy. A 3 Hz stimulation of the ulnar nerve induced a progressive decline in amplitude of abductor digiti minimi response (top) immediately after muscle exercise, which potentiated the initial response, and a gradual increase when tested after resting the muscle (bottom). These findings probably indicate an abnormality of axonal excitability rather than a defective neuromuscular junction. Both decremental and incremental tendency reflect physiologic change, which become manifest depending on the size of the initial response of the train. Calibration, 5 mV and 5 ms per division.(Courtesy of Yusei, Shiga, MD, Department of Neurology, Tohoku University School of Medicine.)

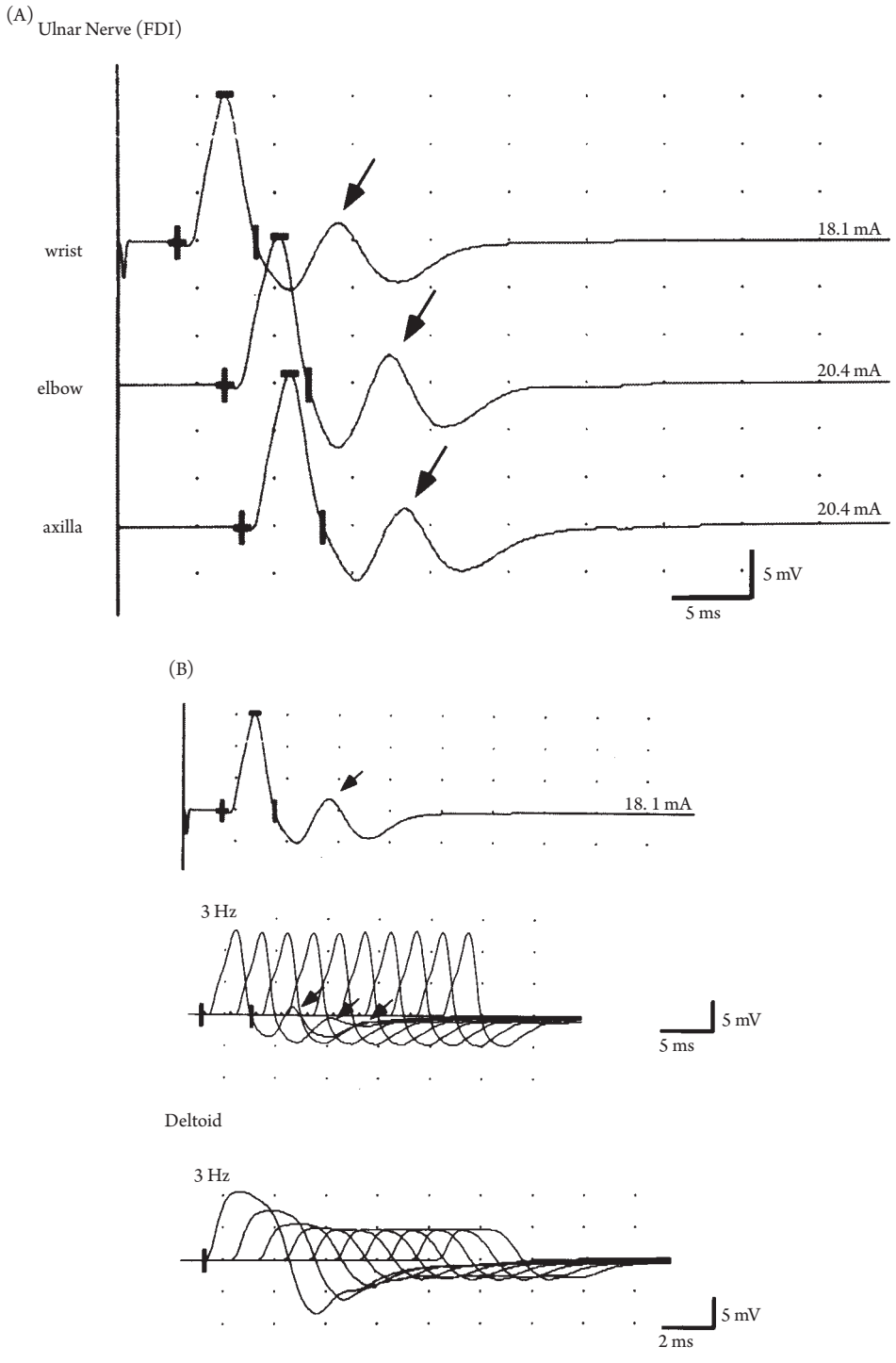


FIGURE 18-10 A 29-year-old woman with congenital myasthenic syndrome from acetylcholinesterase deficiency. Generalized weakness began in her childhood, peaking at the age of 16 years with increasing fatigability of truncal and proximal limb muscles and development of scoliosis on standing. Administration of anticholinesterase worsened the symptoms. (*A*) Single shocks of the ulnar nerve elicited two compound muscle action potentials in the first dorsal interosseous muscle, M_1 and M_2, but not in the deltoid, the weakest muscle of the limb. (*B*) A train of stimuli at 3 Hz caused a decrement of M_2 but not M_1 in the first dorsal interosseous and a clear decrement of M_1 in the deltoid. (Courtesy of Nobuo Kohara, MD, Department of Neurology, Kyoto University School of Medicine.)

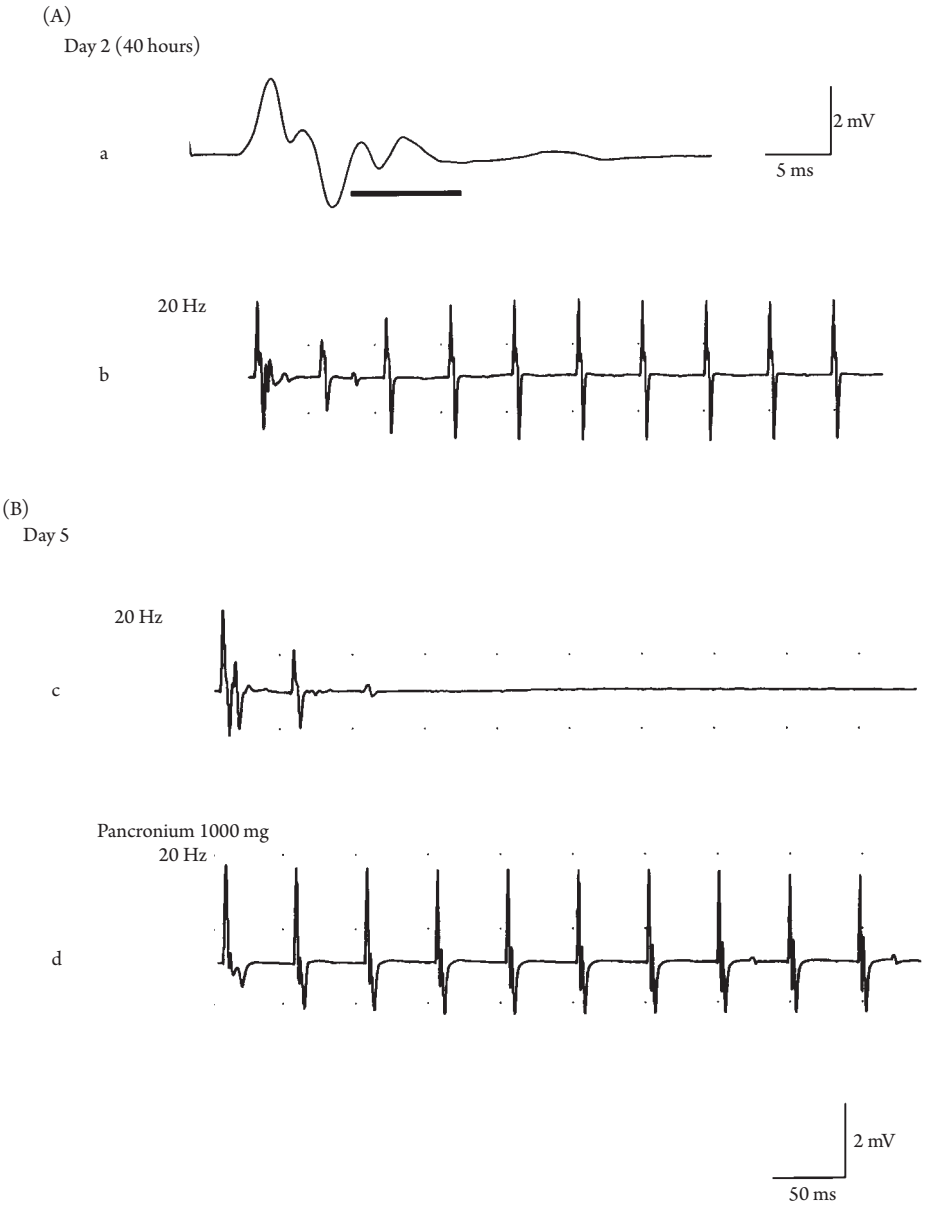


FIGURE 18-11 A 25-year-old woman with organophosphate intoxication after attempting suicide by ingestion of phenitrothion. Severe cholinergic crisis resulted in a respiratory failure necessitating a mechanical ventilation for 3 days. The patient remained comatose for a week, followed by gradual improvement, returning to normal in 17 days. (*A*) On day 2, (a) single shocks of the median nerve elicited three compound muscle action potentials, M_1, M_2 (underline), and M_3 in the thenar muscle, and (b) a train of stimuli at 20 Hz showed a decrement of M_1 and M_2 followed by an increment of M_1 with absent M_2 and M_3. (*B*) On day 5 (c) the same train resulted in complete abolition of all responses after the third train of stimuli, and (d) administration of acetylcholine receptor antagonist, pancuronium, in low dosage (1000 mg) repaired the deficit completely as expected in depolarization block. (Courtesy of Nobuo Kohara, MD, Department of Neurology, Kyoto University School of Medicine.)

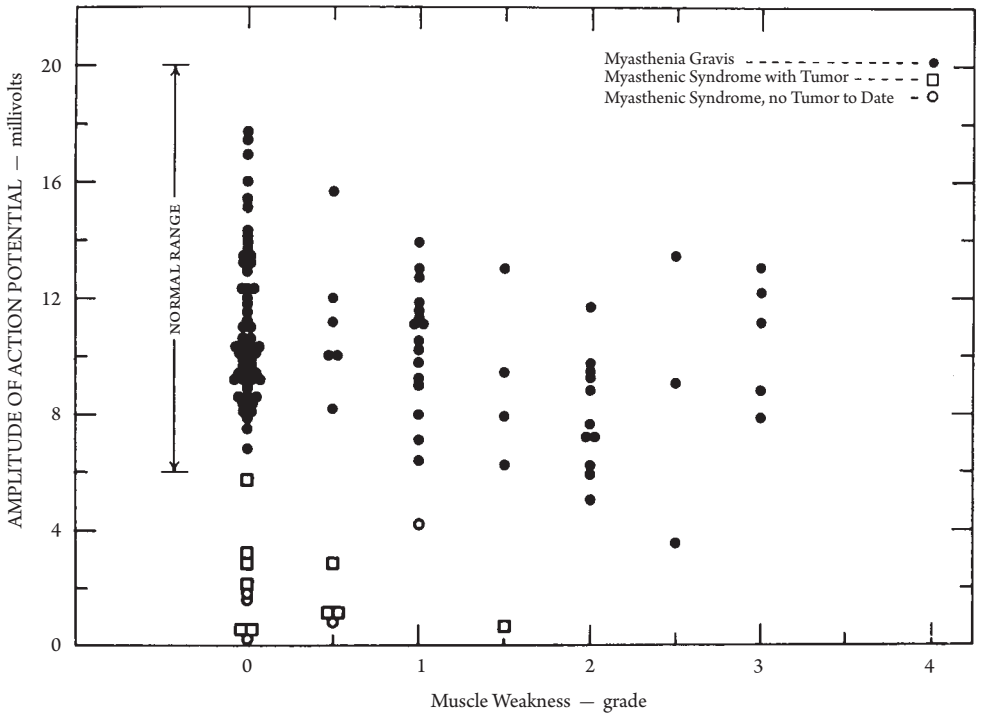


FIGURE 18-12 Relationship between clinical estimate of weakness and the amplitude of muscle action potential in patients with myasthenia gravis and myasthenic syndrome. The histogram plots the amplitude of the hypothenar muscle potential elicited by single maximal stimuli to the ulnar nerve. The scale on the abscissa denotes normal strength (0), 75% (1), 50% (2), 25% (3), and complete paralysis (4). (From Lambert, Rooke, Eaton, et al.,[52] with permission.)

nerve fiber stimulation, four types of short-term synaptic enhancement follow the end of tetanic activation: fast decaying facilitation, slow decaying facilitation, augmentation, and posttetanic potentiation.[57]

In practice, a simple procedure consists of delivering single shocks of supramaximal intensity to the nerve and comparing the size of the muscle response measured before and after a short exercise. A striking increase in amplitude, usually

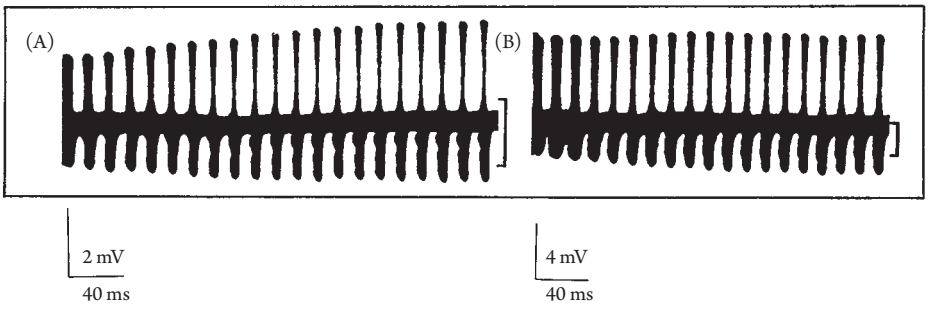


FIGURE 18-13 Muscle action potentials to a train of stimulation applied to the motor nerve at 50 Hz in a patient with botulism. Note incremental responses when the patient received a 7 mg/kg daily dose of guanidine (*A*) and electrophysiologic recovery after the dosage was increased to 35 mg/kg (*B*). (Modified from Cherington.[15])

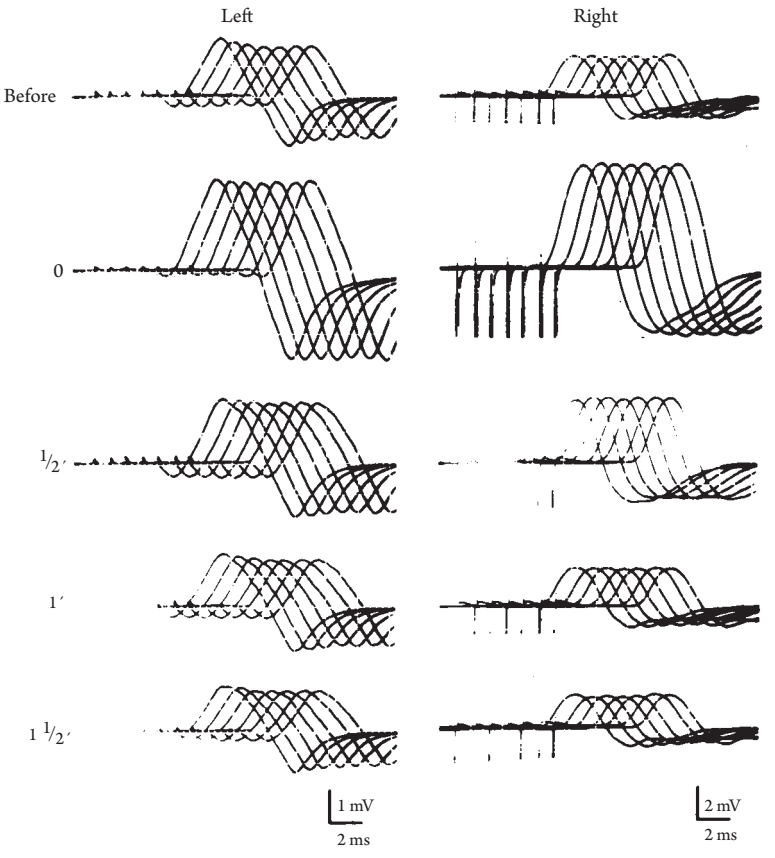


FIGURE 18-14 Thenar muscle potential elicited by a train of 3 Hz stimuli to the median nerve before and after 10 seconds of exercise in a patient with the myasthenic syndrome. Note a posttetanic potentiation of 70% on the left and 160% on the right immediately after the exercise and a posttetanic exhaustion, 1.5 minutes later.

reaching a level more than twice the baseline value, indicates a presynaptic defect of NMT.[52] Posttetanic augmentation lasts about 20 seconds showing less decay after cooling, reflecting slower removal of calcium ions from the nerve terminal.[57] Duration of exercise should not exceed 15 seconds to minimize depletion of ACh during voluntary contraction. In a series of nine patients with the LEMS, 5- and 10-second exercises caused the highest, and 30-second exercises, the lowest increment.[37] In general, a posttetanic potentiation greater than twice the preactivation response suggests the diagnosis, although the magnitude of changes varies considerably from one subject to another and during the course of the illness within the same patient (Fig. 18-16). A lesser degree of facilitation also implies a presynaptic disturbance seen not only in the LEMS but also in CMS, botulism, and occasional cases of MG.

The use of a train of stimuli at 3 Hz instead of a single shock allows simultaneous evaluation of the decremental and incremental trends. The procedure consists of repeating the same train before and immediately after the exercise and then every 30 seconds thereafter for a few minutes. In this arrangement, posttetanic potentiation partially compensates for depletion of ACh during each train, countering the deficit caused by the slow rate of stimulation (see Fig. 18-4). Thus, the characteristic decrement within a train seen in MG tends to normalize immediately after the tetanic stimulation, a phenomenon known as repair, which helps confirm the authenticity of the abnormality seen before the potentiation.

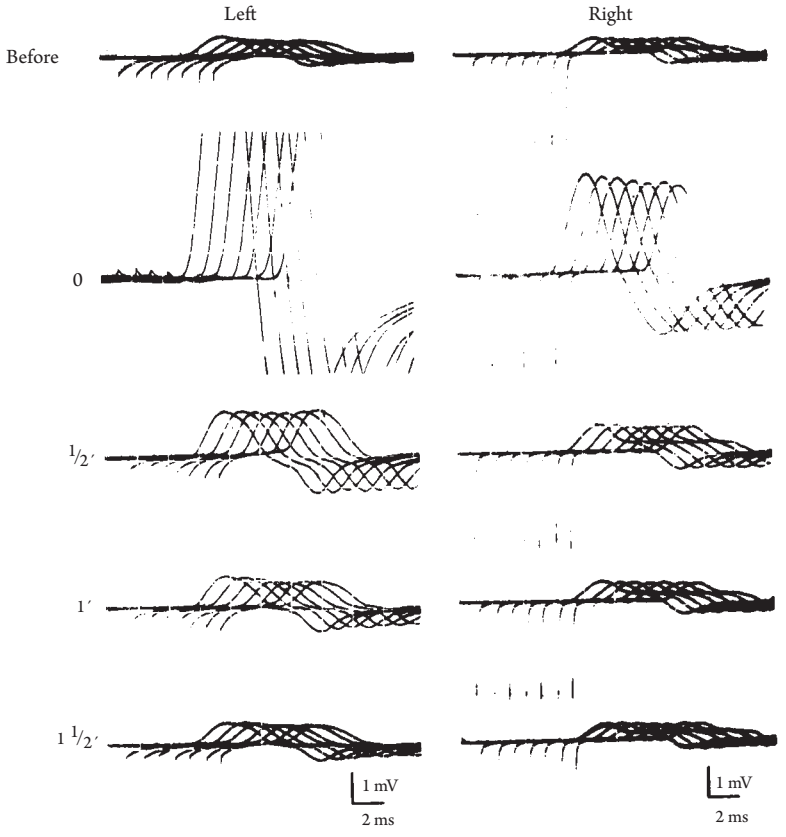


FIGURE 18-15 Repeat studies in the same patient as in Figure 18-14 using the same recording arrangements. Compared with the earlier study, the patient had further diminution in amplitude of the compound muscle action potentials and a greater posttetanic potentiation on both sides.

Posttetanic Exhaustion

In 2–4 minutes after exercise, decreased excitability of the neuromuscular junction follows a transient potentiation. The underlying physiologic mechanism for this phenomenon probably relates to the depletion of the immediately available store of ACh during prolonged contraction, despite an increased rate of ACh mobilization. In normals with a large margin of safety, the reduced amount of ACh released during posttetanic exhaustion will still generate an adequate EPP in each individual muscle fiber. In premature infants and some newborns with limited neuromuscular reserves, however, the CMAP amplitude progressively declines at high rates of stimulation.

In MG, neuromuscular block worsens during posttetanic exhaustion, indicating a reduced margin of safety. Some patients showing an equivocal decrement at rest may develop a definite abnormality after exercise (Fig. 18-4). In LEMS, a reduced endplate activity after exercise results in further diminution of the originally small CMAP (Figs. 18-15 and 18-16). Thus, the use of exercise increases the sensitivity of the nerve stimulation technique as a test of NMT, although it helps the yield in only a small percent of MG patients.[75] In the evaluation of posttetanic exhaustion, voluntary contraction for 1 minute results in optimal depletion of the ACh store. In contrast, a shorter exercise ranging from 10 to 15 seconds avoids excessive depletion of ACh for assessment of the posttetanic potentiation.

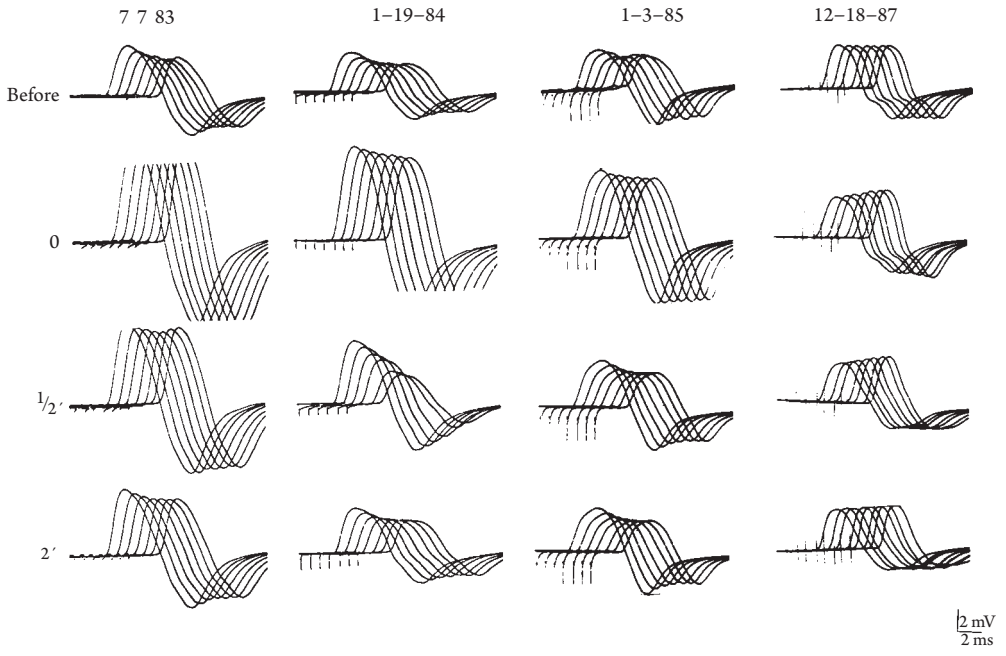


FIGURE 18-16 A 63-year-old woman with proximal weakness of all four extremities since October 1982. Each column shows thenar muscle potentials elicited by 3 Hz stimuli applied to the median nerve at the wrist before and after 15 seconds of exercise. Notice the gradual reduction in the magnitude of post tetanic potentiation from 1983 through 1987. In the last study, the exercise induced only an incrementing tendency within the train rather than the absolute increase in amplitude considered mandatory for the diagnosis of myasthenic syndrome.

8. EXERCISE TEST FOR MYOGENIC DISORDERS

A train of stimuli causes an apparent decrement of the CMAP in a number of myogenic disorders, such as McArdle's disease, myotonic dystrophy (DM1), myotonia congenita (MC), paramyotonia congenita (PMC), and periodic paralysis, but not in proximal myotonic myopathy or myotonic dystrophy Type II (DMII) (see Chapter 26-6).[48,89] Two types of exercise tests may help distinguish different excitability changes in a variety of myotonic disorders.[28,82] The short exercise test consists of obtaining stable baseline CMAP amplitude and 10 seconds of maximal muscle contraction followed by recording series of CMAP with single supramaximal nerve stimulation immediately post exercise and every 10 seconds thereafter up to 60 seconds. The long exercise test depends on 5 minutes maximal voluntary contraction of the target muscle, with a brief 5-second rest period every 25 seconds to prevent ischemia, followed by recording of CMAP by single supramaximal stimulation immediately after exercise and every 1 minute thereafter for 10 minutes, then every 2 minutes for 40 minutes.

Muscle Glycogenosis

In McArdle's disease and other disorders of muscle glycogenesis, painful, electrically silent muscle contracture develops after exercise (see Fig. 12-3 in Chapter 12). With rapid repetitive stimulation of a motor nerve, the amplitude of the CMAP progressively declines, eventually leading to the development of contracture.[12] During regional ischemia, a low rate nerve stimulation also gives rise to abnormal reduction of muscle response in patients with muscle glycogenoses but not in control subjects.[56]

Myotonia

In myotonic muscles, repetitive nerve stimulation commonly, though not invariably, produces decrementing responses.[26] Unlike the responses in MG, a train fails to show a repair, or leveling off, after the fourth or fifth stimulus. Instead, progressive decline continues for the initial few seconds followed by gradual recovery during subsequent stimulation for many seconds. In general, the higher the rate of stimulation, the greater the change in amplitude. The presence of clinical weakness also favors the possibility of finding prominent electrical decrement. The decremental tendency also worsens after exercise, gradually restoring the resting value in about 2–3 minutes. Direct stimulation of the muscle evokes decreasing response, suggesting an excitability change of the muscle rather than the neuromuscular junction.[13] Myotonic responses may show an initial increase after a long exercise, followed by progressive decline to a level below the baseline. In contrast, the amplitude of the muscle response diminishes below the baseline value immediately after short exercise followed by gradual recovery thereafter (Fig. 18-17).

The presence of a decrement varies according to the specific mutation type.[19,27] For example, change appears at a lower stimulation frequency in MC than in DMI, and a large decrement occurs especially in recessive MC.[73,89] The degree of partial inexcitability also depends on the mutation type rather than degree of clinical myotonia, although, in DMI patients, the degree of decrement shows no relationship to CTG repeat.[61] A train of stimulation at 10 Hz may serve better than a short exercise test for demonstrating abnormalities in recessive MC when warm and, to a lesser degree, when cold.[61] Despite clinical resemblance (see Chapter 28-2),[70,71,81,91] a post-exercise depression tends to emerge after 1 minute of voluntary contraction in DMI, and after a 5-minute exercise in DMII.[48,82] Combining repeated exercise with cold exposure may clarify the patterns of abnormalities, enabling a clear correlation between the electrophysiological and genetic defects (see Chapter 28-2).[4,27,28]

The decremental changes in myotonia may result from prolonged afterdepolarization, induced by accumulation of potassium in the transverse tubules.[3] Associated increase in activation threshold probably reflects a compensatory attempt by motor axons to overcome prolonged contraction-induced changes in the muscle membrane.[60] Myotonic bursts may also render some of the muscle fibers refractory to subsequent stimuli. A train of stimulation at 10–20 Hz gives rise to a progressive decline of single muscle fiber action potential associated with either increasing or decreasing propagation velocity.[49,62,93] Intracellular recording of a myotonic discharge also shows a progressive decline in amplitude.[76]

Paramyotonia Congenita and Periodic Paralysis

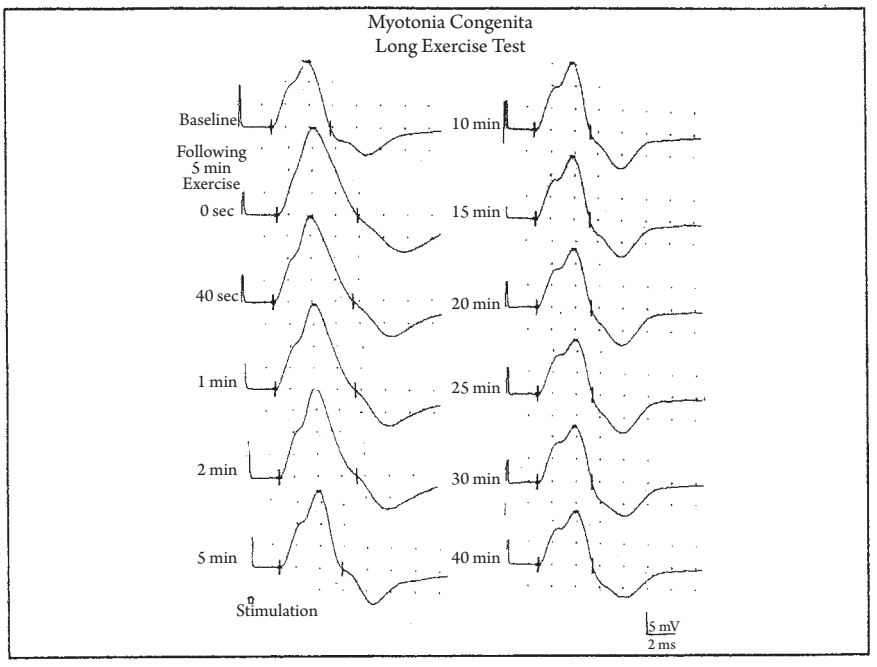
In PMC, cooling worsens both the weakness and electrical abnormalities. Thus, patients characteristically show a decremental response on repetitive stimulation, especially following cold exposure, and an equally typical cold-sensitive decrease in amplitude after exercise.[42]

In vitro study has shown decreased excitability of the muscle membrane in hypokalemic periodic paralysis (HypoPP).[77] This abnormality probably underlies the decline of the CMAP amplitude after prolonged exercise.[4,48] Decrementing response on repetitive stimulation also reflects increasing muscle membrane refractoriness.[72] During paralytic episode, a single stimulus elicits a small CMAP, which may progressively increase with sustained or intermittent repetitive stimulation of the nerve at high rates, although it falls again during rest.[14]

In hyperkalemic periodic paralysis (HyperPP), CMAP elicited by nerve stimulation usually shows an initial increase after a long exercise, followed by progressive decline to a level below the baseline value (Fig. 18-18). Short exercise tests may provide genetic guidelines for assessing myotonia.[28]

Cramp-Fasciculation Syndrome

Repetitive nerve stimulation may also help evaluate peripheral nerve hyperexcitability.[6,34] In one series, a train of stimuli at 1.2 and 5 Hz showed the presence of after-discharges, cramp potentials,



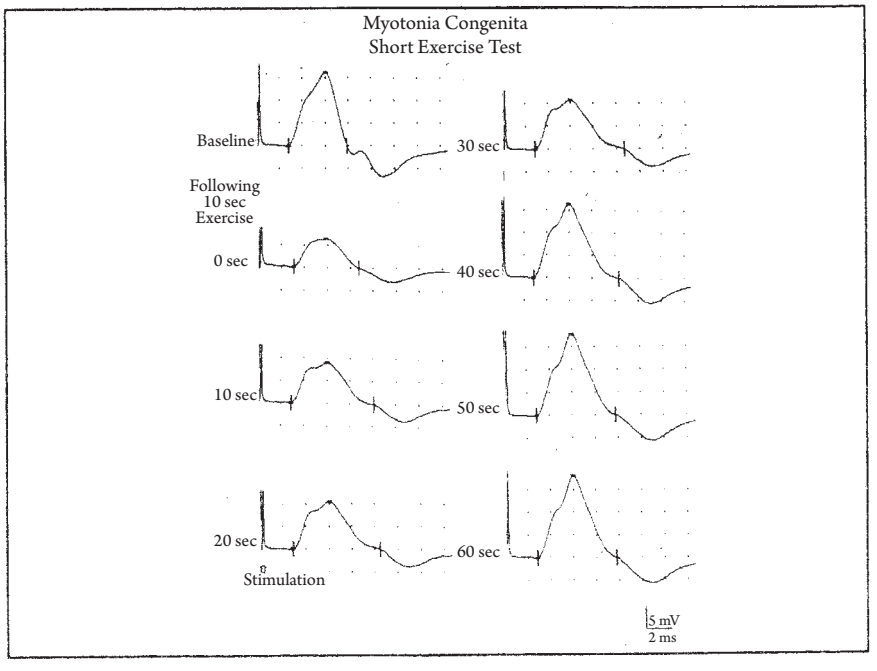


FIGURE 18-17 A 23-year old man with a form fruste of congenital myotonia. A long exercise test for 5 minutes with brief 5-second rest period every 25 seconds revealed a 30% increment compared to the baseline immediately after completion of muscle contraction, followed by an 8% decrement at 20 minutes and a 15% at 40 minutes. A short exercise test showed a 62% decrement immediately after a 10-second muscle contraction with gradual return thereafter. (Courtesy of Mark Ross, MD, Department of Neurology, Mayo Clinic, Scottsdale, AZ.)

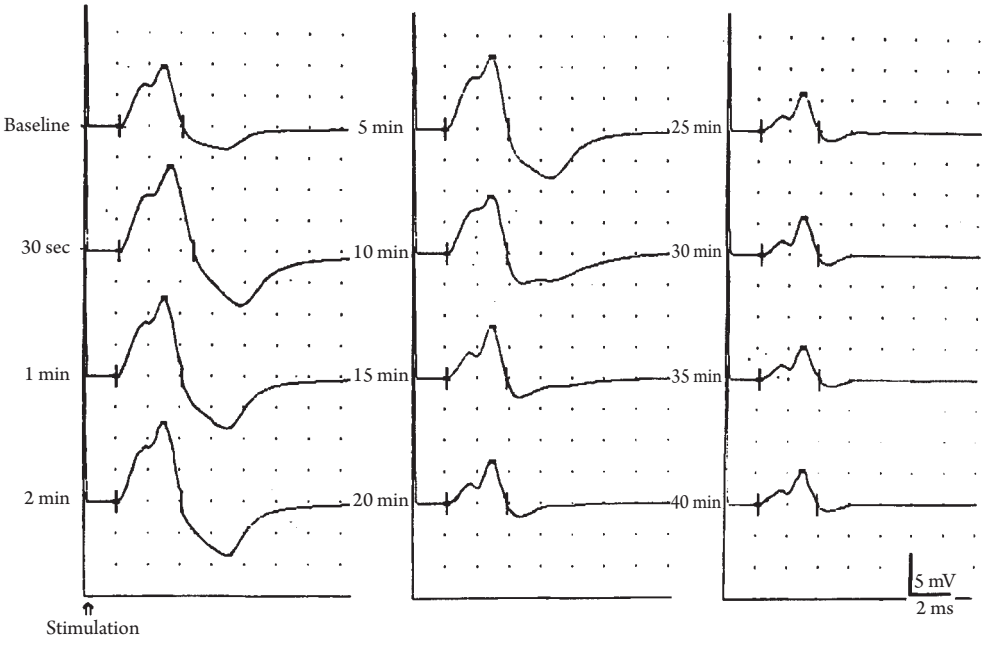


FIGURE 18-18 A 27-year-old woman with a 10-year history of hyperkalemic periodic paralysis occurring two or three times a year. Stimulation of the ulnar nerve at the wrist elicited a normal compound muscle action potential of the abductor digiti minimi (9.7 mV). After a 5-minute exercise alternating 25 seconds maximal contraction and 5 seconds rest, the response initially increased in amplitude, peaking at 30 seconds post exercise (13.5 mV): it then declined progressively throughout the test to a value below the baseline reaching a trough at 40 minutes (4.7 mV). Repetitive stimulation of the median or facial nerve at 3 Hz revealed no change in amplitude of the target muscle. (Courtesy of Mark Ross, MD, Department of Neurology, Mayo Clinic, Scottsdale, AZ.)

or continuous motor unit activity in 29 of 36 subjects with cramp-fasciculation syndrome.[33] In another study,[10] however, after-discharge following RNS commonly lasted more than 500 ms in both healthy controls and patients with peripheral neuropathy. Therefore, one must interpret the RNS-induced abnormalities with caution when evaluating patients for nerve hyperexcitability.

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PART VI

Somatosensory and Motor Evoked Potentials and Monitoring Procedures

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19

Somatosensory Evoked Potential

Abbreviations: BAEP—brainstem auditory evoked potential, CIDP—chronic inflammatory demyelinative polyneuropathy, CMT—Charcot-Marie Tooth disease, CTS—carpal tunnel syndrome, E1—active electrode, E2—reference electrode, ECG—electrocardiogram, EEG—electroencephalogram, FFP—far-field potential, GBS—Guillain-Barré syndrome, HAM—HTLV-I associated myelopathy, HMSN—hereditary motor sensory neuropathy, MND—motoneuron disease, MRI—magnetic resonance imaging, MS—multiple sclerosis, NFP—near–field potential, SEP—somatosensory evoked potential, SNAP—sensory nerve action potential, TMS—transcranial magnetic stimulation, VEP—visual evoked potential

1. INTRODUCTION

In contrast to conventional sensory nerve conduction techniques primarily used to evaluate the distal segment of the peripheral nerve, studies of somatosensory evoked potential (SEP) assess the entire length of the afferent pathways. Early work emphasized changes in amplitude and waveform in diseases of the cerebrum or spinal cord. More recent studies focused on the latencies of spinal and scalp SEP as a measure of central and peripheral neural conduction. This chapter will review

recording techniques and neural sources and discuss diagnostic values and limitations. Published studies have dealt mainly with the median and tibial nerves and, less frequently, with the ulnar and peroneal nerves, and only occasionally with nonlimb nerves such as the trigeminal and pudendal nerves.

2. TECHNIQUES AND GENERAL PRINCIPLES

Stimulation

Electrical, mechanical, or air-puff stimuli applied at any level can elicit an SEP.[55,95,263] The common sites of stimulation include median and ulnar nerves at the wrist, tibial nerve at the ankle, and peroneal nerve at the knee. A shock with intensity adjusted to cause a small twitch of the innervated muscle usually activates all the large myelinated, more easily excitable sensory fibers,[5] although monitoring peripheral sensory nerve action potentials (SNAPs) provides a more precise measure of stimulus strength.[81] The usual intensity for square wave pulses of 0.1–0.2 ms duration ranges from 10 to 30 mA, or for a skin resistance of 5 KΩ, from 50 to 150 V. A considerably weaker current suffices with subcutaneous shocks applied through a needle electrode inserted close to the nerve.

The optimal frequency and number of stimuli vary a great deal, depending on the components under study. Small spinal and scalp-recorded short-latency potentials need up to 4000 stimuli to achieve an adequate resolution. Most subjects tolerate the stimulation rate of 4 Hz or higher poorly. Medium- and long-latency components in the range of 20–200 ms intervals need only 200–400 stimuli delivered randomly at lower rates of 1 to 2 Hz. With shocks given every 30 ms or less, the later stimuli of a train may give rise to a disproportionately smaller response, presumably because of habituation.

Unilateral stimulation elicits short-latency components symmetrically over both hemispheres. Long-latency responses show an obvious asymmetry with major contralateral components, which can vary considerably from one trial to the next.[267] In contrast, simultaneous bilateral stimulation elicits symmetric responses of all the SEP components for instantaneous comparison between the two hemispheres. A routine evaluation in our laboratory consists of right and left unilateral stimulation to delineate abnormalities of short-latency peaks and bilateral stimulation for assessment of any asymmetry of medium- and long-latency components.

Recording

Topographic analyses depend on multichannel recording from 16 to 32 scalp areas. For clinical testing, two to four well-selected channels covering optimal recording sites suffice. The 10–20 International System (Fig. 19-1A) designates the scalp positions according to their specific anatomic locations. It derives its name from spacing the electrodes 10%–20% of the total distance between the nasion and inion in the sagittal plane and between right and left preauricular points in the coronal plane. The use of percentages, rather than absolute distances, provides flexibility for normal variations in head size and shape. On the basis of the anatomic relationship between electrodes placed according to the 10–20 system and cortical landmarks, the C3 electrode, for instance, lies within 1 cm of the central sulcus (Fig. 19-1B). Optimal scalp active electrodes (E1) include P3, P4, C3, or C4 contralateral to the side of stimulus for median and ulnar SEP and C1, C2, or Cz for peroneal and tibial SEP (Fig. 19-1C). A common reference electrode (E2) usually lies at Fz, the chin or connecting the ears, A1 and A2. An active electrode (E1) placed on the cervical or lumbosacral spinous process registers a spinal potential after stimulation of the nerves in the upper or lower limbs.

Unlike a near-field potential (NFP), a far-field potential (FFP) typically affects all scalp points nearly equally. Thus, they tend to cancel, if recorded between two cephalic leads, E1 and E2, which register no potential difference. In contrast, a knee or other noncephalic reference (E2), provides a good resolution for FFP.[269] A greater separation between the two recording leads generally amplifies the signal as well as background noises, which obscure the

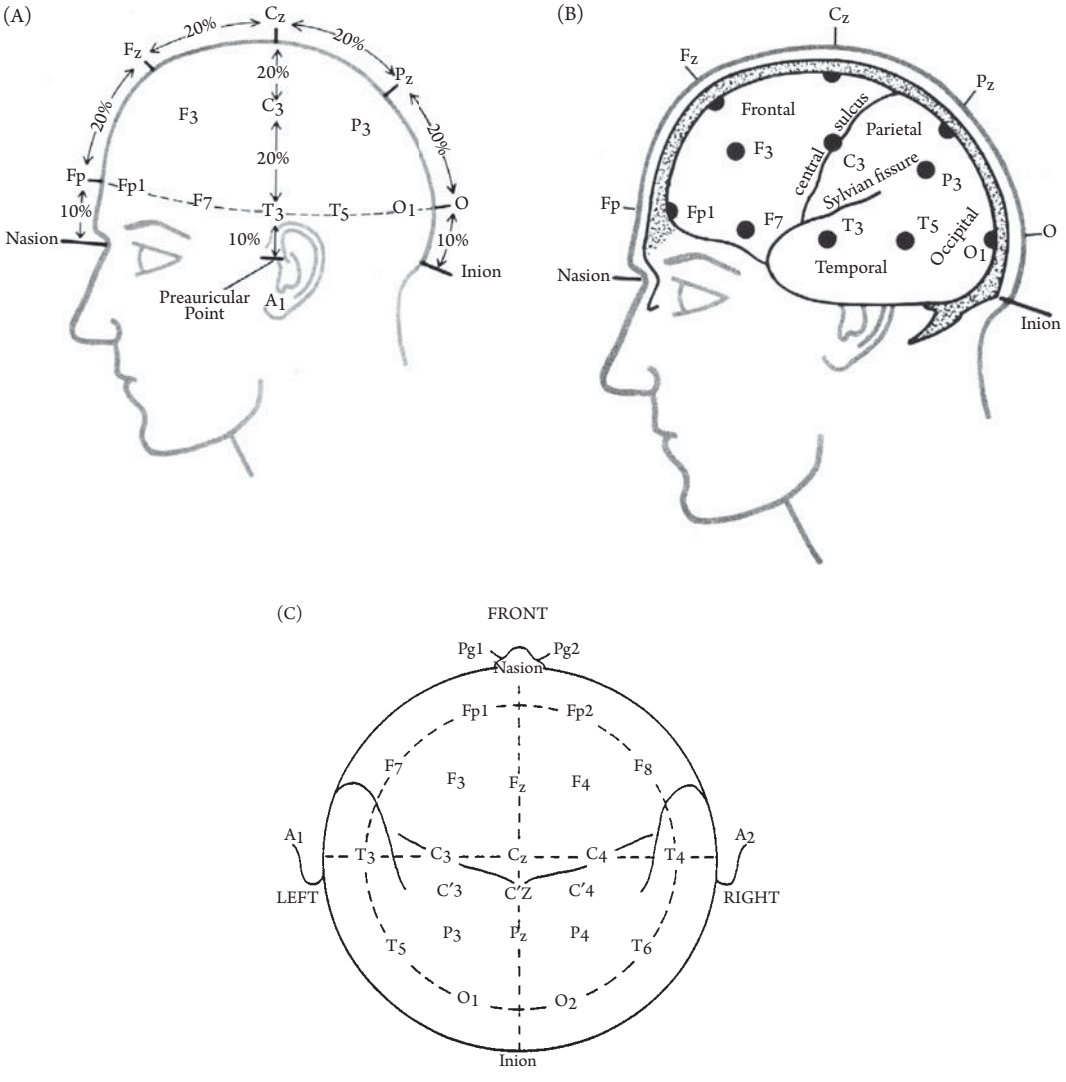


FIGURE 19-1 (***A***) The 10–20 International System based on electrode placement at either 10% or 20% of the total distance between skull landmarks. (From Harner and Sannit,[91] with permission.) (***B***) Relationship between central sulcus, sylvian fissure, lobes of the brain, and electrode positions. (From Harner and Sannit,[91] with permission.) (***C***) In this system, C3 and C4 electrodes correspond closely to the location overlying the central sulcus, whereas C′3 and C′4 electrodes placed 2 cm posterior to C3 and C4 lie over the postcentral gyrus. (Modified from Yamada.[263])

recording. Both E1 and E2 contribute to the size and shape of evoked potentials despite their designation, active, and reference leads. An "active" E2, if opposite in polarity to E1, helps enhance the signal under study, especially in assessing short-latency peaks. For example, recording the negative field with E1 at the neck and a concomitant positive potential with E2 over the ears substantially amplifies short-latency median SEP from the same source.

Averaging Procedure

Single-sweep SEP may emerge from ongoing electroencephalography (EEG) either by pharmacological suppression of background activity

with general anesthesia[105] or probalistic independent component analysis and wavelet filtering.[99] The usual practice, however, depends on averaging techniques. A commonly used instrument averages cerebral potentials after amplification by a factor of 10^4–10^5 with a frequency band of 5–10 Hz to 3–10 KHz. In special studies, a high-pass (low-frequency) restriction of 200–300 Hz may aid in selectively eliminating slowly changing events such as synaptic discharges.[154] A computer will then convert the amplified analog potential into a digital signal for online or offline analyses of the stored data. In general, an adequate study requires analog-to-digital (A/D) conversion with 10 to 12 bit resolution (2^{10}–2^{12} voltage levels or 1024–4096 separate voltage steps) and an intersample interval or dwell time per address of 100–500 μs (measurement taken every 100 to 500 μs or 10 to 20 separate points per millisecond). The study of medium- and long-latency components can use a sampling rate as slow as 1–2 ms per address, or 500–1000 times per second.

The memory core available, the number of channels employed, and the duration of total sweep time for each channel determine the sampling rate. A minimal sampling at twice the frequency of the signals under study provides adequate resolution of waveform to define the peak and trough of each complete cycle of a sine wave. For example, an analysis of 5 KHz components calls for a sampling rate of 10,000 times per second. Thus, the size of the memory core divided by twice the analysis time will dictate the limit of high-frequency analysis. Sampling for duration of 1 second at a 5-KHz cutoff, therefore, requires 10K of memory, whereas a shorter analysis time of 500 ms calls for only 5K of memory.

To exclude electrocardiogram (ECG) artifacts, muscle potentials, and other artifacts from averaging, the operator must either study each tracing separately and select only acceptable trials or use a computer program for automatic editing. A commonly used program, based on amplitude criteria, eliminates any unrealistically large potentials exceeding a predetermined level. Artifacts increase nearly in proportion to the distance separating E1 and E2, with a higher rate of rejection when referenced to the knee rather than the ear. A computer program with random triggering of the stimulus can automatically avoid the ECG artifact. Here, QRS complexes, defined as overloaded artifacts exceeding the duration of 100 ms, trigger the stimulus with a varying time delay of 0–200 ms following the overloaded period. A high-pass (low-frequency) filter setting of 30–100 Hz largely eliminates ECG T waves.

Dividing the sum of the responses by an artificial number lower than the actual trial count used in averaging tends to amplify small peaks that would otherwise barely exceed the baseline. The use of a small divisor, however, would excessively amplify the remaining larger component responses, truncating the peaks, which would fall outside the range of the oscilloscope display. A computer program can circumvent this difficulty by determining the smallest divisor that will retain the largest point within the display range. The oscilloscope displays the sum divided by this "adjusted trial count," with a correction factor applied to the computer measurement. Typically, the divisors range from 1/15 to 1/30 of the actual trial count.

3. FIELD THEORY

Near-Field versus Far-Field Potential

The near field relates to the propagating action potentials recorded as the impulse passes under the pickup electrodes, and the far field, a stationary potential generated by the signal away from the recording site (see Chapter 2-4). By definition, therefore, muscle and nerve potential used for study of the peripheral nerve conduction studies belong to the NFP even if the activity reaches the pickup electrode through a volume conductor. In SEP studies, the impulse elicited at the wrist and at the ankle arrives at the sensory cortex roughly 20 ms and 37 ms after stimulation. Thus, negative peak at 20 ms, or N_{20}, of the median nerve SEP and negative peak at 37 ms, or N_{37}, of the tibial nerve SEP represent the first NFP recorded over the scalp. Any peaks identified earlier imply the generation site before the signal arrives at the recording leads, that is, FFP. A referential montage preferentially detects the far-field activity, although it may also register the

near field if the impulse passes near E1 or E2 electrode. Far-field recording has gained popularity in the study of evoked potentials for detection of a voltage source generated at a distance.[28,54,131,226]

Like a scalp-recorded EKG artifact when studying an EEG recorded at high gain, stationary peaks of cerebral evoked potentials could originate from a fixed neural generator, such as those that occur at relay nuclei. The initial positive peak of the scalp-recorded median (P9) and tibial (P17) SEP, however, occurs before the propagating sensory nerve action potentials reach the second-order neurons in the dorsal column.[61,95,153,273] These peaks, therefore, must surely result from axonal volleys of the first-order afferents.[133] Why, then, does the far-field activity from a moving source appear as a nonpropagating potential at certain fixed points in time? The accumulating evidence indicates that a junction or boundary of volume conductors plays an essential role in the generation of this type of FFP.[71,131,133]

Animal and Human Studies of Peripheral Nerve Volleys

A series of important animal experiments[175] revealed interesting observations of the bullfrog's action potentials recorded by fluid electrodes, or Ringer's solution containing a nerve immersed through a slot of the partition. Stimulation of the nerve at the initial chambers gave rise to a biphasic action potential recorded by adjacent fluid electrodes in the subsequent chambers. With wider separation of the two recording electrodes, the number of action potentials increased to equal the number of the partitions between the electrodes. A subsequent experiment[175] demonstrated that the biphasic action potential recorded between the adjacent fluid electrodes became monophasic after sectioning of the nerve at the point of exit from the slot to the next compartment. Cutting the nerve at the point of its entrance into the slot totally abolished the evoked potential.

Studies of the peripheral sensory potentials in humans, as simple models of far-field recording, elucidated the possible physiologic mechanisms for the generation of stationary peaks from a moving source.[129,131,270] In referential recording of the antidromic median sensory potentials along the long finger, for example, a stationary positive peak developed coincident with the entry of the propagating sensory potential into the palm-digit junction. The same far-field activity may precede the M response as a premotor potential, depending on the electrode placement used for motor conduction studies.[62,185] In referential recording of antidromic radial sensory potentials (Fig. 19-2A), the digital electrodes detected two stationary peaks, PI-NI and PII-NII.[129,131] When compared with bipolar recording of the traveling source, PI occurred with the passage of the propagating sensory impulse at the wrist and PII, at the base of the digit (Fig. 19-2B). Systematic alteration of stimulus intensity has revealed that FFP occurs in proportion to the propagating volley detected at the boundary of the volume conductor (Fig. 19-3).[129]

The traditional concept of far-field activity emphasized a monophasic positivity, which reflects the approaching wavefront of depolarization. Recent findings indicate, however, that stationary activity from a moving source usually contains a major negative component that sometimes far exceeds the preceding positivity in amplitude and duration.[59,129,131] A computer model[227] predicts that the volume entered becomes initially positive compared with the volume departed regardless of the relative size of the adjoining conductors. A consensus has emerged that points on the far side begin to go positive when the generator approaches the boundary followed by a negative rebound (Fig. 19-4). Other major determining factors include the direction of axonal volleys as documented in the analysis of the median SEP.[120]

Concept of Junctional Potential

Why does a potential difference develop at the boundary with the arrival of the propagating volley? The external field induced by the traveling impulse probably undergoes an abrupt change in current density at the junction of the volume conductor regardless of the type of the propagating impulse.[17,106,131] Thus, an FFP may also originate in muscle tissue at the proximal and distal muscle tendinous junctions.[65] The waveforms recorded by surface electrodes in our model (Fig 19-2A)

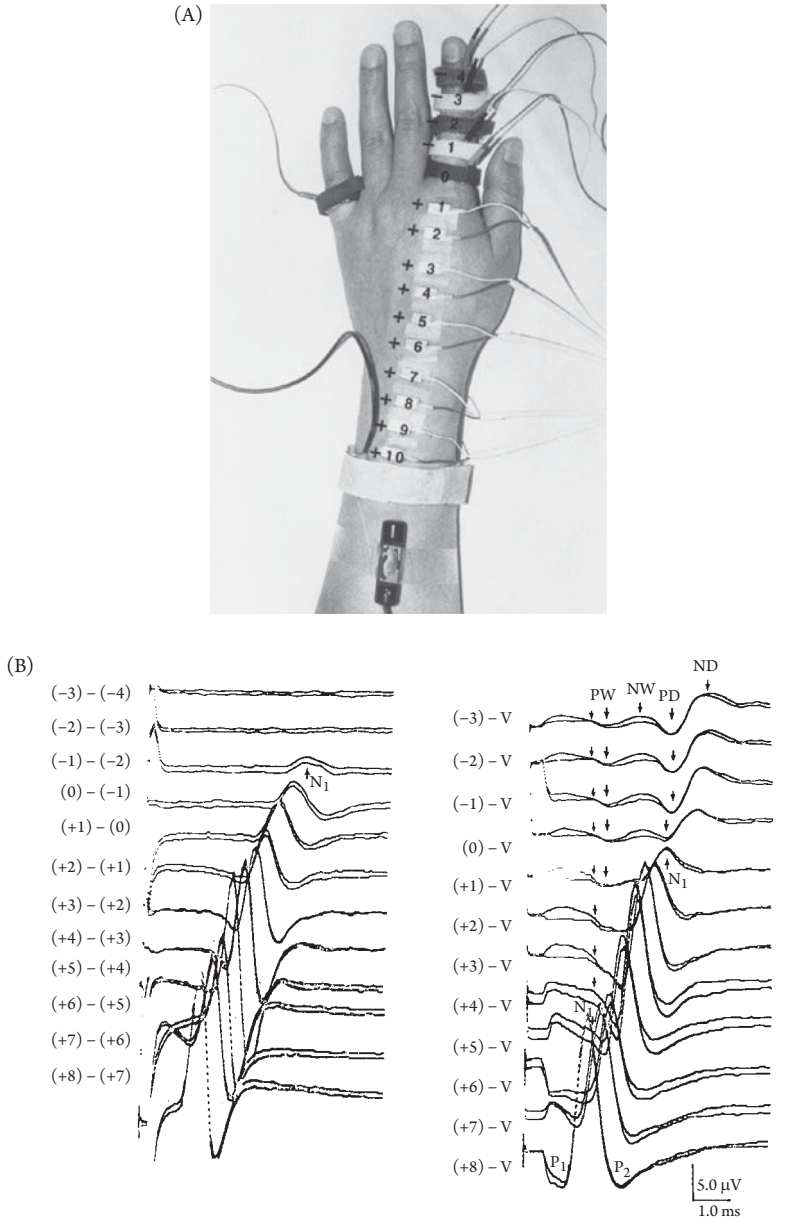


FIGURE 19-2 (***A***) Stimulation of the radial nerve 10 cm proximal to the styloid process of the radius and serial recording of antidromic sensory potentials in 1.5 cm increments along the length of the radial nerve. The "0" level at the base of the index finger indicates the site of abrupt volume conductor changes. In most hands, "+6" lies near the distal crease of the wrist, where another geometric transition takes place. The ring electrode around the little finger served as an indifferent lead for referential recording. (From Kimura, Mitsudome, Yamada, et al.,[131] with perimission.) (***B***) Sensory nerve potentials across the hand and along the index finger in a normal subject recorded antidromically after stimulation of the superficial sensory branch of the radial nerve 10 cm proximal to the styloid process of the radius. In a bipolar recording using adjacent points as E1 and E2 (left), the initial negative peaks, N (arrow pointing up), showed a progressive increase in latency and reduction in amplitude distally and no response beyond "–1." In a referential recording using the little finger (V) as E2 (right), biphasic peaks, P_W-N_W and P_D-N_D (arrows pointing down) showed greater amplitude distally, with a stationary latency irrespective of the recording sites along the digit. The onset of P_W extended proximally to the recording electrodes near the wrist (small arrows pointing down), whereas P_D first appeared at the base of the digit. (Modified from Kimura, Mitsudome, Yamada, et al.[131])

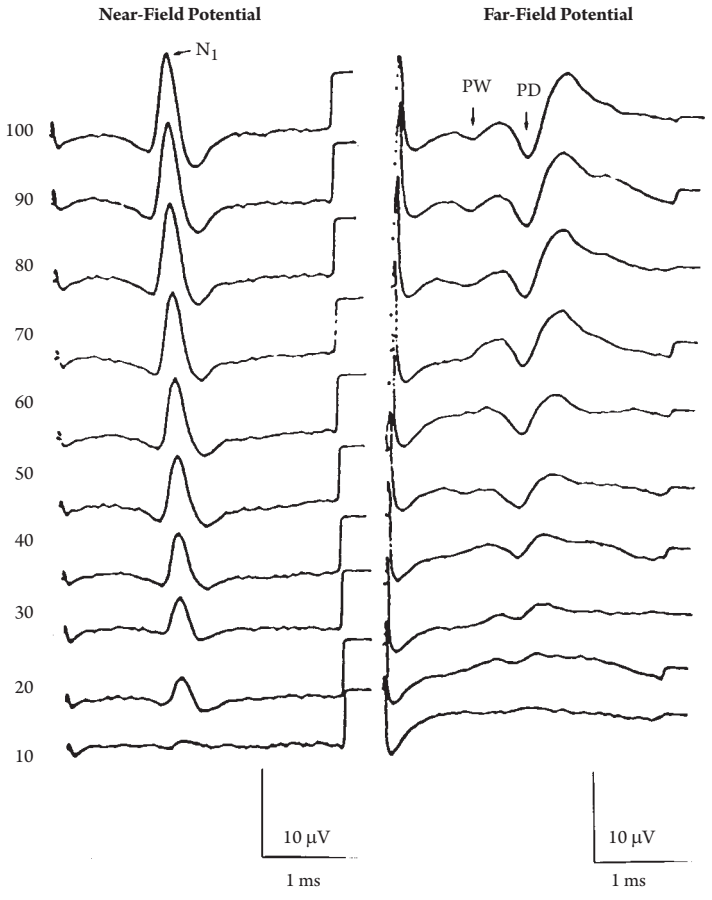


FIGURE 19-3 The far-field potential (FFP) recorded referentially with E1 at the tip of the index finger and E2 at the little finger, and near-field potential (NFP) registered bipolarly with E1 at the base of the digit and E2 2 cm proximally, after stimulation of the radial nerve. With reduction of stimulus from a maximal (top) to a threshold (bottom) intensity in 10 steps, the amplitude of FFP (PI and PII) declined in proportion to that of NFP (N1). (Modified from Kimura, Kimura, Ishida et al.[129])

bear a great resemblance to those registered by fluid electrodes in an in-vitro experiment.[175] As one of the essential characteristics of this phenomenon, the voltage step, once developed at the partition, appears instantaneously as a steady potential difference between the two compartments. Experimental studies using cylindrical and rectangular volume conductors have also contributed in elucidating the sources of stationary potentials.[63]

To draw an analogy (Fig. 19-5A,B), an oncoming train (axonal volley) becomes simultaneously visible (far field) to all bystanders on the far side (Fig. 19-5B) as it emerges from a tunnel (partition of the volume conductor), whereas the same bystanders see the train pass by at different times (near field), depending on their position along the railroad (Fig. 19-5A)[127,129] The designation junctional potential specifies the source of the voltage step by location and differentiates this type of far-field potential from those originating from a fixed neural generator, for example, EKG artifacts recorded from scalp electrodes. A pair of electrodes positioned only a short distance apart provides the best means of detecting such a stationary potential, if placed across the partition in question.[128,218] This observation calls for reassessment of the commonly used dichotomy

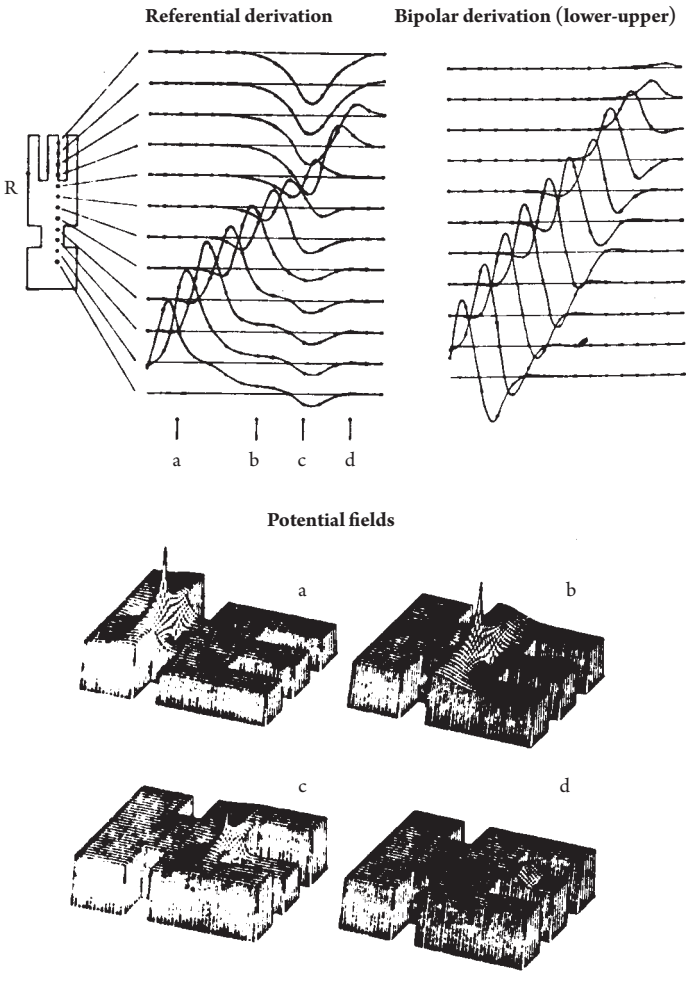


FIGURE 19-4 Representation of antidromic sensory action potentials transmitted through a three-"fingered" "hand" with independent attenuation of sources and sinks on propagation through the hand, such that the initial source reaches zero amplitude first. The examples include calculated potential fields (bottom), and referential (top left) and bipolar (top right) waveforms of potential at 12 recording sites against generator position. In Field a, the whole hand has acquired a potential of the same polarity as the initial generator source. In Field b, a stationary potential begins to appear throughout the length of the middle digit, reaching a peak at Field c. In Field d, the final potential present at the tip of the middle digit shows a negative polarity relative to the reference on the lateral digit, as in the actual recordings (cf. Figure 19-2B). (Modified from Cunningham, Halliday, and Jones.[47])

that equates bipolar and referential montage with near- and far-field recording.

Clinical Implications

Despite common belief to the contrary, the complex waveform of far-field SEP reflects primarily the physical relationships between the nerve and the surrounding conducting medium. The animal and human data provide strong, albeit indirect, support that most, if not all, of the scalp-recorded early stationary peaks result from an abrupt alteration in current flow at various boundaries of the volume conductor. For example, the initial positive peaks of the median (P9) and tibial SEP (P17) arise when the propagating volleys enter the shoulder and pelvic girdles.[131] Similarly, the second positive peaks of the median (P11) and tibial SEP (P24), at least in part, reflect changes in geometry as the impulses reach the cervical cord

and conus medullaris. The latencies of these early components suggest the arrival of impulse at the respective boundary, supporting this view.[71,77] As expected, a change in the position of the shoulder girdle slightly, but significantly, alters its latency and waveform.[93]

Hence, far-field peaks used in clinical analysis of the afferent system do not relate exclusively to a specific neural generator. As an inference, certain abnormalities of somatosensory and other evoked potentials could result from changes affecting the surrounding tissue and not

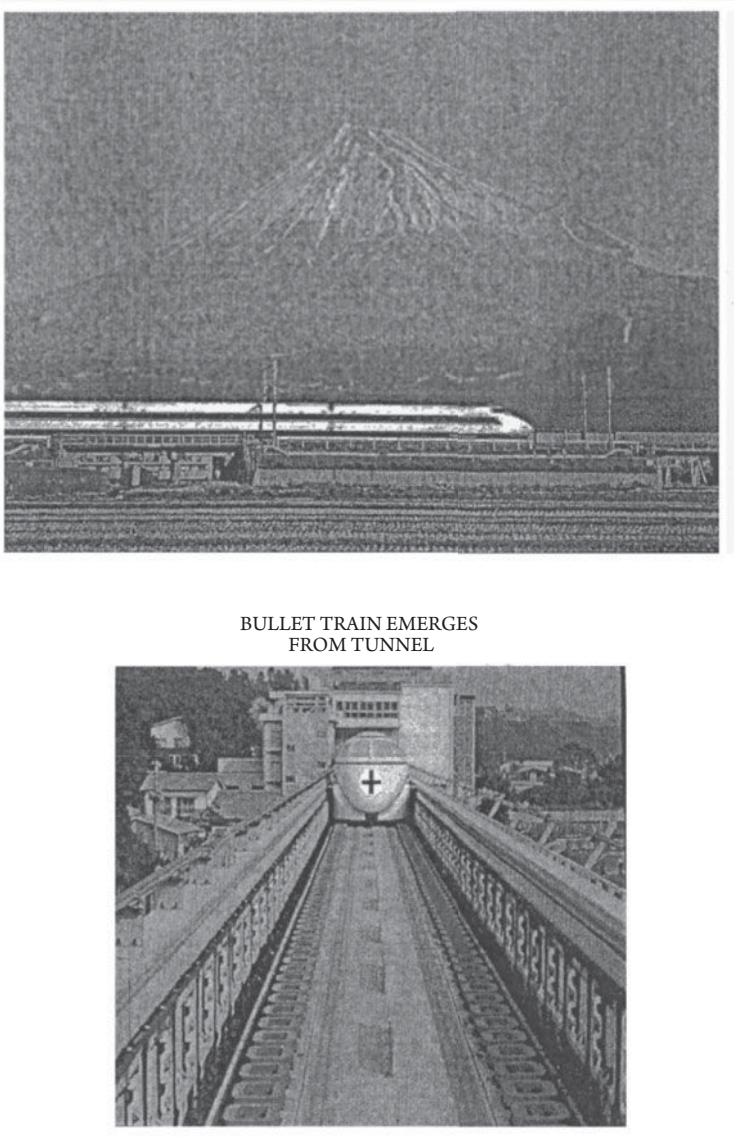


FIGURE 19-5 Train analogy of a near-field (top) and far-field (bottom) potential as described in the text. In near-field recording (top), two bystanders (electrodes) situated along the track can time the train (signal) as it passes under the electrode and measure the position- dependent latency to calculate the speed. In far-field derivation (bottom), any onlookers (electrode) on the far side of the field can time the train (signal) as it emerges from the tunnel (volume conductor junction), enabling measurement of the signal arrival at the boundary before it actually reaches the pickup electrode (onlookers). Note a "+" sign on the train front, indicating an approaching face of positivity.

necessarily from the sensory pathways per se. Nonetheless, clinical studies of cerebral evoked potentials can exploit far-field recording in the evaluation of subcortical pathways not otherwise accessible. These junctional potentials render clinically useful information about the arrival of the impulse at a given anatomic landmark and provide an indirect measure of the sensory potential, which linearly relates to the amplitude of the stationary peak.[129]

4. NEURAL SOURCES OF VARIOUS PEAKS

Nomenclature

Considerable confusion exists in the analysis of SEP because various authors use different nomenclature for the same waveforms.[6,103] Some describe the components by location and sequence, like CP for cervical potential and IP, NI, PI, and NII for initial positive and subsequent negative and positive scalp-recorded potentials. Others specify the average peak latency to the nearest millisecond, like cervical N13 or scalp-recorded P14, N17, P20, and N29. The actual latency of the same component varies individually, reflecting the different lengths of the somatosensory pathways, most peaks showing a good correlation with height. Ideally, the names of the various components should indicate the respective neural sources, but the exact generator sites of most peaks remain unclear.

Median and Ulnar Nerves

Several studies have confirmed the presence of short-latency SEPs in adults[31,44,153] and children.[143] The multichannel SEP recorded simultaneously from the scalp and cervical electrodes helps delineate the field distribution of such short-latency components (Figs. 19-6A,B) as summarized in Table 19-1. Stimulation of the ulnar nerve, although uncommonly done, has revealed comparable results.[68] Some studies have dealt with normative data in children[283] and preterm and term infants[121] (see Chapter 29-9) showing complex maturational changes that complicate the interpretation.[84]

Stimulation of the median nerve at the wrist elicits cervical potentials consisting of four negative peaks, N9, N11, N13, and N14, when referenced to the tied ears (Fig. 19-6A).[266] The corresponding scalp potential recorded with the use of the knee reference contains four positive peaks: P9, P11, P13, and P14 (Fig. 19-6B). Negative peaks, N10 and N12, between these positive components may constitute separate peaks.[221] Recording with ear reference, scalp-recorded far-field peaks consist of P13 and P14 without earlier components, which make the scalp and ear equally positive. These four peaks of the cervical and scalp-recorded SEP normally occur within the first 15 ms followed by a small but distinct negative peak, N18, recorded bilaterally in the frontal region as negative FFP.

As mentioned earlier, the field distribution of the first component shows a diagonal orientation with negativity at the shoulder and axilla and positivity over the entire scalp and neck (Fig. 19-7). Thus, the earliest scalp potential, P9,[44] originates from a distal portion of the brachial plexus and contributes to N9 of the cervical potential recorded by means of a scalp reference.[110] Indeed, the earliest cervical potential shows relative positivity if recorded with a noncephalic reference.

According to an estimation based on nerve conduction studies, sensory impulses reach the spinal cord in 10–11 ms after stimulation of the median nerve at the wrist.[69,132] Thus, N11 starts upon arrival of the peripheral nerve volley at the spinal cord level. It closely relates to the activity recorded from the side of the neck ipsilateral to the stimulation. The characteristics of the refractory period indicate the presynaptic nature of this component.[74] The neural source of N11, therefore, must lie near the entry zone, with scalp-recorded P11 reflecting the positive end of the same field.[266] Some investigators, however, have observed a delayed N11 in patients with cervical cord and medullary lesions. This finding would imply a more rostral origin.[11]

Despite considerable clarification during recent years, the origin and identity of N13/P13 components still rank among the most controversial SEP topics.[281] The negativity reaches a maximum at the cervical level with decreasing amplitude rostrally and caudally.[266] A slight delay

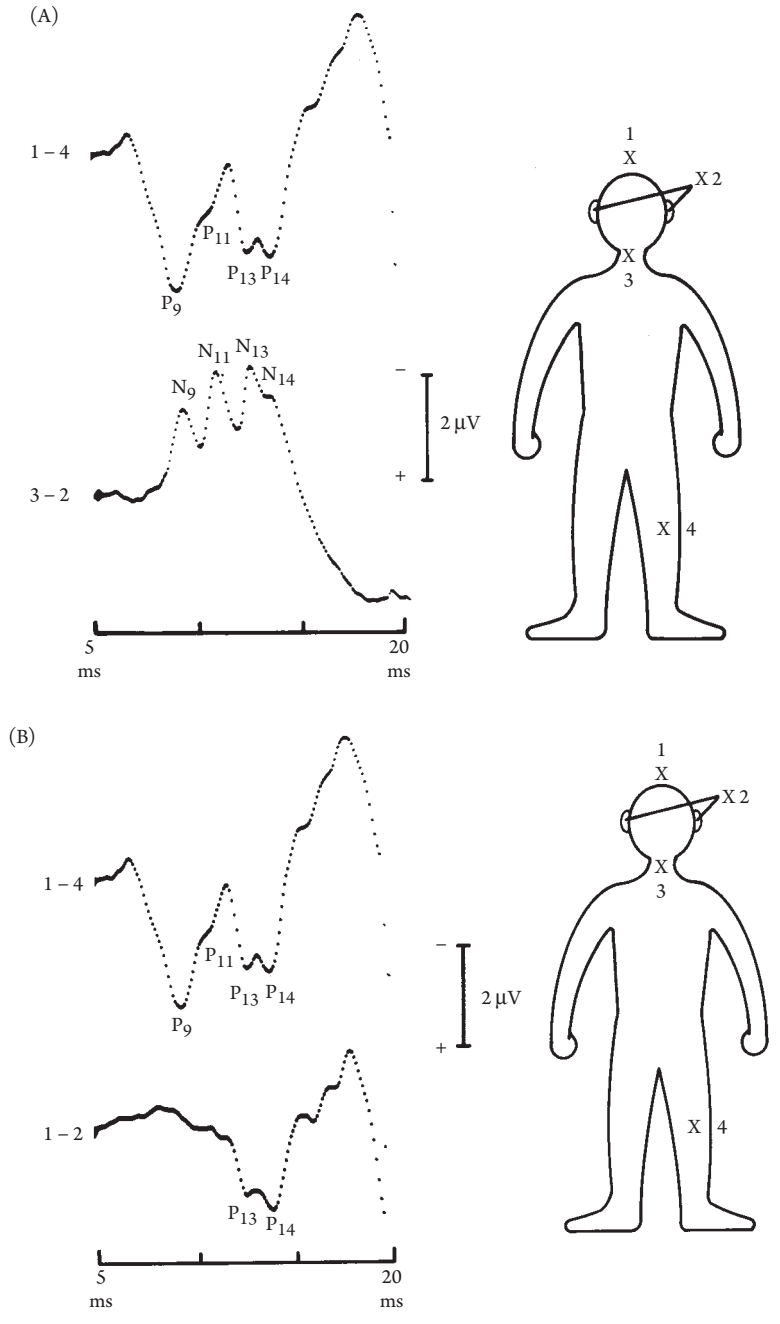


FIGURE 19-6 (***A***) Simultaneous recording from Cz (1) referenced to knee (4) and low cervical electrode (3) referenced to ear (2) after stimulation of the median nerve at the wrist in a normal subject. Four positive peaks, P9, P11, P13, and P14, recorded at Cz showed a nearly identical latency to four negative peaks, N9, N11, N13, and N14, recorded at the low cervical electrode. (***B***) Simultaneous recording from Cz (1) with knee (4) or ear (2) reference after stimulation of the median nerve at the wrist in the same subject as (***A***). Of the four positive peaks, P9, P11, P13, and P14, recorded with a knee reference, only P13 and P14 appeared when referenced to the ear. (Modified from Yamada, Kimura, and Nitz.[266])

Table 19-1 Short-Latency Median Nerve SEPs in 34 Normal Subjects

COMPONENTS	LATENCY (LEFT AND RIGHT COMBINED)			LATENCY DIFFERENCE (BETWEEN LEFT AND RIGHT)		
	NO. IDENTIFIED	MEAN ± SD (ms)	MEAN + 3 SD (ms)	NO. IDENTIFIED	MEAN ± SD (ms)	MEAN + 3 SD (ms)
Short-Latency Peaks						
Erb's potential	68	9.8 ±0.8	12.2	34	0.4 ± 0.2	1.0
P_9	68	9.1 ± 0.6	10.9	34	0.4 ± 0.2	1.0
N_{11}	43	11.2 ± 0.6	13.0	19	0.4 ± 0.3	1.3
P_{13}	68	13.2 ± 0.9	15.9	34	0.5 ± 0.4	1.7
P_{14}	55	14.1 ± 0.9	16.8	25	0.5 ± 0.4	1.7
N_{18}	68	18.3 ± 1.5	22.8	34	0.5 ± 0.5	2.0
Inter-Peak Intervals						
P_9–P_{11}	43	2.2 ± 0.3	3.1	19	0.2 ± 0.2	0.8
N_{11}–N_{13}	43	1.9 ± 0.4	3.1	19	0.2 ± 0.2	0.8
N_{13}–P_{14}	55	1.0 ± 0.4	2.2	25	0.3 ± 0.2	0.9
P_{14}–N_{18}	55	4.2 ± 0.9	6.9	25	0.7 ± 0.5	2.2
P_9–N_{13}	68	4.0 ± 0.4	5.2	34	0.3 ± 0.3	1.2
N_{13}–N_{18}	68	5.1 ± 0.9	7.8	34	0.6 ± 0.5	2.1

(Modified from Yamada, Shivapour, Wilkenson, et al.[273])

of N13 at higher cervical electrodes suggests the presence of a traveling wave.[132] Recordings of N13 from esophageal electrodes or from anterior neck electrodes clearly establish the existence of an anteroposterior field with positivity anteriorly and maximum amplitude below the foramen magnum.[113] These findings suggest that the near-field N13 recorded over the cervical spine probably originates in the dorsal horns, although ascending volleys in the dorsal column may also contribute. Lesions at the cervicomedullary junction spare N13 while abolishing subsequent components.[162] Some investigators have recorded two subcomponents with different orientations, N13a/P13a and N13b/P13b, possibly corresponding to generators in the dorsal horns and the cuneate nucleus.[112] Epidural, pial, and subpial recording allows detection of additional low-amplitude, high-frequency waves superimposed on P9-N13, presumably related to the cuneate fascicles.[56,189]

The third positive scalp potential consists of two different generator sources, P13 and P14, as evidenced by its bilobed appearance.[44] Debates continue on whether scalp-recorded P13 represents the phase reversal of N13 from the dorsal horn[54] or corresponds to the ascending volley of the posterior column.[11,167,266] A small and at times equivocal P13, recorded over the scalp, stands in contrast to N13, which represents the largest cervical potential. Some believe that P13 originates below the foramen magnum[162,251] whereas others,[123] on the basis of intracranial recordings in humans, propose that P13, like P14, arises from volleys ascending in the medial lemniscus at the brainstem level. Although the origin of P13 remains uncertain, it probably corresponds to N13 arising from the cervical cord, which consists of at least two subcomponents, as mentioned earlier.[113,222]

Earlier studies suggested that P14 might arise in the thalamus,[44] as supported by SEP recorded in humans from the nucleus ventralis caudalis at a mean onset latency of 13.8 ms.[27] The preservation of P14 in patients with cerebral,[11] thalamic,[169] or mesencephalic lesions,[31] however, implies a more caudal location of the neural

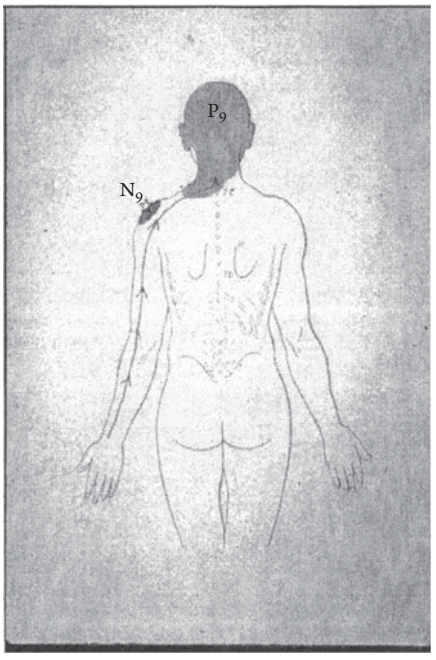


FIGURE 19-7 Relationship between far-field potential recorded at the scalp (P9) and the near-field potential recorded at the shoulder (N9). The positive peak, P9, emerges diffusely in the head as the negative peak, N9, crosses the volume conductor junction at the shoulder.

source. Furthermore, this component shows no phase reversal between scalp and nasopharyngeal recordings,[266] a finding not expected for a potential generated in the thalamus (Fig. 19-8). Unlike N11 or N13, a cervical electrode barely detects N14 in most subjects, indicating its neural source rostral to the cervical spine. All of these observations together suggest that P14 originates rostral to the cuneate nucleus,[184] at least in part representing a junctional potential of the medial lemniscus impulse crossing the foramen magnum.[107,134]

The polarity characteristics of the short-latency SEP suggest that a negative field near the generator site gives rise to the cervical potentials and that scalp recorded peaks reflect FFP from the same source. Based on the polarity and mean latency, the presumed generator sites include (1) entry to the brachial plexus at the shoulder (N9 and P9), (2) entry to the cervical cord at the neck (N11 and P11), (3) dorsal column volley with possible contribution from dorsal horn interneurons and the cuneate nucleus (N13 and P13), and (4) entry to the medial lemniscus at the foramen magnum (N14 and P14). Of these, P9, P11, and P14 represent, at least in part, a junctional potential generated by propagating volleys crossing the geometric partition at the shoulder, neck, and foramen magnum. For clinical application, a combined recording from the scalp with a noncephalic reference or from the neck with a cephalic reference best delineates short-latency SEP (Figs. 19-6B).[262]

Negative-positive peaks, NI, PI, and NII, subsequent to P14 (Fig. 19-9 and 10), show the shortest latency at the frontal electrodes (N17, P20, and N29), with a progressive delay toward the central (N19, P23, and N32) and parietal areas (N20, P26, and N34). In contrast to a small N18 recorded bilaterally in the frontal region, the first major negative peaks, N19 and N20, skew to the hemisphere contralateral to the side of stimulation. The vertex and ipsilateral, and occasionally contralateral, central electrodes may also register the first negative peak, N18. In this case, N18 precedes N19 as an additional separate peak, suggesting the presence of two distinct components of independent neural origin. Table 19-2 summarizes medium-latency and long-latency near-field components, which consist of N19, P22, N30, P40, and N60, or, according to another nomenclature, NI, PI, NII, PII, and NIII (Figs. 19-9 and 10).

The appearance of N18 after P14, which arises in the medial lemniscus, initially suggested its origin in a thalamic or subthalamic structure.[160,250] The slow negative component, N18, however, appears on the scalp with a latency shorter than that of the negativity in the thalamus. An extensive thalamic[161] or pontine lesion,[219] which abolishes N20 and subsequent components, may spare N18. A far-field theory predicts the generation of a slow negative rebound after positive peaks, P9, P11, P13, and P14, as the ascending impulse crosses the shoulder and foramen magnum.[128,235] Documented cases with involvement of P14 without change in N18 [220] and dissociated effect of vibration on these two components[158] may imply even more caudal onset of N18, perhaps representing, at least in part, the slow negative sequelae of P9 generated at the brachial plexus.

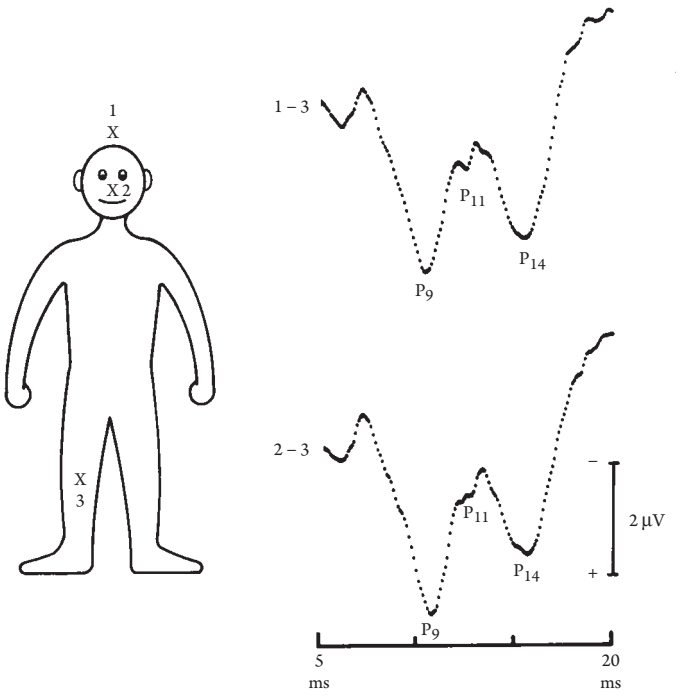


FIGURE 19-8 Responses recorded from Cz (1) and a nasopharyngeal electrode (2) using a knee reference. The identical waveform of P14 in both tracings indicates its generation source caudal to both recording sites below the base of the skull. (Modified from Yamada, Kimura, and Nitz.[266])

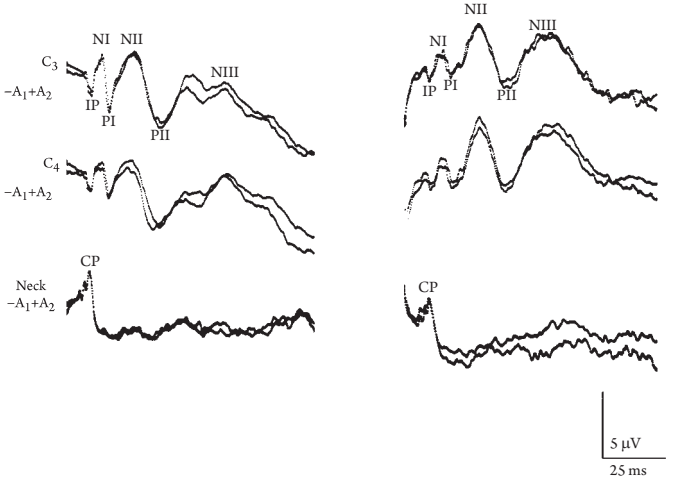
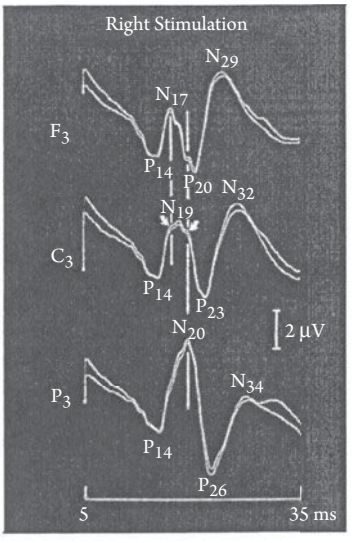


FIGURE 19-9 Tracings recorded from the left (C3) and right (C4) central regions of the scalp and the mid neck, all referenced to the connected ears after simultaneous bilateral stimulation of the median nerve at the wrist in two normal subjects. The initial positive potential (IP) consists of P13 and P14, and cervical potential (CP), N9, N11, N13, and N14. The subsequent negative and positive peaks, NI, PI, NII, PII, and NIII, correspond to N19, N22, N32, P40, and N60. (Modified from Yamada, Machida, and Kimura.[269])



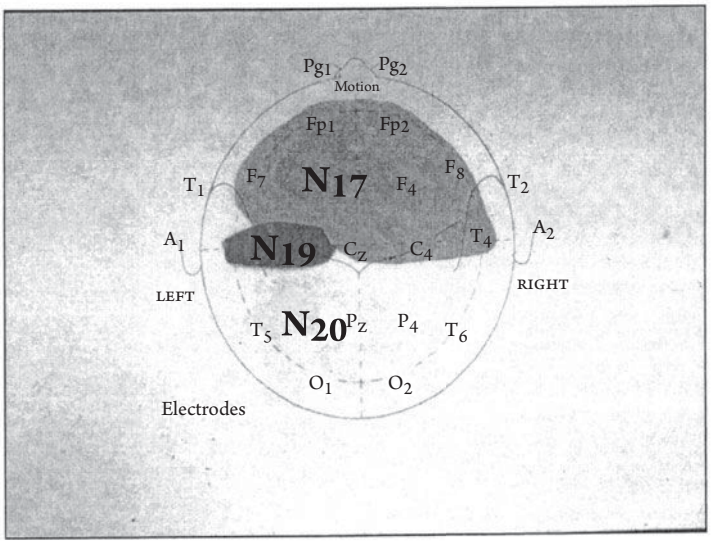


FIGURE 19-10 A median nerve somatosensory evoked potential (SEP), recorded after unilateral stimulation on the right in a normal subject. Topographic analysis indicates regionally specific near-field peaks N17-P20-N29 recorded bifrontally (F3), N19-P23-N32 at contralateral central electrode (C3), and N20-N34 at contralateral parietal (P3) and occipital electrodes. (Modified from Yamada, Kayamori, Kimura, et al.[265])

Topographic analyses have shown conflicting results regarding the possible dipole relationship between parietal N20 and frontal P20.[254] Despite a similarity in latency, close scrutiny reveals that P20 has a slightly later onset than N20.[53] The N20 and P20 show distinct amplitude changes with increasing stimulus frequency, indicating that these potentials arise from separate generators.[52] The dipole theory also falls short of providing an adequate explanation for some of the reported observations in clinical context. For example, patients with motoneuron disease (MND) show selective alteration of prerolandic potentials.[280] Conversely, those with anterior lesions may show preservation of the parietal N20 despite substantial loss of frontal P20. These findings suggest a radially,

Table 19-2 Medium and Long-Latency Median Nerve SEPs in 34 Normal Subjects

COMPONENTS	LATENCY (LEFT AND RIGHT COMBINED)			LATENCY DIFFERENCE (BETWEEN C3 AND C4)		
	NO. IDENTIFIED	MEAN ± SD (ms)	MEAN + 3 SD (ms)	NO. IDENTIFIED	MEAN ± SD (ms)	MEAN + 3 SD (ms)
N_{19} (NI)	68	18.1 ± 1.6	22.9	34	0.4 ±0.4	1.6
P_{22} (PI)	68	22.8 ± 2.3	29.7	34	0.6 ± 0.4	1.8
N_{32} (NII)	68	31.6 ±2.6	39.4	34	0.5 ± 0.4	1.7
P_{40} (PII)	68	43.6 ± 3.6	54.4	34	0.6 ± 0.5	2.1
N_{60} (NIII)	64	62.8 ± 9.3	90.7	32	1.5 ±1.1	4.8

(Modified from Yamada, Shivapour, Wilkenson, et al.[273])

rather than tangentially, oriented dipole mainly in the parietal area.[96] To further confound the issue, the central P22 may have yet another independent source, showing radial orientation over the precentral gyrus[255] or postcentral gyrus.[26]

Electrical stimuli applied to the proximal but not distal phalanx of the thumb evoke the subsequent component, NII (N30).[192] The proximal phalanx have both deep and cutaneous afferent, whereas the distal phalanx contains only the cutaneous afferents. Therefore, joint and tendinous input may evoke fontrocentral N30 in either precentral or postcentral areas.[193] The last negative peak, NIII (N60), shows a wider distribution over the cortex, with greater temporal variability than the earlier peaks. In contrast to the short-latency responses relayed by specific oligosynaptic routes, a nonspecific polysynaptic pathway probably mediates the middle-latency and long-latency response. Scalp topographic analysis showed distinct fronto-central N60 and supra-sylvian N70 components.[14]

Table 19-3 Short-Latency Tibial Nerve SEPs (A) and Negative Peaks along the Somatosensory Pathway (B) in 21 Healthy Subjects

RECORDING (A) POSITIVE COMPONENTS	SCALP					
	P_{11}	P_{17}	P_{21}	P_{24}	P_{27}	P_{31}
Mean ± SD (ms)	11.4 ± 2.7	17.3 ± 1.9	20.8 ± 1.9	23.8 ± 2.0	27.4 ± 2.1	3l.2 ± 2.1
No. recorded	22	40	21	39	30	40
No. tested	40	40	40	40	40	40
RECORDING (B) NEGATIVE COMPONENTS		GLUTEUS	L4	T12	C7	C2
		N_{16}	N_{21}	N_{23}	N_{28}	N_{30}
Mean ± SD (ms)		16.4 ± 3.2	20.9 ± 2.2	23.2 ± 2.1	27.6 ± 1.8	30.2 ±1.9
No. recorded		20	40	40	18	25
No. tested		22	40	40	22	26

(Modified from Yamada, Machida, and Kimura.[269])

Tibial and Peroneal Nerves

The tibial SEP serves better for routine clinical use, showing a larger amplitude and less inter-subject variability in waveform and topography than the peroneal SEP.[187] The scalp-recorded potentials usually begin with N33-P35 after stimulation of the peroneal nerve at the knee and N37-P40 after stimulation of the tibial nerve at the ankle .[132,257] The peroneal or tibial SEP also contains earlier peaks (Table 19-3) that correspond to the short-latency components of the median SEP.[117,152,218,258,269] Recording these small potentials requires particular attention to technical details and a greater number of trials for averaging. Stimulation of the tibial nerve at the ankle evokes three regular components, P17, P24 and P31, when referenced to the knee; P24 and P31, when referenced to the iliac crest; and only P31 when referenced to the ear or shoulder (Fig. 19-11). Less consistent peaks include P11, P21, and P27 diffusely over both hemispheres depending on the location of reference.

Simultaneous recordings from multiple levels along the somatosensory pathway suggest that P17 originates in the peripheral nerve, P24 in the spinal cord, and P31 in the brainstem (Fig. 19-12). The initial component results when the propagating nerve potential renders the trunk and scalp more positive (P17) than the leg, concomitant with its arrival at the gluteus (N16). The second component shows the positive peak rostrally (P24) with the largest negativity over the T-11 to T-12 spinous processes when the impulse reaches the spinal cord (N23). The last component, best recorded as a positive peak at the scalp (P31), coincides with the arrival of the negative source at the brainstem (N30). The less consistent peaks, P11, P21, and P27, indicate the arrival of the peripheral nerve potential at the popliteal fossa (N11), and of the ascending spinal potential at L4 (N21) and C7 spinous process (N28).[168] Figure 19-13 compares far-field peaks of median (Fig. 19-6) and tibial (Fig.19-11) nerve SEPs with those of the radial nerve recorded from the thumb (Fig. 19-2).

In contrast to the diffuse distribution of the early positive components, the first negative peak shows interhemispheric asymmetry with the ipsilateral response, N35, appearing

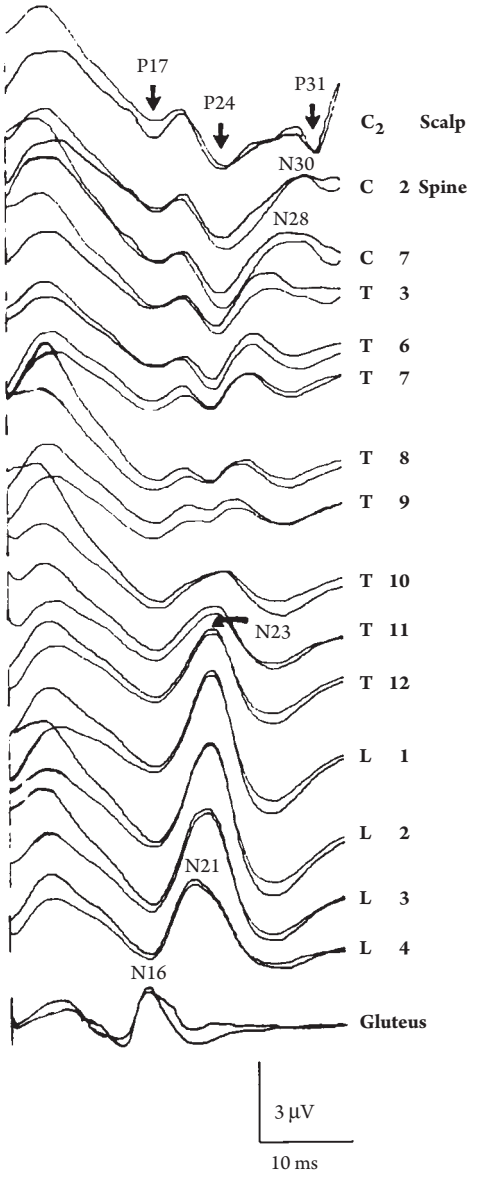


FIGURE 19-11 Far-field peaks of a tibial nerve somatosensory evoked potential (SEP) recorded from scalp lead and longitudinally placed electrodes over the spine. The first two positive peaks, P17 and P24, appeared diffusely not only over the scalp but also along the entire spine. The gluteal lead registered a negative peak, N16, which slightly preceded P17. The second component, P24, extended caudally to the T11 spine, corresponding to negativity, N23, best recorded at the T12 spine. A negative peak, N30, recorded at the C2 spine slightly preceded P31. (Modified from Yamada, Machida, and Kimura.[269])

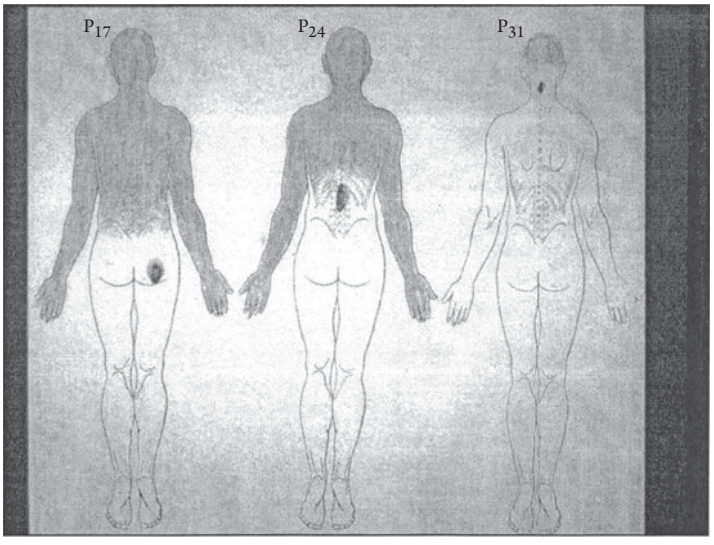


FIGURE 19-12 Relationship between far-field potentials recorded at the scalp (P17, P24, and P31) and the near-field potentials recorded at the gluteal fold and T12 and Cz spinous process (N16, N23, and N30). The first two positive peaks, P17 and P24, appear diffusely not only over the scalp but also along the entire spine as the negative peak, N16 and N23, cross the volume conductor junctions in the hip and the spinal canal. The last positive peak, P31, then emerges diffusely in the head as the negative peak, N30, passes the area of the foramen magnum. (Modified from Yamada, Machida, and Kimura.[269])

before the contralateral response, N37. These two peaks probably represent the subthalamic or subcortical responses generated by two independent sources in each hemisphere. The subsequent positivity, P40, probably has two subcomponents, central and parietal, showing different orientation of the generator.[253] In clinical studies, central P40 serves best for measuring the conduction time to the cortex because of its consistency (Figs. 19-14 and 19-15). The cortical potentials often, though not always, show a paradoxical lateralization with higher amplitude ipsilaterally. This finding may reflect transverse, rather than perpendicular, orientation of the generators located in the mesial surface of the postcentral sulcus.[183,231,258]

Trigeminal Nerve

In eliciting SEP from the trigeminal nerve, the sites of stimulation include the peripheral nerve bundle,[146] the upper or lower lip,[76] the gums,[29] tongue,[3] and other parts of the face.[13] Each of these methods evokes a major triphasic waveform, which varies considerably, depending on the technique used. In one study, scalp SEP elicited by stimulation of the second division (upper lip) consisted of N8, P14, and N18, whereas stimulation of the third division (lower lip) reversed the polarity to P8, N13, and P19.[76] A bipolar recording with E1 placed at C3 and E2 at F3 also revealed an inverted sequence, NI, PI, and NII, or N13, P19, and N26 following simultaneous stimulation of both the upper and lower lips unilaterally as summarized in Table 19-4.[229] With an ear reference, stimulation of the gum above the first maxillary bicuspid elicited scalp responses N20, P34, and N51.[18] Stimulation of the infraorbital nerve elicited three peaks over the scalp, W1, W2, and W3, corresponding to the activity at the entry into the gasserian ganglion, the pons, and the trigeminal spinal tract. Awake subjects also had additional components P4, N5, P6, and N7 when recorded with the use of a noncephalic reference.[147] These peaks probably correspond to FFP in cats generated at the mandibular foramen, foramen ovale, and gasserian ganglion or trigeminal root after stimulation of the mandibular nerve.[1]

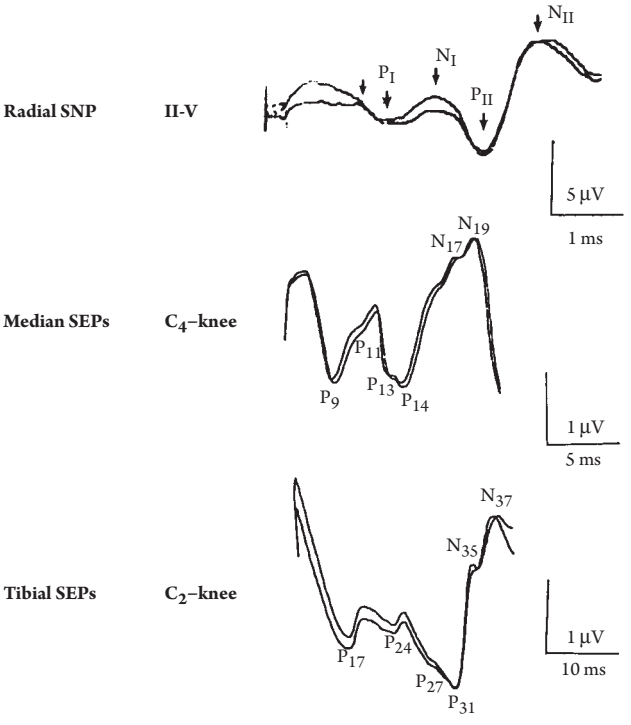


FIGURE 19-13 A scalp-recorded somatosensory evoked potential (SEP) using a noncephalic reference after stimulation of the median nerve at the wrist (middle) and tibial nerve at the ankle (bottom). Both median and tibial nerve recordings consist of four positive peaks initially and two negative peaks thereafter, all within the first 20 and 40 ms following the stimulus, respectively. For comparison, the top tracing shows far-field potentials, PI-NI and PII-NII, recorded from index finger referenced to little finger, after stimulation of the radial sensory fibers in the forearm. (Modified from Kimura, Yamada, and Walker.[134])

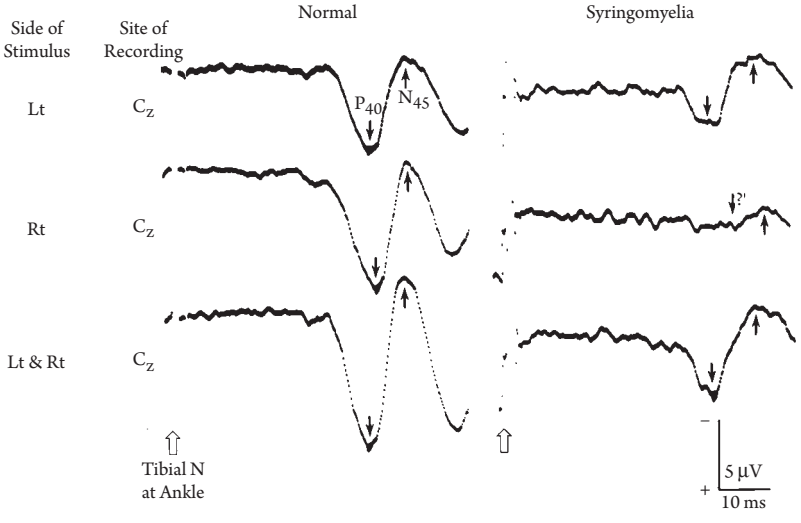


FIGURE 19-14 A tibial nerve somatosensory evoked potential evoked after stimulation of the nerve at the ankle in a normal subject (left) and a patient with syringomyelia and loss of vibration sense in the right leg (right). Note markedly reduced P40 and N45 to right-sided stimulation in the patient (middle tracing). The use of ear reference precluded the recording of short-latency positive peaks, P17 and P24, and minimized P31 and the subsequent negative peak, N37, preceding P40.

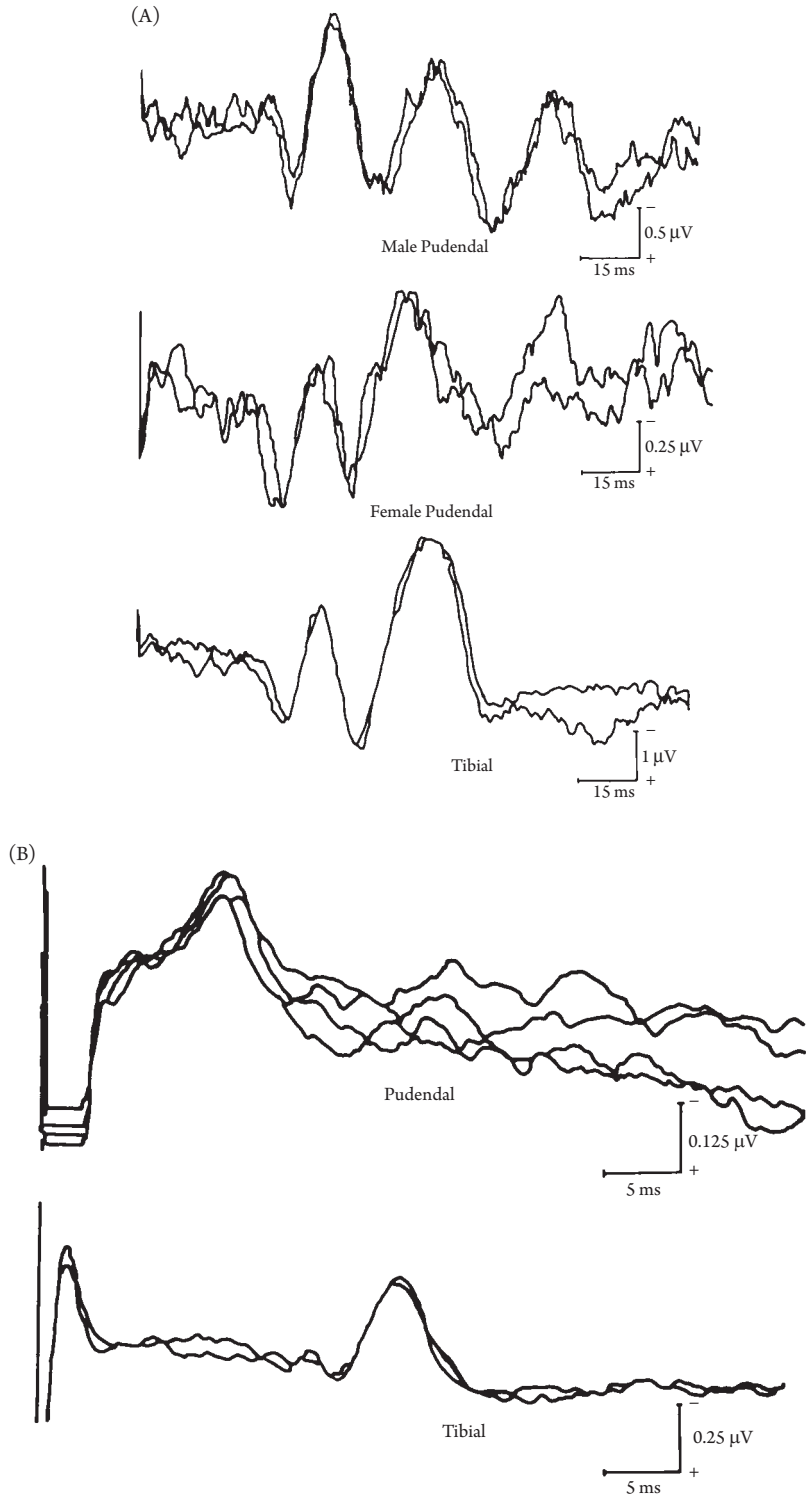


FIGURE 19-15 (***A***) Scalp-recorded somatosensory evoked potential recorded 2 cm behind Cz on stimulation of pudendal and tibial nerves. (***B***) Pudendal somatosensory evoked potential during wakefulness (top) and sleep (bottom), which tends to abolish the response. (Courtesy of Thoru Yamada, MD, Department of Neurology, University of Iowa Health Care.)

The dependence of the waveform on the mode of stimulation and recording montage makes it imperative to standardize the test for clinical use in each laboratory. Each published method has advantages and disadvantages. Surface stimulation of the trigeminal nerve bundle or the lip tends to activate facial muscles, causing major interference with the signal. Needle stimulation of the peripheral division, although invasive, accomplishes more selective activation of the sensory fibers. Stimulation of the gum requires a special supporter to maintain optimal contact between the electrodes and the surface. Regardless of the method, surface current from stimulation readily spreads to the pickup electrodes because of their proximity. This results in a large stimulus artifact that tends to preclude accurate analysis of short-latency components. Technical problems limit the clinical usefulness of trigeminal SEPs despite their theoretic applicability to a number of entities such as trigeminal neuralgia[18] and paratrigeminal syndromes.[145] Air-puff stimulation induces neither stimulus nor muscle artifacts.[92] This, combined with high-amplitude evoked potentials, enhances the signal-to-noise ratio.

Pudendal Nerve

Stimulation applied either to the base of the penis through a pair of ring electrodes or to the clitoral branch of the pudendal nerve elicits SEP over the sensory cortex and spinal cord.[89,230] The concurrent measurement of the cortical and spinal potentials and bulbocavernosus reflexes (see Chapter 9-6) permits the evaluation of the peripheral and central sensory and motor pathways.[176] Stimulation of the vesicourethral junction also elicits cerebral evoked responses with a prominent late negativity.[203] In contrast to distal urethral or pudendal nerve stimulation that activates the somatic afferents,[90] this technique probably excites the visceral afferents. Rectal stimulation may elicit two distinctly different potentials, presumably representing excitation of either the pudendal nerve or the visceral afferents.[150] Most patients with detrusor acontractility from suprasacral cord lesions have normal lumbosacral SEP, indicating the multifactorial nature of neurogenic bladder dysfunction.[151]

The pudendal SEPs recorded with E1 placed 2 cm behind Cz and E2, over the forehead, closely resemble those of the tibial SEPs (Fig. 19-15A,B), with an initial positive deflection and subsequent negative and positive sequence.[89] The peak-to-peak amplitude of the maximal response recorded over the midline ranges from 0.5 to 2 μV in men and from 0.2 to 1 μV in women, compared with 1–5 μV in the tibial SEPs. Table 19-5 summarizes the mean latencies and standard deviations of pudendal SEPs in each of the populations studied. After stimulation of the pudendal nerve, the spinal potential recorded by E1 over the L1 and E2 over the L5 spinous process consists of a dominant negative peak with the onset latency of 9.9 ± 3.4 ms (mean ± SD).[89] The amplitude ranges from 0.1 to 0.5 μV, showing an inconsistent response in overweight subjects. In comparison, stimulation of the tibial nerve at the ankle elicits spinal response with an onset latency of 20.8 ± 1.8 ms and an amplitude of 0.25–1 μV. Based on the latency of spinal potentials, the impulses arrive at the L1 spinous process level about 10 ms earlier after stimulation of the dorsal nerve of the penis than after stimulation of the tibial nerve at the ankle. Pudendal and tibial SEP over the scalp, however, show similar latencies, presumably because the muscle afferents

Table 19-4 Latency and Amplitude of Trigeminal SEPs in 82 Healthy Subjects

LATENCY (ms) (MEAN ± SD)	UPPER LIMIT (ms) (MEAN + 2 SD)	SIDE-TO-SIDE DIFFERENCE (ms) (MEAN ± SD)	UPPER LIMIT (ms) (MEAN + 2 SD)	AMPLITUDE (μV) (MEAN)	SIDE-TO-SIDE DIFFERENCE (μV) (MEAN)
18.5 ± 1.51	22.3	0.55 ± 0.55	1.93	2.6	0.51

(Modified from Stohr and Petruch.[229])

Table 19-5 Tibial and Pudendal Nerve SEPs in Healthy Subjects (Mean ± SD)

	ONSET (ms)	P_1 (ms)	N_1 (ms)	P_2 (ms)	N_2 (ms)	P_3 (ms)	N_3 (ms)
Men (13)							
Tibial	34.0 ± 2.8	41.2 ± 2.9	50.5 ± 3.0	62.7 ± 3.3	78.5 ± 4.4	99.5 ± 6.0	117.9 ± 9.0
Pudendal	35.2 ± 3.0	42.3 ± 1.9	52.6 ± 2.6	64.9 ± 3.4	79.3 ± 4.0	96.6 ± 4.7	116.0 ± 7.2
Women (7)							
Tibial	32.7 ± 1.7	39.3 ± 1.4	49.4 ± 2.1	60.0 ± 2.0	76.1 ± 4.2	96.1 ± 5.8	119.2 ± 7.9
Pudendal	32.9 ± 2.9	39.8 ± 1.3	49.1 ± 2.3	59.4 ± 2.8	73.4 ± 4.6	90.1 ± 5.8	110.0 ± 10.2

(Modified from Haldeman, Bradley, Bhatia, et al.[89])

of the tibial nerve conduct much faster than the cutaneous afferents of the pudendal nerve.

Other Nerves

The femoral nerve SEPs consist of widely distributed P15 and N19, and localized scalp components P26, N34, P44, and N56.[261] Percutaneous stimulation of the phrenic nerve in the supraclavicular fossa[21] evokes a scalp-recorded PI at an average latency (mean ± SD) of 12 ± 0.8 ms and NI at 17 ±1.3 ms with peak-to-peak amplitude of 0.3–0.6 μV, and a more variable PII ranging in latency from 20 to 26 ms and NII from 31 to 45 ms.[286] Stimulation of the intercostal nerve also elicits an SEP, which may assist in the diagnosis of both central and peripheral thoracic neural compromise.[57] Other nerves of possible clinical interest include calcaneal and medial and lateral plantar nerves for plantar neuropathies,[60] lateral and anterior femoral cutaneous nerve for meralgia paresthetica,[42] saphenous nerve for entrapment neuropathies,[237] digital nerve for cervical spine disorders,[140] and spinal roots[245] with the use of magnetic stimulation.

Dermatomal Stimulation

Stimulation of the cervical or lumbosacral dermatomes evokes an SEP for possible evaluation of radiculopathies.[149] Eliciting an SEP with paraspinal stimulation, which excludes most of the peripheral nervous system, may serve as a measure of spinal lesions.[85] Dermatomal SEP may also help monitor individual nerve root function during degenerative spinal surgery despite considerable variability of innervation patterns.[182] Clinical values of all these techniques, however, remain uncertain.

5. PATHWAYS FOR SOMATOSENSORY POTENTIALS

Peripheral Inputs and Their Interaction

Early clinical studies revealed an abnormal SEP only in patients with impaired vibration or position sense, whether the lesions involved the spinal cord, cerebral hemisphere, or brainstem. Patients with selective involvement of either modality showed a better correlation of SEP abnormalities with the loss of position than vibration sense.[278] These data suggest the dependency of SEP components on the integrity of the dorsal column medial lemniscal system in humans. Magnetic stimulation of paraspinal muscles also elicits an SEP, which attenuates by vibration applied locally or by voluntary contraction of the muscle.[284] Thus, muscle spindle receptors at least in part provide the afferent input responsible for early components of SEP.

Brief air-puff and electric stimuli applied to the tip of the index finger produce an SEP of similar morphology. A longer latency of air-puff SEP probably reflects a transduction time at the skin receptors rather than differences in conduction velocities of the afferent volleys.[93] Mechanical stimuli evoke lower amplitude responses with fewer components than electric stimulation, which activates more fibers synchronously.[78]

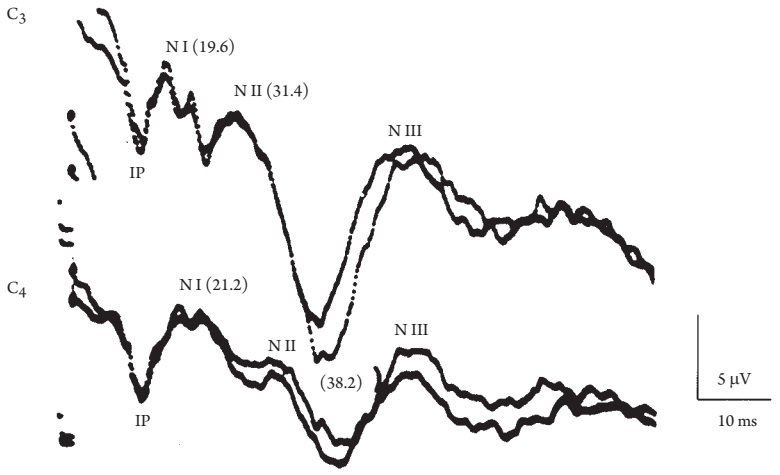


FIGURE 19-16 Scalp-recorded potential to bilateral stimulation of the median nerve in a 33-year-old man with traumatic avulsion of C8, T1, and probably T2 roots on the left. Myelography demonstrated a large meningocele at C7. Interhemispheric comparison revealed no asymmetry for IP, NI, and NIII despite an obvious delay of NII on the right (C4) as compared to NII on the left (C3).

Passive plantar flexion of the ankle can elicit cerebral potentials in humans, presumably via the afferent fibers that originate from muscle mechanoreceptors.[225] These findings suggest that the fast-conducting, large myelinated sensory fibers of either cutaneous or muscle afferents primarily, though not exclusively, mediate SEP components via the dorsal column-medial lemniscal system.[80]

The first-order afferent fibers outside the posterior column also contribute to some of the SEP peaks. Clinical observations support the experimental evidence in favor of separate sensory pathways mediating various SEP peaks. A pinprick, but neither touch nor tactile tap, elicits SEP in patients with loss of vibration and touch sensations.[211] A high-intensity electrical stimulation elicited a cortical SEP with a latency of 84 ms for an estimated propagation velocity of 12 m/s in a man who had a complete loss of large myelinated sensory fibers.[40] Occasional patients with selective impairment of pain-temperature sensation without loss of position-vibration sense have a depressed or absent NII despite relative preservation of NI (Figs. 19-16 and 19-17).[268] Conversely, lesions of the brainstem, cervical cord, or brachial plexus[274] may affect NI and earlier peaks selectively, sparing NII and subsequent components (Fig. 19-18).

Such dissociated abnormalities of early and late components suggest the presence of at least partially independent central pathways mediating NI, NII, and NIII. These findings also tend to refute the traditional view that successive peaks of the SEP represent the sequential activation of a unitary somatosensory pathway. To support this contention, tourniquet-induced ischemia diminishes the short-latency SEP peaks, P9 and P14, and the first cortical response, NI, along with a parallel loss of N9 at Erb's point.[271] Relative sparing of the later components, PII, NII, PIII, and NIII, implies the presence of independent routes, possibly involving different sensory nerve axons. Interestingly, ischemia prolongs the latencies of PII and later peaks more than those of the earlier peaks (Fig. 19-19), again indicating the heterogeneity of the afferent fibers contributing to the various peaks of SEP.

Nociceptive Evoked Potentials

Brief heat pulses applied to the skin excite the afferent pathway of pain and temperature sensitivity.[240] Such stimulation with CO_2 laser radiant heat elicits a large P320 in normal subjects, maximal at vertex but distributed widely over the scalp.[114,238,252] Reduction in stimulus

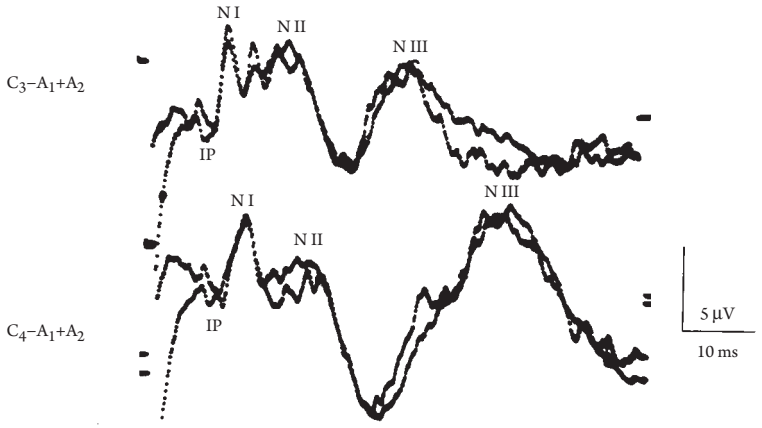


FIGURE 19-17 Scalp-recorded potential to bilateral stimulation of the median nerve in a 46-year-old woman with multiple sclerosis. Interhemispheric comparison showed a slight delay of IP and NI and far greater delay of NII and NIII on the right (C4) as compared to the corresponding peaks on the left (C3). (Modified from Yamada, Kimura, and Young.[268])

intensity causes a decrease in amplitude and an increase in latency. Calculations using this method revealed an estimated conduction velocity of 9 m/s for the Aδ fibers in the peripheral nerve[115] and 8–10 m/s for the slowly conducting spinothalamic tract in humans.[116] Other studies[148,179,196] revealed comparable results, indicating that laser evoked potentials permit studies of Aδ and C fibers, although C-fiber volley coming after Aδ volley may not reach the cortex by occlusion.[244]

Clinical studies showed a positive relationship between pain SEP and densities of small myelinated fibers of the sural nerve in neuropathies.[119] Latencies show a drastic increase in neurosyphilis with delayed pain reception[242]

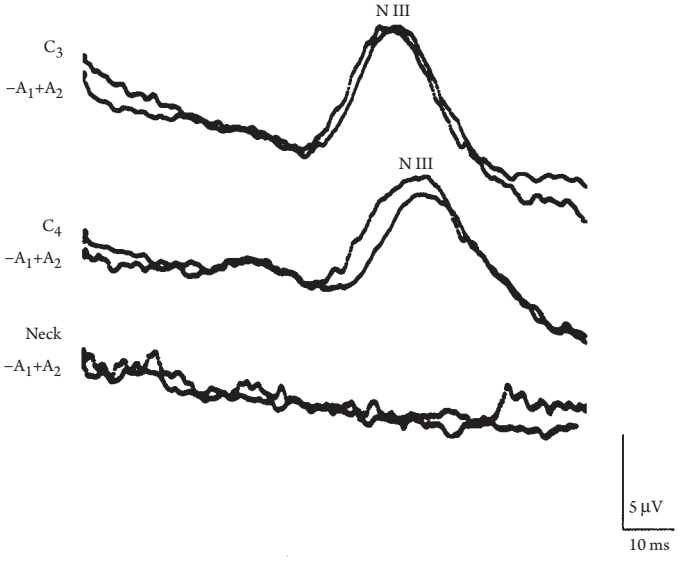


FIGURE 19-18 Scalp-recorded and cervical potentials to bilateral stimulation of the median nerve in a 47-year-old man with multiple sclerosis. A well-preserved NIII occurred as the initial potential in the absence of preceding peaks, IP, NI, and NII. (Modified from Yamada, Machida, and Kimura.[269])

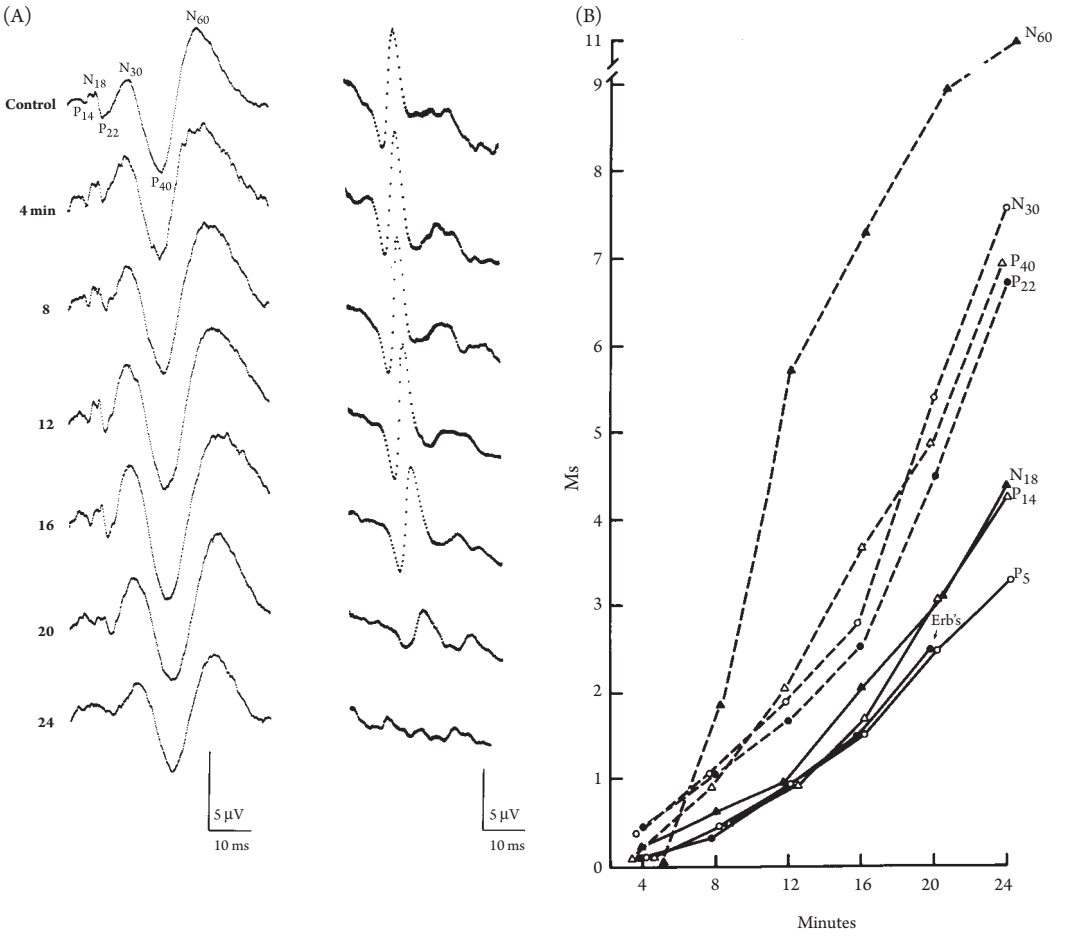


FIGURE 19-19 (***A***) Sequential changes of scalp-recorded somatosensory evoked potentials (left) and Erb's potential (right) during application of a pressure cuff around the upper arm in a normal subject. Ischemia affected the initial positive and negative components, P14 and N18, along with Erb's potentials earlier than the subsequent components, P22, N32, P40, and N60. A 24-minute compression abolished the "ischemia-sensitive" peaks while keeping the "ischemia-resistant" peaks relatively intact. (Modified from Yamada, Muroga, and Kimura.[271]) (***B***) The change in latency in milliseconds (ordinate) plotted against duration of ischemia in minutes (abscissa) showed a clear dissociation in the time course of latency change between the "ischemia-sensitive" and "ischemia-resistant" components. (Modified from Yamada, Muroga, and Kimura.[271])

but remain normal in hereditary motor and sensory neuropathy (HMSN) with the preservation of C-fiber function.[142] Other conditions evaluated by this technique include cortical reflex myoclonus,[118] dissociated sensory loss of pain and temperature,[25,239] carpal tunnel syndrome (CTS),[12] syringomyelia,[191,241] stroke,[275] facial hypesthesia,[46] nerve regeneration after topical capsaicin,[190] and diabetic small-fiber neuropathy.[170]

Central Mechanisms for Integration

Gating experiments, testing input interactions, have revealed different kinds of movement affect the cortical SEP[173,180,199,234,256] as well as subcortical components generated by dorsal column nuclei.[102] One study showed selective gating of SEP with movement that involves the areas of stimulation.[232] In another study, aged healthy subjects

had a larger SEP amplitude at rest and showed greater amplitude reduction by voluntary movement than younger controls.[236] Thus, the magnitude of gating may depend on SEP amplitude at rest. Pre-movement gating of frontal N30, with no effect on N20, suggests a rostral projection of its source from the primary somatosensory area or direct projection from the thalamus to the motor cortices.[212] Mental imagery, or movement simulation, also affects the N30 frontal component.[197]

Vibration attenuates spinal and cerebral potentials evoked by stimulation of the mixed nerve or muscle spindle but has no effect on cutaneous input.[37,38,165] Paired shocks given to the peripheral nerve at various intervals can establish recovery functions of SEP in health and disease.[157,171,208,249] The final waveform of the recorded potential depends on complex interaction of varied sensory inputs from different sources, some facilitatory and others inhibitory.[98] Dramatic reorganization of the primary sensory cortex occurs within minutes to hours following deafferentation. Transient deafferentation of the radial nerve, for example, results in a rapid modulation of cortical processing of median nerve input, leading to a significant increase in amplitude of N30.[172] Theta burst transcranial magnetic stimulation (TMS) also modulates median SEP, enhancing N20 when given intermittently and suppressing later component N25-N33 when given continuously.[122]

Despite this complexity, an SEP generally favors the inputs from the fast-conducting fibers that reach the synapse first, occluding those from the slow-conducting fibers by prior activation of the common pathway shared by the afferent fibers. This phenomenon together with central amplification that compensates for peripheral conduction block[72] would explain the generation of a relatively preserved SEP despite a very abnormal sensory nerve action potential in patients with peripheral neuropathies. In one study, early SEP components attained a maximum amplitude before the responsible muscle afferent volley reached 50% of its maximum.[82] Therefore, a few large afferent fibers that survive peripheral pathology may suffice to evoke a nearly normal SEP. In addition, the differential effect of desynchronization on peripheral axons and central synaptic relays may cause apparent dissociation between central and peripheral sensory responses. The nerve action potential undergoes substantial diminution based solely on phase cancellation between unit discharges of fast- and slow-conducting fibers (see Chapter 11-5).[130] Similarly, the diminution of early SEP may result from temporal dispersion of axonal volleys, rather than from conduction block. If so, the cortex, operating as an integrator, may generate sizeable later components after several synaptic relays, which tend to resynchronize the incoming inputs.

Regardless of the underlying physiologic mechanisms, these observations have practical implication in the clinical assessment of SEP abnormalities. Patients with severe sensory neuropathy may have absent peripheral nerve potentials with preserved, albeit delayed, SEP peaks (Fig. 19-20). These disorders may affect the amplitude of the initial SEP peaks selectively without concomitant diminution of the later components. More important, conduction abnormalities of the peripheral nerve can lead to increased interpeak latencies of scalp responses as the result of disproportionate delay of the late components. Thus, a latency dissociation between early and late SEP peaks does not necessarily imply a central lesion. This possibility underscores the importance of demonstrating the integrity of the peripheral nervous system by appropriate conduction studies as part of SEP evaluations.

Measurement of Conduction Time and Various Factors

In the clinical assessment of SEP, two separate trials with the same stimulus setting serve to confirm the consistency of the recorded response. Repeat studies on successive occasions show better SEP stability with stimulation of the upper- than lower-limb nerves. One serial study of median nerve SEP revealed a small systematic and a larger random side-to-side difference originating from both peripheral and central pathways.[41] The usual measurements include onset and peak latencies and peak-to-peak amplitudes (Tables 19-1 through 19-3). Available data suggest a linear relationship between the subject's height and the latency

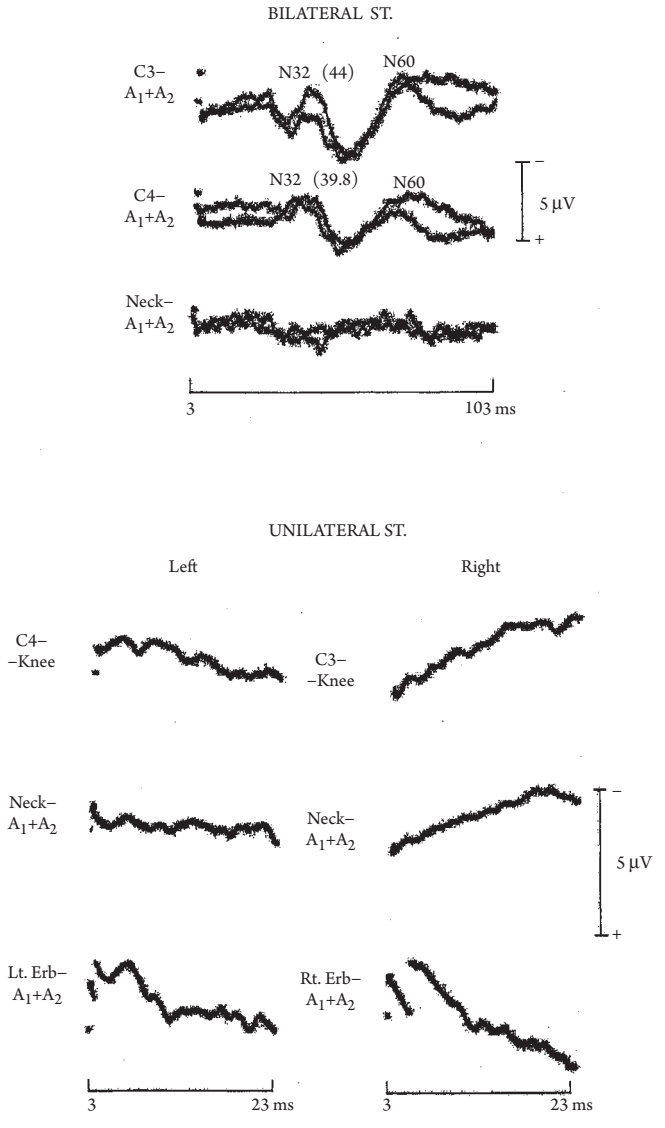


FIGURE 19-20 A male patient with recurrent symptoms of polyneuropathy, which always improved during hospitalization and worsened after discharge. On questioning during the third admission, he declared that coffee tasted bitter at home. This triggered a search for toxins, leading to the eventual diagnosis of arsenic poisoning. Studies revealed absent scalp-recorded short-latency peaks as well as peripheral sensory nerve action potential (bottom) but relatively normal late scalp components, N32 and N60, because of central amplification (top).

of a given peak elicited by stimulation of a lower limb.[124] SEP latencies, which include synaptic delay, also change as a function of body temperature, affecting central, more than peripheral, conduction times.[159]

The somatosensory latency has two parts: peripheral conduction from the stimulus site to the spinal cord entry and the central conduction along the remaining segment of the first-order afferent up to the dorsal column nuclei and subsequent relay through the lemniscal system and thalamocortical fibers over at least three synapses. The spinal potentials recorded over the C7 and T12 spinous processes reveal peripheral conduction time in the upper and lower limbs. The remaining central latency for the median and

tibial nerves measures the sensory pathways from the cervical enlargement (C7 spinous process) and the conus medullaris (T12 spinous process). The difference between the two provides the spinal cord conduction from the conus medullaris to the cervical enlargement.[67] The latency difference between cortical potentials elicited by epidural stimulation of the cervical and thoracic spinal cord also serves as a measure of spinal cord conduction.[19] Because of a cumulative error, the currently available indirect estimate provides only a gross approximation of spinal cord conduction. In addition, the technique applies only to SEP components mediated by large, myelinated, fast-conducting fibers.

6. CLINICAL APPLICATION

Studies of SEP have made steady progress since the original description by Dawson[49] some 65 years ago. The advent of microcomputers and digital processors has freed the student of clinical neurophysiology from the limitations of analog analysis. This, in turn, has led to a rapid escalation in the use of SEP and other evoked potential studies in the clinical domain, and a great number of patients currently undergo such a test as a routine procedure. Important questions remain, however, to clearly delineate the practical scope of the SEP and its proper usage.[126] These include standardization of the technique and nomenclature, precise localization of neural generators, elucidation of various factors that affect the measurements, and establishment of normative values.[45,166]

Common Derivations and Normal Values

NERVES OF UPPER LIMB

A median nerve SEP generally has larger and better defined responses than the corresponding peaks of an ulnar nerve SEP or those elicited by stimulation of pure sensory nerves. The median nerve enters the spinal cord through C5 to T1 roots. The large myelinated fibers that carry proprioception, conveying touch, pressure, and vibration sense, ascend the dorsal column, reaching the cuneate nucleus at the medulla. Following synaptic connection there, the second-order neuron crosses to the opposite side via the medial lemniscus and ascends to the ventral posterolateral nucleus of the thalamus. The third-order neuron then reaches the somatosensory cortex, posterior to the central sulcus.

We use a four-channel montage to trace the signal along the anatomic route of somatosensory pathways from Erb's point (Channel 4) to cervical spine (Channel 3), and then to scalp (Channel 1 and 2) (Fig. 19-21 and 19-22) (Tables 19-6 and 19-7). Channel 4 records N10, or the nerve potential at Erb's point, with a mean latency of 10 ms, which monitors the peripheral nerve impulse. Channel 3 registers three negative peaks, N9, N11, and N13, derived from combination of near- and far-field activities. Of these, N9 represents a positive FFP, P9, recorded by the reference electrode as the impulse crosses the distal portion of the brachial plexus. Most propose N11 to arise from the root entry zone as a presynaptic potential and N13, from the cervical cord, the posterior columns, or cuneate nucleus as a postsynaptic potential.

The FFP of clinical interest includes four positive peaks, P9, P11, P13, and P14, recorded from C3 or C4 scalp electrodes usually by means of a noncephalic reference (Fig. 19-6). This derivation often poses substantial technical difficulty because interfering noise increases in proportion to the distance between the active and reference leads. To circumvent this problem, channels 1 and 2 register P13 and P14 with the ear as the reference. The scalp leads from the frontal but not parietal region register a negative FFP, N18 following positive FFP, P13, and P14. In our montage, therefore, a combination of scalp channels referenced to the ears and a neck channel using anterior-to-posterior derivation substitutes the cumbersome scalp noncephalic recording in measuring the FFP. These far-field peaks show resistance to anesthesia, a distinct advantage when monitoring cervical cord function during surgery.

In contrast to bifrontally distributed far-field negativity (N18), the first near-field peak, N20, shows a clearly localized area over the somatosensory cortex in the contralateral parietal region,

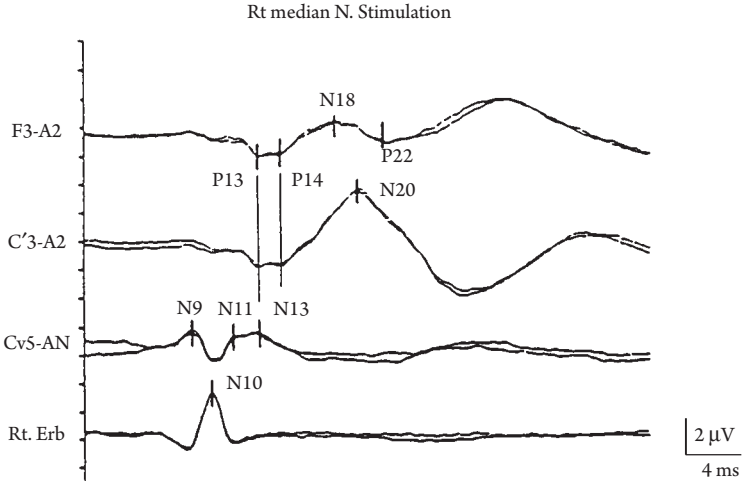


FIGURE 19-21 Four-channel recording of median somatosensory evoked potentials showing P13 and P14 recorded at F3 and C3 electrodes, N18 at F3 electrode, and N20 at C3 electrode. The derivation connecting the cervical spine 5 to the anterior neck (Cv5-AN) registers mixed near and far-field potentials, N9, N11, and N13. Of these, N13 matches P13 in latency despite a different generator source. The propagating signal, N10, recorded at Erb's point falls in between two far-field peaks, N9 and N11. (Modified from Yamada.[263])

providing a means for evaluating thalamocortical projection and sensory cortex. Thus, the four-channel derivation described here can register propagation of impulse along the anatomic pathway of somatosensory signals. The median SEPs also include later potentials such as N30, P40, N60, P100, and N130. These intermediate and long latency components vary considerably, reflecting the subject's vigilance, attention to the stimulus, and other cognitive functions. Each wave has its own characteristic scalp distribution, presumably representing neuroanatomic and

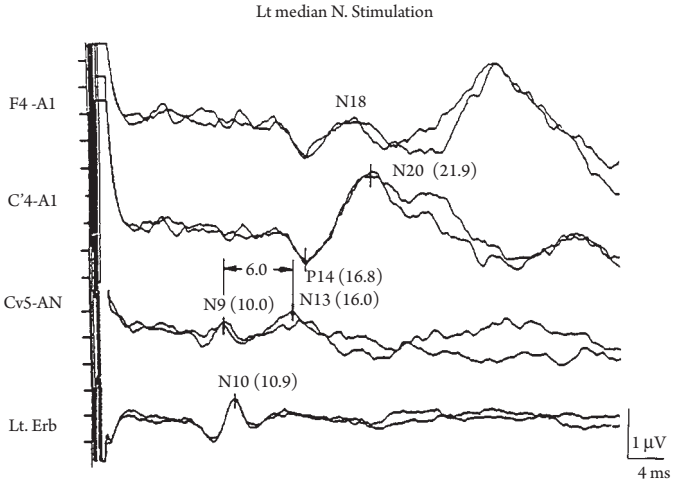


FIGURE 19-22 An abnormal median nerve evoked potential with normal N9 and N10, and delayed N13, N14, and N20. A prolonged N9 to N13 interwave peak latency beyond the upper limit of normal (5.3 ms) indicates a lesion either involving the proximal segment of the peripheral nerve or the cervical cord. (Modified from Yamada.[263])

Table 19-6 Four-Channel Derivation for Median Nerve SEP

STIMULATION OF LEFT MEDIAN NERVE		STIMULATION OF RIGHT MEDIAN NERVE	
Channel 1:	F4–A_1	Channel 1:	F3–A_2
Channel 2:	C′4–A_1	Channel 2:	C′3–A_2
Channel 3:	Cv_5 to anterior neck	Channel 3:	Cv5 to anterior neck
Channel 4:	Lt Erb to Rt Erb	Channel 4:	Rt Erb to Lt Erb

F3, F4, C′3 and C′4 according to the 10–20 International Electrode Placement System (Fig. 19-1). Cv5: a point just below the C5 spinous process. Lt, left; Rt, right.

Table 19-7 Upper Limit of Normal Values for Median Nerve SEPs, Mean + 2 SD (ms)

	LATENCIES	LEFT–RIGHT DIFFERENCES
N_9	10.8	0.8
N_{13}	15.5	0.5
P_{14}	17.1	0.9
N_{20}	21.7	1.1
N_9– N_{13}	5.3	1.0
N_{13}–N_{14}	2.2	0.8
N_{13}–N_{20}	7.4	1.0

Short latency peaks, N_9, N_{13}, P_{14}, and N_{20} on top and inter-peak intervals in the bottom.

physiologic substrates for cortical sensory processing. Thus, these late waves may provide useful information in the evaluation of higher cortical functions, although their clinical values remain uncertain.

NERVES OF LOWER LIMB

The usual sites of stimulation include the tibial nerve at the ankle and less commonly, the peroneal nerve at the knee. We use a four-channel recording of the tibial nerve SEP, which shows less intraindividual and interindividual variability than peroneal nerve SEP (Figs. 19-23 and 24 and Tables 19-8 and 19-9).

Channel 4 registers N8, or the peripheral potential with a latency of about 8 ms. Channel 3, similar to its counterpart in median nerve SEP, registers a combination of near- and far-field activities. Of these, N24, recorded at L1 and T12 spinal processes, derives from the conus medullaris and N21 from the cauda equina, which in some cases appears as a small notch over the rising phase of N24. These two components correspond to N11 and N13 of the median nerve SEP. Spinal potentials recorded from a series of surface electrodes placed along the spine show propagation of a traveling impulse above the T12 spinal level, but these small responses often escape detection. Channel 2 with the scalp electrode Cz referenced to the ear registers P31, N35, and P40. Of these, P31 corresponds to P13/P14 of the median nerve SEP, arising from medial lemniscus. Like P13/P14, P31 remains stable under anesthesia, providing a useful measure for spinal cord monitoring (see Chapter 21-4). The onset of N35 at least in part represents a negative FFP equivalent to N18 of the median nerve SEP.

Unlike N20 of the median SEP, its counterpart, N35 of the tibial SEP, generally shows a small amplitude even in normal subjects. Channel 1 with Cz-Fz (Fpz) derivation is best suited for defining P40, the most consistent scalp-recorded cortical component, showing maximum amplitude at the vertex on the hemisphere ipsilateral to the side of stimulation. The interwave peak latencies of N24-P31 or N24-P40 serve as a measure of conduction time along the spinal and central somatosensory pathways. Tibial SEP latencies, in general, show a linear relationship to the subject height

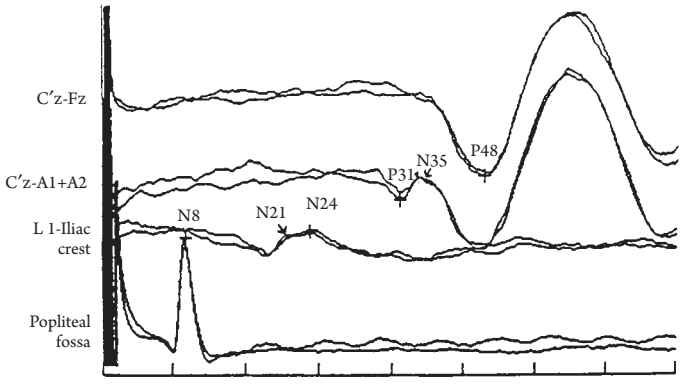


FIGURE 19-23 Four-channel recording of a tibial nerve somatosensory evoked potential (SEP) showing a cortical potential, P40, in scalp to scalp or scalp to ears derivation, and preceding far-field potential, P31, seen only when referenced to the ears, whereas L1-iliac crest derivation registers a far-field potential, P17, and near-field peak, N21 and N24, from cauda equina and conus medullaris. The latency difference between P31 and N24 approximates the spinal conduction time. The propagating signal, N8, recorded at the popliteal fossa monitors the peripheral nerve. (Modified from Yamada.[263])

in both children and adults (see Chapter 29-9).

CLINICAL VALUES AND LIMITATIONS

Studies of SEPs have helped in delineating the pathophysiology in a variety of disorders affecting the peripheral or central nervous system. Clinical correlation, however, does not necessarily lead to practical application. A statistical difference between control and patient groups may add little in evaluating individual cases. In the clinical domain, the test must unveil relevant information pertinent to the diagnosis or management of the patient in question. Even unequivocal SEP abnormalities often fail to clearly localize the lesion because the neuroanatomic origin of each peak still awaits elucidation. Abuse and misuse,

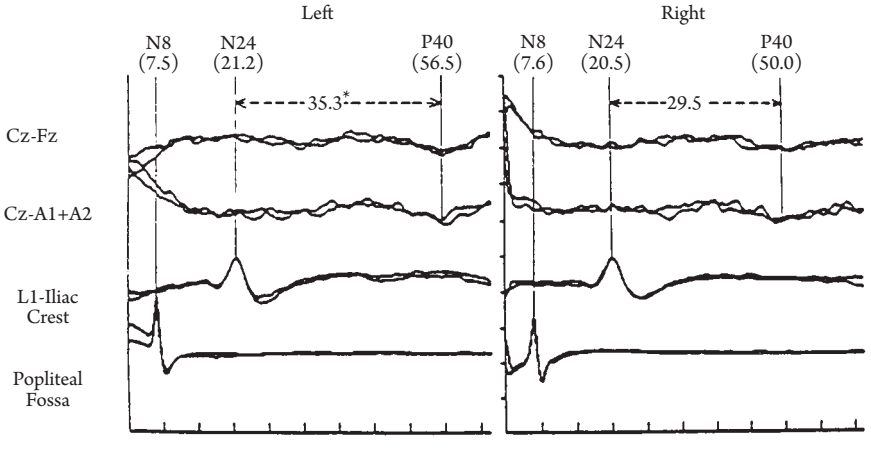


FIGURE 19-24 An abnormal tibial nerve study in a patient with thoracic spinal cord injury, showing normal N8 and N24 and diminished and delayed P40. A prolonged N24-P40 interwave peak latency beyond the upper limit of normal (21.5 ms) indicates a lesion involving the spinal cord or higher levels.

Table 19-8 Four-Channel Derivation for Tibial Nerve SEPs

STIMULATION OF LEFT OR RIGHT TIBIAL NERVE	
Channel 1:	C′z (C′1) to Fz (Fpz)
Channel 2:	C′z (C′1) to A1 +A2
Channel 3:	LI (T12) spine to iliac crest
Channel 4:	Popliteal fossa (conventional bipolar recording)

C′z is 2 cm posterior to Cz, and C′1 is 1 to 2 cm lateral to C′z on the hemisphere ipsilateral to the side of stimulation.

common with any diagnostic procedure, pose a particular problem in SEP studies, which became routine before their time, while the technique still continued to evolve. Despite widely publicized clinical applications, these investigative procedures, in many instances, can provide only limited information useful for the diagnostic workup of individual patients.

Conservative and selective use of the test in proper clinical contexts would maximize its impact in electrodiagnostic medicine. Only with such precaution will SEP studies play a meaningful role as a diagnostic procedure. This type of study can directly assess the transmission of impulses that underlie the fundamental function of the nervous system. Thus, the technique has a wide range of application in physiologic studies of the peripheral and central nervous system in humans. Such clinical and experimental data will help precisely define its diagnostic values and limitations. With better understanding of the anatomy and physiology of the sensory pathways and standardization of the technique, SEP will secure its unique position as an important electrophysiologic measure for a number of neural dysfunctions.

Table 19-9 Upper Limit of Normal Values of Tibial Nerve SEPs, Mean + 2.5 SD (ms)

	LATENCIES	LEFT–RIGHT DIFFERENCES
Popliteal (N_8)	10.0	1.0
N_{24}	26.5	2.0
P_{30}	34.7	1.7
P_{40}	44.0	4.1
N_8– N_{24}	16.9	2.1
N_{24}–P_{30}	11.0	2.1
N_{24}–P_{40}	21.5	4.1
N_8– P_{30}	25.2	1.8
N_8– P_{40}	34.9	3.8

Short latency peaks, N_8, N_{24}, P_{30}, and P_{40} on top and inter-peak intervals in the bottom.

PERIPHERAL NEUROPATHY

The studies of SEP supplement conventional sensory nerve conduction tests in general and assessment of the proximal sensory fibers in particular. Selective stimulation of the afferent fibers elicits only a small peripheral sensory response, especially in diseased nerves. Mixed-nerve potentials, although relatively large, contain not only the sensory volleys from skin, joint, and muscle afferent fibers but also antidromic motor impulses. In contrast, spinal or scalp-recorded responses result solely from sensory potentials, primarily mediated by the large afferent fibers, even after stimulation of a mixed nerve.

Disorders commonly tested by this means include lesions involving the root, plexus, or thoracic outlet.[136] A number of studies explored the use of segmental and dermatomal SEP in the diagnosis of cervical[205] and lumbosacral radiculopathy[58,260] and spinal stenosis.[217] Some advocate its clinical value,[182] whereas others refute such contention.[4,8,58]

Studies of longer pathways tend to obscure latency changes across a short segment because normal conduction in the remaining region dilutes the focal delay (see Chapter 11-7). Thus, intertrial and side-to- side variation tends to mask any small change attributable to a focal lesion. The currently available data provide only insufficient evidence to support the use of dermatomal SEP as a clinical diagnostic tool for radiculopathy except perhaps in cases of spinal stenosis.[217, 214] Surgical decompression of lumbar spinal stenosis may shorten the latency of tibial, peroneal, or sural SEP.[51] A pudendal SEP, together with the bulbocavernosus reflex, may help evaluate sacral

nerve root or plexus injuries and bowel, bladder, and sexual dysfunction.[89,174]

Albeit indirectly, SEP measurements help assess sensory conduction of the median, ulnar, radial, musculocutaneous, sural, superficial peroneal, and saphenous nerves.[68,237] Less commonly studied nerves include posterior femoral cutaneous nerve[64] and lateral and anterior femoral cutaneous nerve.[42,206] Studying SEP may characterize peripheral sensory conduction abnormalities, especially if peripheral neuropathies abolish sensory nerve action potentials (Fig. 19-20).[198] In one series,[277] SEP studies helped differentiate various subtypes of chronic acquired demyelinating polyneuropathy. In another series of eight patients with chronic inflammatory demyelinating neuropathy (CIDP), the results often revealed misleadingly normal data, presumably as the result of central amplification of an attenuated response arising from a few surviving axons conducting normally.[186] Segmental evaluation with tibial nerve SEP, however, helps document proximally dominant involvement in CIDP, as compared with distally prominent slowing in diabetic neuropathy.[246] In 27 patients with the Guillain-Barré syndrome (GBS), 7 had a normal SEP despite an abnormal F wave from the same nerve, whereas none with normal late responses had an abnormal SEP.[194] Other conditions tested usefully include cisplatin-induced neuropathy,[139] retrograde effects of digital nerve severance,[34,35] and system disorders such as Machado-Joseph disease.[39] Despite sparing of the sensory system clinically, patients with MND may exhibit various SEP abnormalities.[22,86]

Unfortunately, the test improves the accuracy of diagnosis less than one might have expected on theoretic grounds in many instances. For example, in a combined study of SEP and peripheral SNAP, preoperative findings correlated well with the discovered locus of brachial plexus lesions in only 8 of 16 patients.[111] In the remaining 8 patients, 5 had only minor discrepancy between electrophysiologic and operative data, but the other 3 had unexpected root avulsions at surgery despite a prediction of a purely postganglionic lesion. The use of SEP alone would have provided less help because abnormalities of peripheral SNAP contributed substantially to the accurate localization of the pathologic process. A major limitation of this technique stems from its inability to test preganglionic involvement in the presence of a postganglionic lesion, which precludes the evaluation of a more proximal segment. Nonetheless, SEP may have a useful role as a monitor for brachial plexus surgery.[207]

SPINAL CORD AND BRAINSTEM LESIONS

Simultaneous recordings of SNAP and SEP have revealed central involvement in various neuropathies[210] and many systemic disorders, such as late-onset ataxia,[178] Kennedy's disease,[188] HIV infection,[215] and myotonic dystrophy.[15] In Friedreich's ataxia, studies of the sural nerve showed normal conduction velocity despite reduced amplitude. Similarly, the median nerve SNAP recorded at the clavicular fossa had a marked attenuation but little evidence of delay. Studies of SEP, however, revealed a dispersed and delayed cortical response, suggesting slowed conduction in central pathways.[108] Spinal SEP also shows frequent defects in spinal afferent transmission in diabetes,[43,285] Charcot-Marie-Tooth disease (CMT),[109] and other peripheral neuropathy.[216]

In syringomyelia (Fig. 19-14), SEP abnormalities accompany clinical sensory loss despite normal sensory nerve conduction studies.[10,104] Patients with subacute myelo-opticoneuropathy (SMON) also have marked attenuation of the cortical SEP component and delayed central but not peripheral conduction.[209] Lumbosacral recording of a tibial nerve SEP may or may not show abnormalities in patients with neurogenic bladder resulting from suprasacral cord injuries.[151] A focal asymptomatic compression of the spinal cord causing little symptoms generally results in few SEP abnormalities.[233] In contrast, symptomatic lesions of the spinal cord often lead to slowing of spine-to-spine and spine-to-scalp propagation velocities or the absence of scalp response.[204] In assessing evolution of tibial SEP after traumatic spinal cord injury, initially absent responses do not necessarily imply poor outcome.[224]

MULTIPLE SCLEROSIS

Symptoms and signs of multiple sclerosis (MS) result from abnormal conduction of central

nerve fibers across areas of demyelination. A delayed median SEP in patients with impairment of position or vibration sense indicates conduction abnormalities of the posterior column (Figs. 19-17 and 19-18). Studies of SEP can also uncover clinically silent lesions and document dissemination of disease.[30,87,273] A scalp-recorded SEP shows an overall incidence of abnormality ranging from 50% to 86% in patients with an established diagnosis[30] and subclinical abnormalities in 20% to 40% of suspected or possible cases[30,273] with greater sensitivity after stimulation of the lower-limb nerves.[7,213,269]

Recording a short-latency median SEP (N13) from the neck or FFP (P14) from the scalp revealed abnormalities in 69%–94% of those with a definite diagnosis and in 44% to 58% of patients with a possible diagnosis.[73,83] The latency difference between cervical and scalp-recorded negative peaks showed an 83% incidence of abnormality in the definitive group and 68% overall.[70] The incidence of SEP abnormalities generally increases in proportion to the duration of clinical illness,[23] although it correlates more strongly with neurologic status of the functional subsystems.[202] Unfortunately, intertrial variability sometimes exceeds the expected changes brought about by disease processes, leading to a tenuous temporal correlation between clinical and electrical changes.[9,163] Indeed, evoked potential studies may not provide information for monitoring progression of disease, with frequent disparity between the clinical and electrophysiologic courses.[48,50]

As a diagnostic study of MS, SEPs and visual evoked potentials (VEPs) contribute more than brainstem auditory evoked potentials (BAEPs) or electrically elicited blink reflexes. Laser-evoked potentials, testing spinothalamic function, also detect subclinical lesion.[223] Morphologic lesions seen in magnetic resonance imaging (MRI) of the cervical cord usually accompany appropriate electrophysiologic deficits in SEP.[247] Combined evoked potential testing yields a higher sensitivity than MRI,[79] but MRI offers a better yield than any single evoked potential study alone.[228] In contrast to a high incidence of SEP abnormalities in MS, patients with acute inflammatory transverse myelopathy usually have entirely normal responses.[195]

STROKE

Capsular lesions tend to spare P14 and N18 but alter all the subsequent SEP components or involve NII or NIII selectively. In contrast, a sizeable lesion in the frontal or parietal lobe may affect only NII or NIII.[267] A variety of SEP abnormalities observed in restricted nonhemorrhagic thalamic lesions reflects the presumed vascular territories.[264] Involvement of the primary sensory nuclei, causing the thalamic syndrome or the loss of all modalities of sensation, characteristically eliminates all SEP components with preservation of only P14[32] and N18.[161] Anterior thalamic lesions not involving primary sensory nuclei often delay NI, whereas medial thalamic lesions tend to affect central NIII. Posterior capsular or lateral thalamic lesions may involve both NII and NIII or NIII alone. The complex relationship between the type of SEP abnormalities and the location of thalamic lesions suggests the presence of multiple, at least partially independent, thalamocortical projections mediating regionally specific somatosensory inputs.[161,266] SEP studies also help localize subcortical[141] or cortical infarction[137,138,279] and establish functional prognosis in stroke.[75,125,155]

MYOCLONUS

Patients with cortical myoclonus characteristically have grossly enlarged responses.[101,135,164,181,200] Measurements of SEP using paired stimulation reveal hyperexcitability of the central nervous system associated with myoclonus.[97,248] Some patients with adult ceroid lipofuscinosis have a nearly monophasic, very high-amplitude SEP totally unlike those found in normal control subjects.[144] Large SEP amplitude seen in a previously healthy adult with anterior spinal artery syndrome may reflect loss of anterolateral inhibitory influences on the dorsal column medial lemniscal system.[243] Similarly, a giant SEP seen in children without clinical myoclonus may also represent a form of hyperexcitability of the central nervous system.[201,276]

OTHER DISEASES

In contrast to myoclonus, Huntington's disease shows a drastic diminution in amplitude of early cortical potentials in general and the

N20-P25 component of median nerve SEP and the N33-P40 component of tibial nerve SEP in particular.[20,66,177,272] In Wilson's disease, most patients with neurologic manifestations have some abnormalities of a median or tibial nerve SEP as expected from widespread degeneration of the brain.[33] Other disorders showing abnormal cortical potentials include portal-systemic encephalopathy,[36] a coma after cardiopulmonary resuscitation,[24] developing brain death,[259] head injury,[100] coma,[16,156] locked-in syndrome,[88] and critical illness.[2,282]

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20

Motor Evoked Potentials

Abbreviations: ALS—amyotrophic lateral sclerosis, BAEP—brainstem auditory evoked potential, BP—Bereitschafts potential, CCT—central conduction time, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CSP—cortical silent period, D wave—direct wave, EEG—electroencephalography, EMG—electromyography, EPSP—excitatory postsynaptic potential, HMSN—hereditary motor sensory neuropathy, I wave—indirect wave, IS—intermediate shift, LLICI—long latency intracortical inhibition, LTP—long-term potentiation, MEP—motor evoked potential, MERRF—myoclonic epilepsy ragged red fiber, MFS—Miller Fisher syndrome, MMN—multifocal motor neuropathy, MND—motoneuron disease, MP—motor potential, MS—multiple sclerosis, MUP—motor unit potential, NS—negative slow, PAS—paired associative stimulation, PLS—primary lateral sclerosis, PMP—premotion positivity, PP—paired pulse, rPPS—repetitive paired pulse transcortical magnetic stimulation, rTMS—repetitive transcortical magnetic stimulation,

SCA—spinocerebellar atrophy, SEP—somatosensory evoked potential, SICI—short-latency intracortical inhibition, SNAP—sensory nerve action potential, SOD1—superoxide dismutase 1, TES—transcranial electrical stimulation, TMS—transcortical magnetic stimulation, TST—triple stimulation technique, VEP—visual evoked potential

1. INTRODUCTION

Early studies recorded muscle twitches caused by the application of electrical stimuli to the exposed brain to map the motor cortex in animals and humans.[304] With the advent of technology, high-intensity electric stimulation applied over the scalp can now excite the motor cortex univasively.[257] This type of stimuli, given over the cervical spine, activates the C8 and T1 motor roots in the region of the intervertebral foramina.[258] Stronger shocks excite the descending tracts directly at the level of the spinal cord[249,266] and the pyramidal decussation[417] Transcranial electrical stimulation (TES) has provided important insights into motor physiology and pathophysiology, although discomfort associated with scalp stimulation limits its practical application.

Painless transcranial magnetic stimulation (TMS) has generally replaced electric shock, gaining wide acceptance in the clinical study of motor evoked potentials (MEPs).[20,131] A specially constructed coil can also activate the pyramidal decussation,[420] but not descending motor tracts within the spinal cord.[416] In addition, magnetic stimulation can also excite the motor roots in the region of the intervertebral foramina as well as deep-seated nerves and plexuses.[107,433] At the present, this technique has little use in the assessment of the peripheral nerve for two reasons: uncertainty of the exact activation site and difficulty in achieving supramaximal stimulation without exciting neighboring structures.[37,108,297] Advances in coil design will further improve the technical precision and the clinical utility.

2. ELECTRICAL STIMULATION OF THE BRAIN AND SPINAL CORD

Animal Experiments

A brief low-intensity anodal electrical stimulus delivered to the exposed motor cortex of a monkey activates the axon hillock of pyramidal tract neurons. This results in a single descending volley, or direct wave (D wave), so termed because of its short latency, with no interposing synapse. A stimulation of higher intensities induces a series of descending volleys, or indirect waves (I waves), which follow the D wave at intervals of about 2 ms. They represent transynaptic activation of the same corticospinal neurons through interneurons. Removal of the cortex abolishes the I wave but not the D wave. The twitch force produced in the first dorsal interosseus by a single high-intensity anodal shock to the contralateral scalp can greatly exceed the force produced by supramaximal stimulation of the peripheral nerves.[76] This indicates that a single cortical shock gives rise to repetitive firing of the spinal motoneurons, which summate to produce a very large force.

D Waves and I Waves

With anodal stimulation of the motor cortex, the current applied to the scalp hyperpolarizes the dendrites near the surface, thereby depolarizing the axon and the cell body in the depth. With surface positivity, current flows out of the dendrites (source) of the pyramidal tract cells and enters the axon hillock (sink). This depolarization, if sufficient to open the sodium channel, will generate an action potential at the first internode, producing a D wave. Stimulation with higher intensities activates interneurons and afferents to the cortex, resulting in transsynaptic excitation of the pyramidal output neurons that generate I waves. With cathodal stimulation, current flows to hyperpolarize the axon hillock, raising the threshold for D-wave activation. This tends to enhance the indirect transsynaptic excitation of I waves.[335]

The peristimulus time histogram can assess the firing pattern of D and I waves noninvasively by recording the firing probability of a voluntarily activated motor unit altered by randomly

timed cortical stimulation.[31] In this technique (see Chapter 20-3), low-intensity shocks elicit a single peak corresponding to the excitatory postsynaptic potential (EPSP) from a D-wave volley. Stimulation of higher intensities induces multiple peaks representing both D- and I-wave volleys in the pyramidal tract. Direct recordings from the cervicomedullary junction during surgery also show a D wave with a latency of about 2 ms, followed, with increasing intensity, by a series of I waves. The short-latency D wave generated only with stimuli of very high intensity resists anesthesia.[122]

Technical Considerations

Bipolar stimulation involves placing an anode over the motor cortex and a cathode at the vertex.[264,265] With specially made equipment capable of delivering a high-voltage pulse up to 2000 V with a short duration of 10 μs, a single stimulus to the scalp elicits a submaximal muscle action potential of 1 mV or more. With moderate voluntary contraction of the muscle under study, a single scalp stimulus not much above threshold yields a muscle action potential of near maximal amplitude (Fig. 20-1). In patients with severely affected corticospinal tract, a very high-intensity cortical stimulation may cause activation around the cerebral peduncle or at the foramen magnum.[413] Foramen magnum and spinal cord stimulation may excite slower conducting descending tract instead of corticospinal tract.

High-voltage electrical stimulation at the base of the skull may activate the descending motor tracts at a point midway between the cortex and the cervical enlargement.[417] A small voluntary contraction of the target muscle tends to facilitate the muscle response with no change in latency. One study[417] yielded a 1.5 ms latency difference

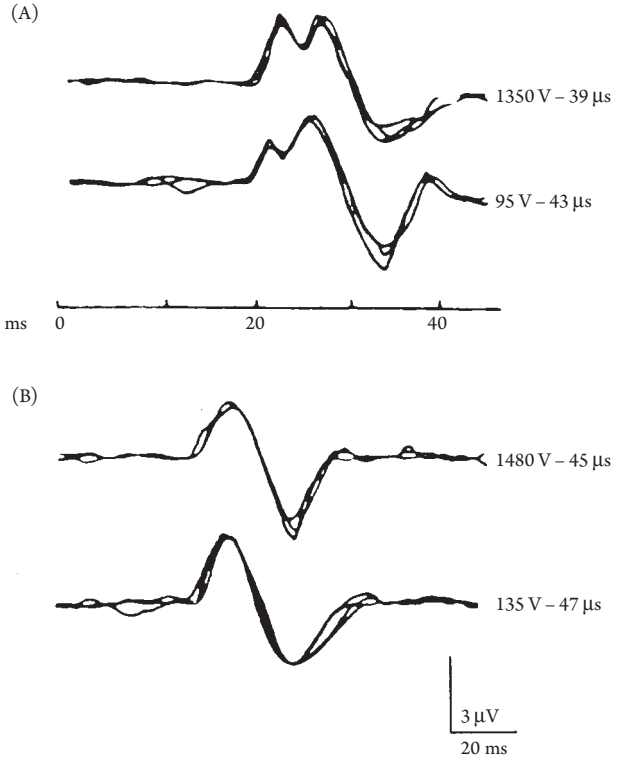

FIGURE 20-1 Compound muscle action potentials evoked by electrically stimulating hand (***A***) and leg (***B***) motor areas over the scalp in the same subject. Comparison between bipolar (first and third tracings) and unipolar (second and fourth) stimulation show a substantial difference in stimulus voltage (V) and duration (μs) required to elicit similar muscle action potential waveform, amplitude and latency in the two conditions. (Modified from Rossini.[329])

between cortical and brainstem stimulation, and a 3.9 ms difference between cortical and cervical stimulation for the first dorsal interosseous. Thus, this method seems to activate the pyramidal decussation at the level of cervicomedullary junction. Unlike cortical stimulation, which elicits multiple descending volleys, brainstem stimulation evokes a single impulse. Stimulation of the pyramidal tract at two levels along the spinal column allows the calculation of central conduction velocities in the same way as in the study of the peripheral nerve. The very large electrical stimuli necessary for transcutaneous stimulation of the spinal cord, however, make it unsuitable for routine clinical studies.

Clinical Studies and Limitations

Despite the advent of magnetic stimulation, certain physiologic studies still use an apparatus that delivers single electrical stimuli of up to 700 V with a half-decay time for discharge of 50 or 100 μs.[22] Near-threshold transcranial anodal stimulation can activate single motor unit potentials in the upper- and lower-limb muscles, allowing estimation of motor conduction velocities for first recruited slow-conducting units.[72] The unifocal method requires relatively low-intensity stimuli delivered from an ordinary stimulator built according to the established safety standards. High-intensity stimulation of the scalp causes discomfort associated with contraction of the scalp and facial muscles. It also poses concerns regarding electrical hazards, although shocks used to produce convulsions as a therapeutic regimen far exceed those required to evoke motor potentials. Seizures as a result of kindling typically develop after trains of long-duration stimuli of about 1.0 ms. Thus, the delivery of single stimuli of very short duration on several occasions will produce few side effects, if any.

3. TRANSCRANIAL MAGNETIC STIMULATION

Design of Magnetic Coil

Magnetic stimulation relies on Faraday's principle that an electric current of a primary circuit will induce a time-varying magnetic field that in turn causes an electric current in the secondary circuit. A magnetic coil generates a brief but intense magnetic field by quick discharge of a capacitor charged to 4 KV passing a current of about 5 KA. This technique, first tested in peripheral nerve stimulation, soon found its extended application for studies of the motor cortex.[18] The magnetic field induced by a coil placed over the scalp penetrates unattenuated through the skull. This, in turn, induces monophasic or biphasic electrical currents[9] inside the skull to a level that excites the motor cortex. In contrast to electrical stimulation, which excites corticospinal axons directly, magnetic stimulation acts at the axon hillocks of the output neurons or at a presynaptic site.[262] Analysis of the electric field orientation localizes the site of maximal intensity to the level of the gray-white junction in good position to activate the layer VI of the cerebral cortex.[103]

In conscious, alert subjects, magnetic coil stimuli, applied to the human brain through the intact scalp and skull, can elicit an MEP painlessly.[433] Up to 10% of normal subjects may have no lower-limb responses with a circular coil. Compared to a round coil, the figure-eight and "butterfly" configuration coils have a better yield with very focal excitation under the site of intersection.[69] Other coil shapes tested favorably include the "four-leaf," "slinky,"[455] and "double cone."[43,420] An appropriate type of coil can activate proximal lower-limb muscles,[6] masseter,[127] and bulbocavernosus, sphincter, and pelvic floor muscles.[39,104] Other recording sites reported include laryngeal muscles,[190] nasalis,[96] orbicularis oculi and mentalis,[200] and cricopharyngeal muscles.[106] The coil can activate the peripheral nerves, roots, and cerebellum,[410] in addition to cortex but, for some unknown reason, not the spinal cord.[416] Possible coactivation of the corticospinal tract confounds interpretation of cerebellar effects of posterior fossa stimulation.[116] Magnetic stimulation also induces sensation, described as tingling, descending along the leg, usually accompanied by responses evoked in the leg muscles.[67]

Discharge Pattern of Motoneurons

The factors that dictate the latency and size of MEP include the stimulus intensity, pulse duration,[334] coil-cortex distance, location, and

orientation of the coil and intrinsic excitability of neural elements.[38,88,379] Responses elicited on the contralateral side of the body have a latency consistent with conduction in the fast central pathways (Fig. 20-2). A stimulus intensity set approximately 20% higher than the threshold evokes a fairly reproducible response in distal muscles. Stimuli of a still higher intensity can also activate the proximal muscles in the upper limbs. The evoked responses in small hand muscles have an onset latency about 2 ms longer than those elicited electrically. This difference equals the time interval between the D wave and the first I wave, suggesting that magnetic stimulation preferentially excites interneurons rather than motoneurons.[247]

The direction of current flow in the magnetic coil also dictates the efficacy of cortical current

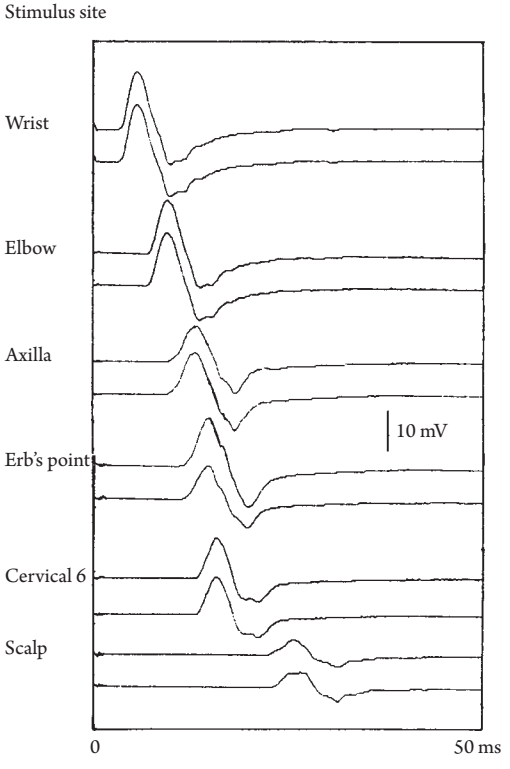

FIGURE 20-2 Motor evoked potentials recorded from abductor pollicis brevis after magnetic coil stimulation at various points along the motor pathways. Scalp stimulation characteristically evokes smaller response despite the use of an optimal stimulus, primarily because of temporal dispersion and phase cancellation along the long motor pathway.

for the interneurons or motoneurons.[436] The circular coil centered at the vertex directing the inducing current anticlockwise as viewed from above (Fig. 20-3) activates the left hemisphere. Reversing the direction of the current, by turning the coil over, stimulates the opposite side. In one study,[237] activation of the left hemisphere required less intensity compared to the right to evoke the same response in the contralateral abductor digiti minimi. In another study,[78] motor threshold and MEP amplitude showed a hemispheric asymmetry with dominant cortex showing a greater excitability. A large circular coil activates descending outputs less selectively than figure-of-eight coil, sometimes activating pyramidal neurons at the initial segment.[89]

According to the size principle, small cortical motoneurons with slow-conducting axons fire first during voluntary effort, followed by recruitment of larger, faster conducting neurons (Fig. 20-4). Magnetic stimulation also activates the cortical motoneurons in the same order, with the first motor units showing a relatively long latency. Threshold brain stimuli can test this principle by eliciting single motor unit discharges in the intrinsic hand muscles at a constant latency. As expected, magnetic stimulation even from different coil positions up to 7 cm apart initially activates those motor units with the lowest threshold for voluntary activation. A Poisson distribution can model motor unit potentials (MUPs) evoked by repetitive, low-intensity TMS.[176] Stronger stimuli cause the same motor units to discharge with a shortened latency and recruit other motor units.

Like electrical shocks, single magnetic stimuli applied over the scalp may cause multiple firing of the anterior horn cell.[131] Thus, the duration and complexity of the evoked muscle response continue to increase with greater stimulus intensity even after the peak-to-peak amplitude has saturated. In fact, a single maximal cortical stimulus may produce a twitch force greater than expected by supramaximal excitation of the peripheral nerve alone. Collision studies can confirm multiple repetitive firing of alpha motoneurons in response to a descending volley.[76] Hence, a maximal antidromic volley set up by stimulation at the wrist fails to completely eliminate the orthodromic volley of the peripheral nerve

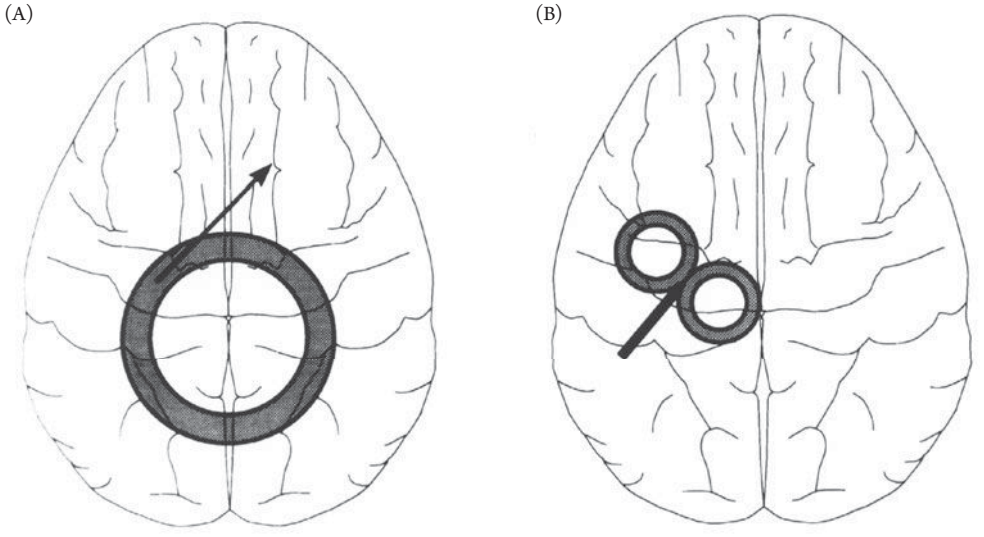

FIGURE 20-3 With a circular coil of diameter 10–12 cm centered at the vertex, the circumference of the coil overlies the hand area of the motor cortex, tangent at approximately 45° to the parasagittal plane (***A***). With a figure-eight coil, its central segment lies angled along the same tangent over the hand area for most effective delivery of stimulation (***B***). (From Mills,[262] with permission.)

induced by electric[76] or magnetic brain stimulation. Here, the remaining response corresponds to the spinal motoneurons firing more than once. Multiple firing increases as TMS intensity rises and saturates at about 1.25 times threshold in healthy subjects.

Increasing background voluntary contraction also augments repetitive firing, saturating at force levels about 50% maximum.[286] These findings suggest that such volitional enhancement depends not only on the additional recruitment of higher threshold motor units but also on multiple firing of the same motoneurons (Fig. 20-5). Despite repetitive discharges, desynchronization of impulses through the long corticospinal tract tends to reduce the MEP amplitude, on the average, by one-third compared to the peripherally induced CMAP. Although this effect shows marked interindividual variations, neither the intensity of TMS nor the level of facilitory voluntary background contractions influences the degree of change.[326]

Cortically applied TMS can also modulate the firing of tonically active hand muscle motor units (see Chapter 20-6). This technique involves constructing a peristimulus time histogram, building up a picture of motor unit firing probability over many trials.[261,263] In normal subjects, firing probability increases approximately 20 ms post stimulus, constituting the primary peak, which reflects the EPSP induced in motoneurons. This type of assessment revealed abnormal excitability of the corticospinal pathway in patients with amyotrophic lateral sclerosis (ALS)[204,268] but not in Kennedy's disease, which characteristically involves only the lower motoneuron.[432] The same technique also elucidated the influence of the corticobulbar system on the orbicularis oris, providing the evidence for a short-latency activation of EPSP consistent only with a direct monosynaptic projection.[227]

Effect of Motor Imagery and Voluntary Effort

A voluntary effort to contract the muscle,[136] or even having the thought without actually making the movement,[378] facilitates the MEP in the target muscle,[147,148] affecting small hand and forearm muscles unequally, probably based on different degrees of corticomotoneuronal inputs.[442] Similarly, imagined foot dorsiflexions evoke an increase in corticospinal excitability, involving the same muscle.[15] In contrast to MEP, which assesses the excitability of the entire motor system, F-wave characteristics serve as a measure of the spinal excitability per se, which,

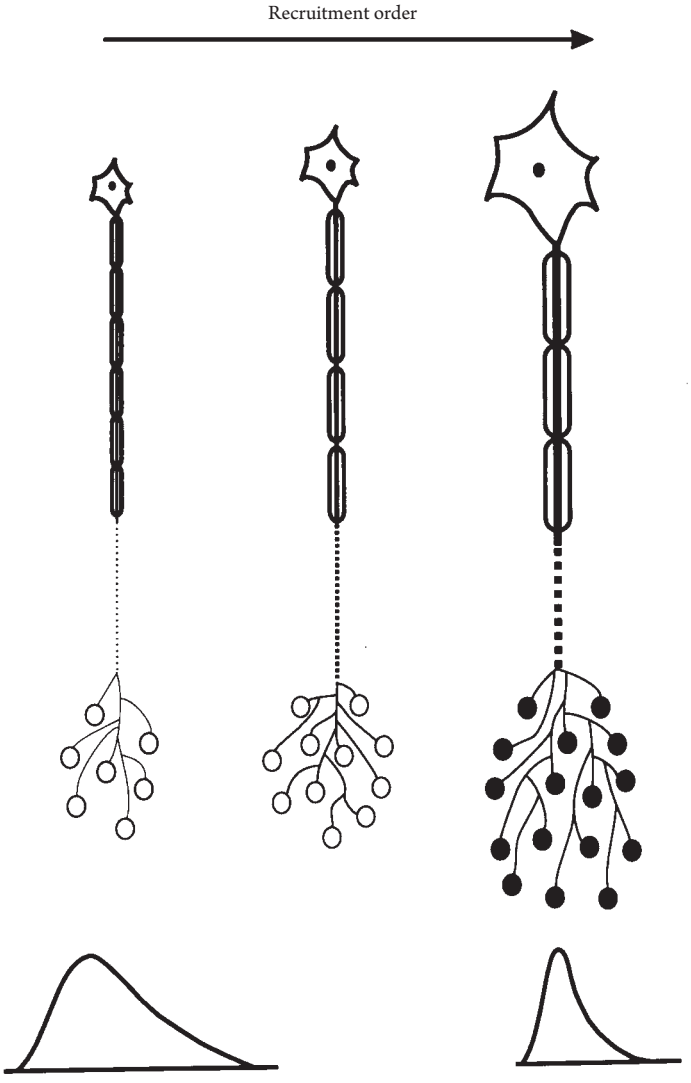

FIGURE 20-4 The recruitment order of spinal motoneurons under increasing voluntary or reflexive drive based on their physical size, according to Henneman's size principle. Small motoneurons, which discharge first, have thin axons and innervate the slow twitch muscle fibers. Large motoneurons, which fire later, have thicker axon and produce fast twitch. (From Mills,[262] with permission.)

therefore, can monitor the spinal contribution of MEP changes (see Chapter 7-2).[120,295,386] Motor imagery induces movement-specific enhancement in corticospinal excitability whether tested by MEP [41,221] or F wave.[386] Thus, this type of facilitation, which precedes the onset of movement,[312] depends primarily on lowering the motoneuron threshold at the level of the spinal cord.[385]

When using electric stimulation, voluntary contraction causes the otherwise insufficient D wave to discharge the motoneuron by summation, reducing the onset latency by 2 to 4 ms and increasing the amplitude approximately linearly with the degree of effort. With magnetic stimulation, a small contraction reaching only 5% of maximum has a marked effect on amplitude[280] probably as the result of spinal summation,[182] shortening the onset latency of the MEP by about 3 ms with no further change when the background contraction increases (Fig. 20-6).

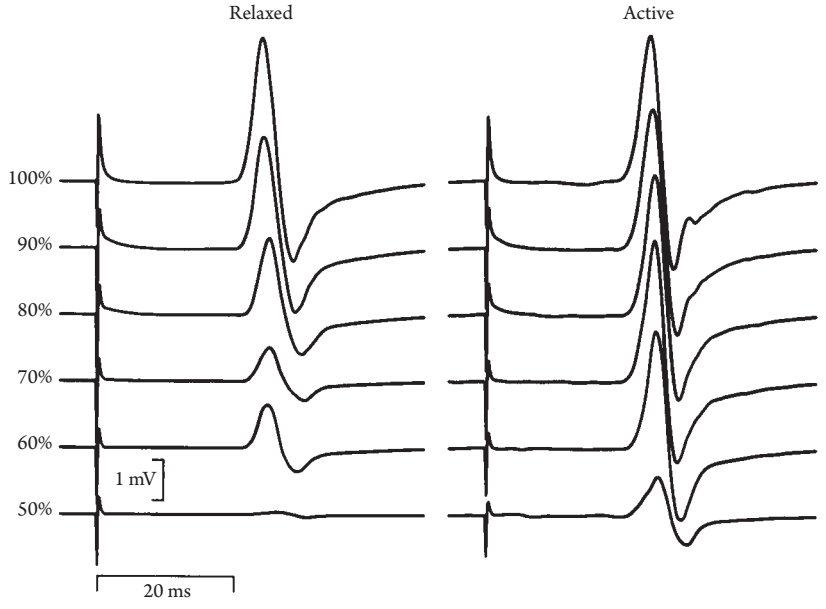

FIGURE 20-5 Motor evoked potentials recorded from the first dorsal interosseous muscle at stimulus intensities from 50% to 100% of maximal stimulator output, averaging five trials for each tracing. At all intensities voluntary activation maintaining a 10% maximum contraction facilitated the muscle response with shortening of the latency from 24.2 ms in the resting state (left column) to 22.8 ms in the active state (right) at 100% intensity (top tracings). (From Mills,[262] with permission.)

An increase in F-wave amplitude in the same muscle suggests that this facilitation primarily, if not exclusively, results from changes of spinal motoneuron excitability.[139] Based on TMS study using paired stimuli, repetitive movements of the agonist induced intracortical facilitation rather than disinhibition.[351] A Jendrassik maneuver, preceding the magnetic stimulation by 200–400 ms, also gave rise to a nonspecific facilitation.[29,389]

Opposite to voluntary contraction, sustained volitional muscle relaxation generally leads to progressive but quickly reversible decline of MEP evoked in that muscle (Figs. 20-7 and

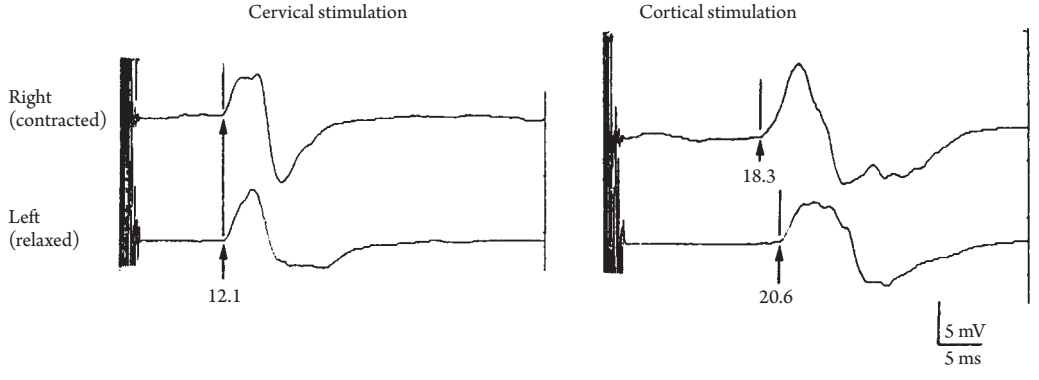

FIGURE 20-6 Motor evoked potentials recorded from abductor digiti minimi muscle after magnetic stimulation over the neck and scalp (Cz). Responses in each column represent simultaneous recording from the minimally contracted muscle on the right and relaxed muscle on the left. Note the effect of voluntary facilitation with cortical but not with cervical stimulation.

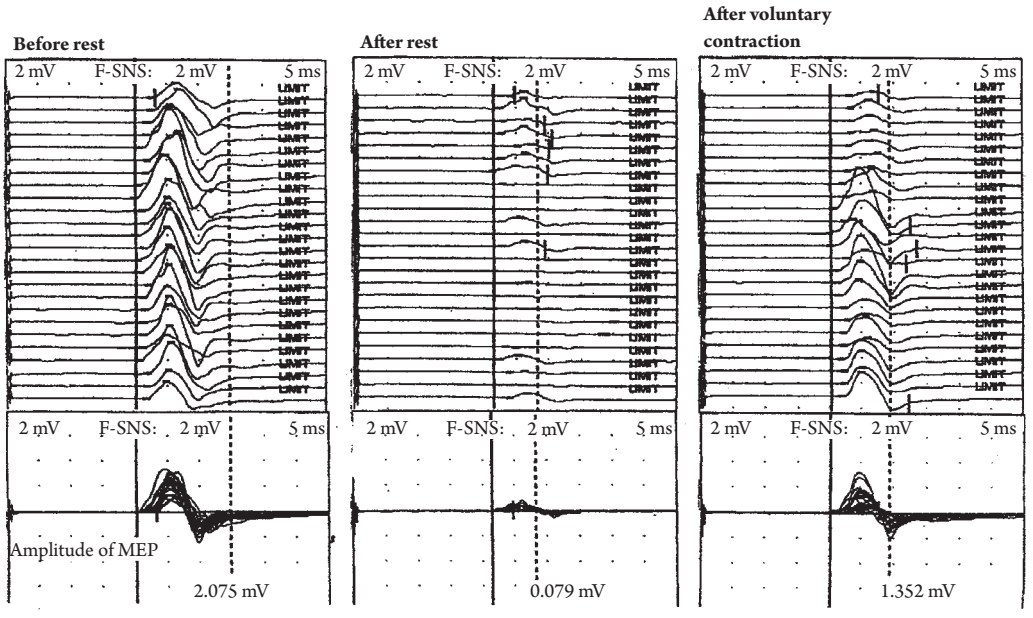

FIGURE 20-7 Motor evoked potentials from the abductor pollicis brevis muscle showing 25 consecutive traces before (left) and after (middle) 12 hours of volitional muscle relaxation, and after a subsequent voluntary muscle contraction (right) in a 29-year-old healthy man. Note a reduction in mean amplitude from 2.08 mV initially to 0.08 mV after volitional muscle relaxation and its partial recovery to 1.35 mV after subsequent voluntary muscle contraction. (Modified from Okada, Kimura, Yamada, et al.[295])

20-8),[110,123,195,295] althoughwithout universal agreement.[395] Most early studies on limb immobilization attributed observed MEP changes to cortical modulation based on the preservation of F-wave excitability.[110] A specific instruction to volitionally relax the immobilized muscle, however, resulted in suppression of not only MEP but also F waves recorded from the target muscle,[295] indicating excitability changes of the anterior horn cells. A series of studies confirmed that rest-induced suppression primarily involves the motoneurons at the spinal level as measured by H reflex[443] (see Chapter 9-2) or F wave (see Chapter 7-2).[386] Furthermore, mental imagery without overt motor output can counter this type of suppression, restoring both MEP and F waves. Thus, subliminal central drives suffice to maintain the spinal excitability, which would otherwise decline with muscle relaxation (Fig 20-8).[162] Comparison between MEP and F-wave excitability changes induced by this task indicates that a simple motor imagery, like thumb abduction, primarily affects the spinal motoneurons, where it projects to, rather than the motor cortex, where it originates from (Fig. 20-9).[123] Various factors such as sustained joint immobilization may also influence the effect of motor imagery on corticospinal excitability.[184]

Mild nonfatiguing exercise facilitates the MEP with a decay to baseline over 2–4 minutes, whereas fatiguing exercise suppresses the MEP with a return to baseline after about 12 minutes.[33,338,343] Testing transcallosal modulation of excitability, voluntary contraction of the dominant hand facilitated the MEP recorded from the contralateral hand in some studies[32,374] but not in others.[341] Facial muscle contraction or eye movements induced a nonspecific facilitation of the abductor pollicis brevis response.[8] Maximal voluntary muscle contraction altered postexercise corticospinal tract and motoneuron excitability detected by cervicomedullary MEP and F wave of the first dorsal interosseous muscle.[126]

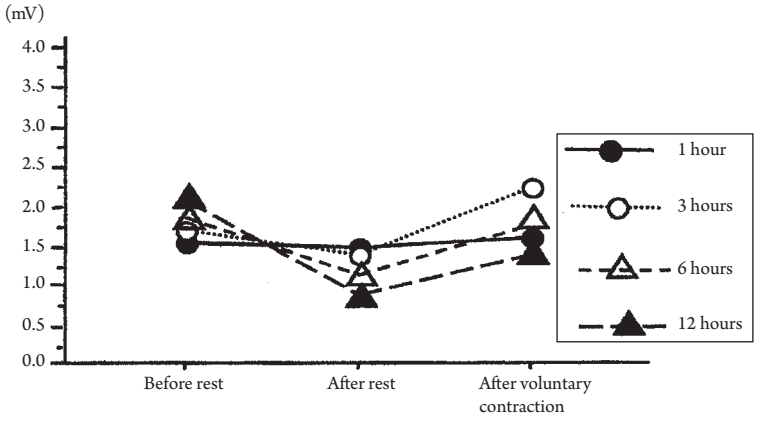

FIGURE 20-8 Reduction in the mean amplitude of motor evoked potentials in the abductor pollicis brevis muscle after 1, 3, 6, and 12 hours of volitional muscle relaxation, and its recovery after a brief, standardized voluntary muscle contraction in 10 healthy subjects. Note progressively greater suppression with longer relaxation time, which prevents a complete return of excitability with exercise. (Modified from Okada, Kimura, Yamada, et al.[295])

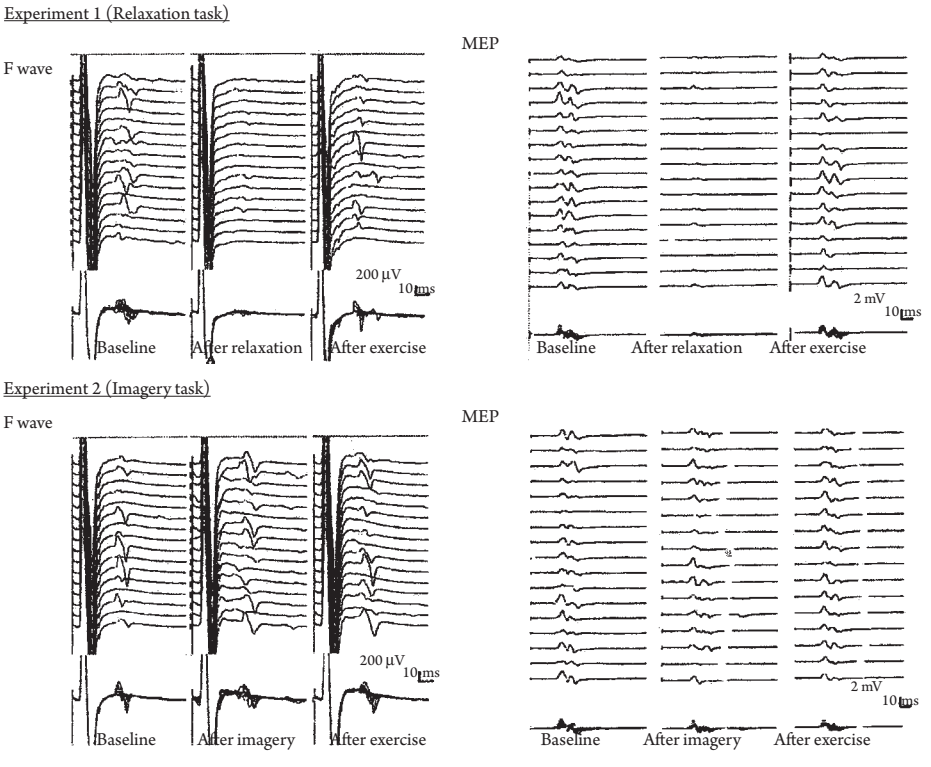

FIGURE 20-9 Temporal changes of motor evoked potentials (right half) and F waves (left half) before and after 3 hour immobilization of abductor pollicis brevis and after brief exercise in a 33-year-old healthy woman. Motor evoked potential analyses of 50 traces showed a change from 2.0 mV to 0.7 mV and 1.9 mV in amplitude with relaxation tasks (right top). Corresponding values consisted of 1.6 mV, 1.6 mV, and 1.6 mV with motor imagery task (right bottom). F-wave analyses of 100 traces showed a change from 62% to 44% and 66% in persistence and from 108.8 μV to 60.8 μV and 87.2 μV in trial average of amplitude with relaxation task (left top). Corresponding values consisted of 65%, 60%, and 58%, and 84.2 μV, 112.7 μV, and 61.3 μV with motor imagery task (left bottom). In 10 healthy subjects, both motor evoked potentials and F waves showed a significant change ($p < .01$) among three sessions for experiment 1 with relaxation task. Corresponding values for experiment 2 with imagery task in the same 10 subjects showed no significant changes among three sessions.

4. STUDIES OF THE PERIPHERAL NERVE

Attempts to stimulate the peripheral nervous system with magnetically induced electric current date back to 1959, first in a frog nerve-muscle preparation and later in a mixed human nerve,[26] producing visible muscle contractions. A single pulsed magnetic field can elicit a CMAP[18] with its possible clinical utility to activate the proximal nerve segments not easily accessible to ordinary electrical stimulation.[108] A high-frequency TMS of a nerve provides a well-tolerated means to activate the muscles in the rehabilitation.[212]

Stimulator Characteristics

In nerve conduction studies, a stimulator must adequately excite various nerves focally at different definable points along their course without coactivating nearby nerves. Optimal orientation of a coil allows depolarization of the nerve at the stimulator position. The nerve running through the center of the coil receives less current because of its transverse orientation to the nerve fibers. A longitudinal current depolarizes the axons more effectively, although transverse fields also contribute.[337] Results may vary depending on soft tissue heterogeneity, which dictates current flow.[201] Lifting part of the stimulator head from the skin makes stimuli markedly less effective. A clockwise or counterclockwise current in the stimulator coil causes no major differences in effect.[7]

Using a round coil, differences between repeat measures of conduction velocity assessed on two separate occasions ranged from 5 to 11 m/s for motor and up to 14 m/s for antidromic sensory studies.[297] The use of a butterfly coil showed intertrial changes of less than 7 m/s for sensory and motor conduction velocities in most segments. Calculated conduction velocities varied more with magnetic than electric stimulation, especially for the short segment of the ulnar nerve across the elbow with differences reaching 18 m/s.[297] Although electrical stimulation preferentially activates sensory over motor axons, magnetic stimuli show no such tendency, activating both fiber populations equally. Thus, electrical stimulation is better suited for eliciting H reflexes by selective submaximal activation of the sensory axons.[297] Magnetic stimulation applied directly over skeletal muscle elicits contraction indirectly through nerve activation at the motor point.[101,239] Such stimulation also evokes cerebral potentials[408] by activating terminal afferents in the muscle independent of muscle contraction.[449]

Available data do not justify the use of a magnetic coil stimulator in the routine clinical practice of peripheral electrodiagnosis. As a test for a commonly studied peripheral nerve, round magnetic stimulators generally fail in the minimal requirement, providing no real advantages over conventional bipolar electrical stimulation.[108] The technique falls short in achieving the accuracy of electrical stimulation, showing a marked intertrial variability of latencies, uncertainty about the point of stimulation, and instability in the evoked waveforms. Difficulties in obtaining supramaximal responses compound the problem of locating the exact site of impulse generation when stimulating the peripheral nerve distally.[297] Smaller stimulator heads with a higher power output together with improved coil configuration may perform more acceptably.

Proximal Nerve Segment

In studying the peripheral nerve distally, magnetic stimulation offers no distinct advantage over conventional electrical stimulation, which has better precision for the site of excitation. Magnetic fields attenuate little through tissues such as bone, providing a useful addition when studying the deeply located proximal nerve segments. Fat tissue, however, alters quadriceps' response to femoral nerve magnetic stimulation in overweight or obese subjects.[398] High-voltage electrical stimulation given over the spinal column activates the roots or spinal nerves and evokes supramaximal motor responses in the limb muscles. This technique may help assess radiculopathies and proximal abnormalities in acquired demyelinating neuropathies.[4,5] Although paravertebral magnetic stimulation can also elicit potentials in the limb muscles with relatively little pain, a flat 12 cm coil design fails to produce supramaximal responses. Nonetheless, preferential activation of the largest diameter axons makes the

onset latency stable irrespective of the positioning of the coil or the stimulation strength.[37] Modified designs may improve the capacity of a coil for focal supramaximal stimulation. Magnetic stimulation of the cervical spine also excites the sensory root near the spinal foramina, eliciting sensory potentials recordable with ring electrodes around the fingers.[456] Similarly, magnetic stimulation at the T10, T12, and L5 vertebral levels elicits a cortical SEP, their latencies showing a correlation to the body height.[407]

Voluntary contraction does not appreciably facilitate the effect of spinal, as opposed to cortical, stimulation in healthy subjects. A cervical magnetic coil stimulation near the C6 spinous process elicits a CMAP with onset latencies less than peripheral conduction times estimated from the F wave. Based on the difference between these two measures, electric or magnetic cervical stimulation must excite the nerve axons 2–4 cm distal to the motoneuron.[346] A coil placed over the appropriate nerve roots elicits the largest responses, further localizing the site of excitation at the root exit zone. The clockwise inducing current in the coil as viewed from behind tends to activate greater responses in the right arm and vice versa.[346] In addition to the relative excitability of neural elements, the electric field in heterogenous volume conductors dictates the site of activation. In clinical practice, however, a slight shift in position of the magnetic coil induces no noticeable change in latency of the evoked response.[232] These findings indicate that depolarization probably originates in the axon hillock known to have the lowest threshold for excitation. A cervical magnetic stimulation helps establish a rate-dependent conduction block induced by maximum voluntary contraction in the demyelinated proximal nerve segment.[150]

Similar strategies apply to the lumbosacral region to evoke muscle action potentials in the lower-limb muscles or the efferent neural pathway of urinary tract.[316] Stimuli delivered over the cauda equina elicit a response less effectively than those delivered at the T12 spinous process over the conus medullaris.[415] A round coil magnetic stimulator placed over the lumbar spinal column activates the motor roots at their exit from the spinal canal, some 3.0 ms or 15 cm distal to the motoneuron for the motor axons with a conduction velocity of 50 m/s.[37] Consequently, the peripheral conduction time estimated by this means excludes the radicular part of the nerves. With progressively higher levels of the supramaximal stimuli, latency often decreases further, reflecting the spread of effective current distally.[308] Collision studies by concomitantly applied distal stimulation[193] also reveal the presence of F waves, which, buried in the M response because of short latency, do not otherwise appear (see Chapter 7-3, Fig. 7-5). Such an F wave starts 6–8 ms after the onset of M response when evoked by paravertebral stimulation. Configurations of the M responses elicited by proximal magnetic stimuli may vary from one trial to the next, in part reflecting the addition of the intermittently generated F waves. This variability of successive trials theoretically allows indirect recording of proximally activated F waves by consecutive subtraction of sequentially elicited M responses. The onset latencies of the proximally evoked F waves provide a measure of the most proximal parts of the motor axons (see Chapter 7-3).

With the use of a figure-eight coil, horizontally orienting the junction of the coil over the distal cauda equina optimally excites the lumbar roots, whereas vertically orienting the junction tends to activate the sacral roots.[234] Orienting induced current cranially through vertically placed junction, magnetic stimuli can also excite the cauda equina proximally near or at the root exit zone.[234,250] Lumbar or sacral root stimulation distally near the foramina provides the distal latency for calculation of cauda equina conduction time. With optimal stimulation of the sacral root, simultaneous recording of the M wave and H reflex reveals a short interval corresponding to the latency of the central loop (see Chapter 9-2, Figure 9-8).[448]

Cranial Nerves

Intracranial stimulation of the facial nerve generates an impulse a few centimeters proximal to the usual site for electric stimulation near the stylomastoid foramen. The actual site of stimulation lies in the proximal part of the facial canal, with a transosseal conduction time of 1.2 ms.[324] In our series,[354] we used tangential placement of

magnetic coil over the scalp area designated as T5 or T6 based on the 10–20 electroencephalogram (EEG) electrode placement system,(see Chapter 19-1) combined with electrical stimulation applied 1 cm below the anterior tragus. The onset latencies of CMAP recorded from the ipsilateral nasalis muscle averaged 4.5 ± 0.5 ms (mean ± SD) with proximal magnetic stimulation and 3.2 ± 0.4 ms with distal electrical stimulation.

Stimulation of the extracranial facial nerve at two sites yielded a conduction velocity of 59.6 ± 4.5 m/s. Based on these findings, the site of magnetic activation must fall at the root exit zone of the facial nerve, 79.0 ± 8.6 mm proximal to the point of electrical stimulation below the ear. In fact, direct electrical stimulation at this site intraoperatively elicits a response with the same latency as TMS.[397] This technique helps evaluate Bell's palsy,[325,354,397] facial myokymia,[294] Miller-Fisher syndrome (MFS),[10] and other disorders affecting the proximal segment of the facial nerve.[129] Electrical and magnetic stimulation of extra- and intracranial segment of facial, accessory, and hypoglossal nerves revealed subclinical cranial nerve involvement in hereditary motor and sensory neuropathy (HMSN).[215]

5. CENTRAL CONDUCTION TIME

Method and Normal Values

The total conduction time comprises activation of the cortical structures, conduction down the corticospinal pathway, activation of spinal motoneurons, and conduction along the peripheral nerve to the muscle. Stimulation over the cervical area with the cathode between the C7 and T1 spinous processes excites the motor roots at the foramina where they leave the spinal canal. The CCT, calculated as the difference in latency between scalp- and root-evoked muscle responses, therefore, contains a small peripheral component. Thus, the total motor conduction time of about 20 ms from the scalp to the intrinsic hand muscle consists of a peripheral latency of 13 ms, synaptic and root delay of 1.5 ms, and CCT of 5.5 ms. The use of F waves[342] yields a similar peripheral latency and calculated CCT.

Use of Root Stimulation

High-voltage electrical or magnetic stimulation over the spinal column excites C8 and T1 in the region of the intervertebral foramina, providing a means of assessing peripheral conduction time. For this purpose, a magnetic coil centered over the C7 spinous process best excites the cervical motor roots on the right when the inducing current flows clockwise as viewed from behind. The values thus obtained show the same range as measured by needle stimulation of the lower cervical roots using the cathode placed near the C7 to T1 interspinous space and the anode 6 cm rostrally or laterally (see Chapter 6-4). Cervical stimulation evokes muscle responses only slightly smaller in amplitude than those elicited by electrical stimulation of the peripheral nerve at the wrist or elbow. Thus, in addition to its use for estimation of peripheral latency, this technique also can determine proximal conduction block in the motor roots. Surface stimuli on the order of 300 or 400 V cause moderate local discomfort associated with a sudden twitch of the arm. Nonetheless, electrical, as compared to magnetic, stimulation elicits a larger amplitude and provides a more reliable means of studying the waveforms.

The calculated CCT using root stimulation for the peripheral latency includes 0.4 ms conduction time across the cervical roots. This root conduction time increases with diffuse slowing of motor conduction as expected in peripheral neuropathy, for example, 0.46 ms at 30 m/s and 0.89 ms at 20 m/s.[65] Increasing the stimulus intensity in an attempt to obtain larger amplitude will move the site of activation distally along the motor root, decreasing the peripheral latency and increasing calculated CCT. In estimating the peripheral conduction in the lower limb, the stimulating cathode or the magnetic coil placed over the conus medullaris excites intradural motor roots close to the cord.[416] The CCT determined by these techniques also includes a short radicular latency. The cathode or coil placed more caudally can stimulate the motor roots in the region of the intervertebral foramina. The use of a specially constructed coil can activate the most proximal cauda equina at around the conus medullaris, allowing an estimation of cortico-conus motor conduction time.[234,250]

Calculation Based on F Wave

In estimating peripheral conduction time using the F wave, one of the main technical concerns relates to small changes in stimulator position that may shift the actual point of activation. This poses a particular problem with magnetic coil stimulation, which fails to pinpoint the exact site of nerve activation. Thus, with a shift of coil placement, both F-wave and M-response latencies vary from one stimulus to the next. The sum of the two latencies, however, remains the same because the increase in F-wave latency precisely compensates for the decrease in M-response latency, or vice versa (see Chapter 7-3). Thus, the value calculated by the following formula equals the conduction time along the entire length of the peripheral motor pathway, which remains the same regardless of the site of nerve excitation:

$$\text{Total peripheral conduction time} = (F + M - 1) / 2$$

where M and F indicate the latencies of the M response and F wave, whereas 1 ms represents the turnaround time at the anterior horn cell. In contrast to root stimulation, this method determines the peripheral motor conduction time in total, thus eliminating peripheral contribution in the calculated CCT. In two monkeys, the indirect calculation of the CMCT with the F-wave method overestimated the corticospinal conduction time slightly but to a significant extent. If only slow-conducting motoneurons respond to a weak corticospinal input, using the longest rather than the shortest F-wave latency may yield a more accurate estimate of the CMCT.[296]

Triple Stimulation Technique

Triple stimulation technique (TST) provides a useful means of detecting conduction block in the spinal cord or the peripheral nerve and peripheral nerve proximal to the Erb's point[83,243] and latency distribution of MEP.[114] The technique involves applying TMS followed by two maximal electrical stimuli, one at the wrist and the other at the Erb's point, delivered to the ulnar and median nerves simultaneously to circumvent the ambiguity induced by volume conducted activity.[161] With appropriate interstimulus intervals, the TMS-induced impulse collides with the antidromic impulse from the wrist, thus clearing the passage for the orthodromic impulse from the Erb's point. In the presence of conduction block proximal to Erb's point, reduction in the TMS-induced impulse allows passage of the distally induced antidromic impulse, which now collides with proximally induced orthodromic impulse, making the median and ulnar responses recorded over the thenar and hypothenar eminence smaller than normal (Fig. 20-10, see Fig. 11-20A,B). The method allows, in effect, synchronization of asynchronously conducting proximal impulses[194] to distinguish temporal dispersion from conduction block.[83] Disease entities showing abnormalities by this method include spinocerebellar ataxia,[339] multiple sclerosis [159,160] and multifocal neuropathy.[12]

6. MODULATION OF CORTICAL EXCITABLITY

Cortical Mapping and Motor Reorganization

A number of studies have used MEP as a means of noninvasively mapping the human motor cortex.[133,245,439] The technique identified small motor areas clearly separate from each other and from corresponding somatosensory areas.[302,437] Although motor and prefrontal cortices show a distinctly different cortical reactivity to TMS, most authors use motor thresholds determined over the motor area when describing the stimulus intensity of prefrontal TMS.[173,177] In one study,[401] a cortical TMS elicited a larger MEP on the left compared to the right orbicularis oris muscle, suggesting asymmetry of corticobulbar projection to muscles of facial expression. Caffeine, known to facilitate the spinal motoneurons, as tested by H reflex,[429] had no effect on measures of cortical excitability.[299]

Learning motor skills with repetitive execution of identical movements enhances the MEP elicited by TMS.[141] For example, motor practice synchronized with external pacing may promote use-dependent plasticity and facilitate

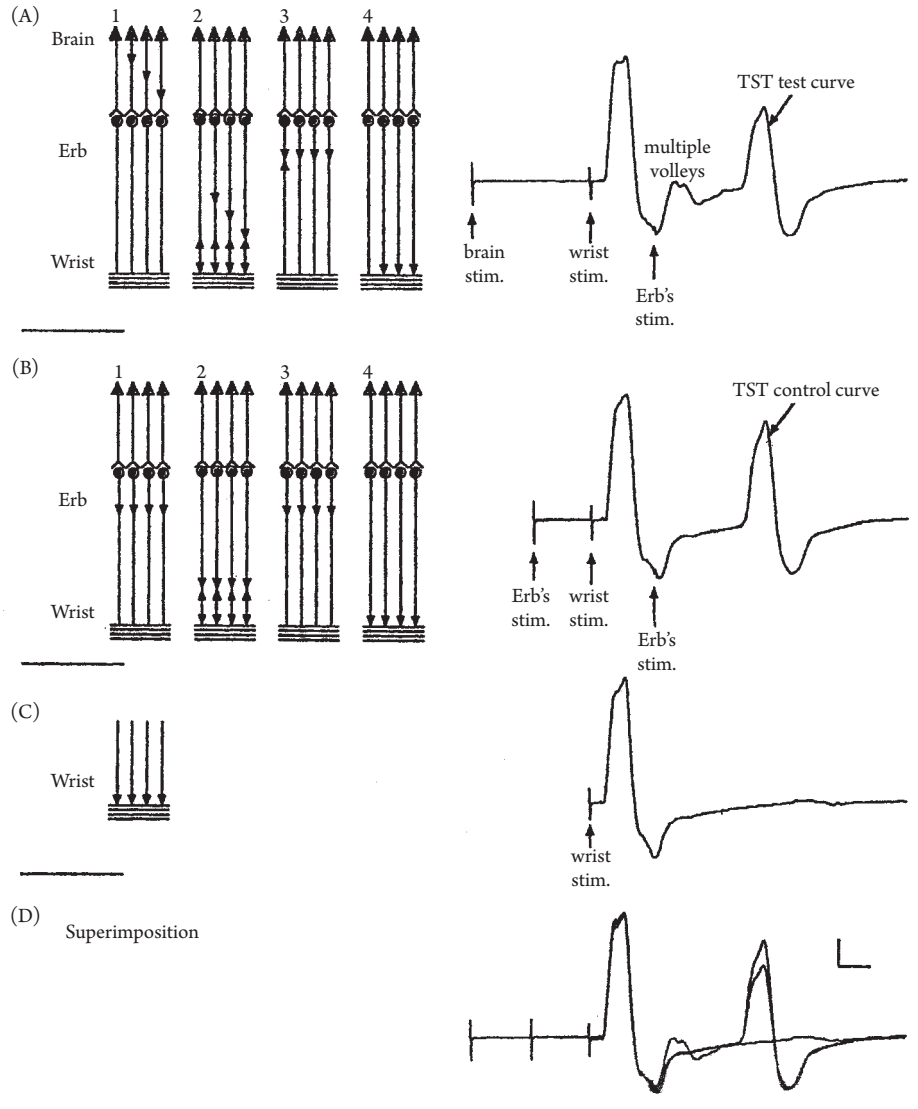

FIGURE 20-10 The triple stimulation technique (TST) principle (cf. Fig. 11-20A,B). The left column shows a schematic diagram of the motor tract simplified to four corticospinal axons with monosynaptic connections to four peripheral axons and the muscle fibers. (***A***) TST test, (***B***) TST control, (***C***) response to a single stimulus at wrist, and (***D***) superimposition of (***A***), (***B***), and (***C***). In this example, a submaximal transcranial stimulus excites 75% of the axons (three axons out of four). (*A,1*) Transcranial stimulation excites three out of four axons. (*A,2*) After a delay, a maximal stimulus applied to the wrist evokes the first negative (upward) deflection in the TST test trace, followed by that of the multiple-discharge volleys (not figured on the left scheme). (*A,3*) After a delay, a maximal stimulus applied to Erb's point (*A,4*) evokes a synchronized response from the three axons excited initially by the transcranial stimulus giving rise to the second large deflection of TST test trace. (*B,1*) A maximal stimulus applied to Erb's point, (*B,2*) and after a delay a maximal stimulus applied to the wrist evoked the first deflection of TST control trace. (*B,3*) after a delay a maximal stimulus applied to Erb's point elicits (*B,4*) a synchronized response from the four axons as the second deflection of TST control trace. (***C***) The response evoked by stimulating the wrist serves as a baseline for measurement of the amplitude and area of the second deflection of the TST curves. (*D*) On the superimposed traces, the smaller size of the second deflection of TST test trace, compared with that of the TST control trace, demonstrates excitation of only 75% of spinal axons by transcranial stimulation. Calibrations: 2 mV and 5ms. (From Magistris, Rosler, Truffert, et al,[243] with permission.)

corticomotor excitability.[3] Delayed facilitation of motor cortical excitability following repetitive finger movements may represent a form of short-term potentiation.[47] This ability of the healthy motor cortex to reorganize in response to training decreases with age.[345] In braille readers, reading activity modulates the motor cortical outputs to the reading hand.[301] Other studies related to local cortical reorganization include effect of repetitive hand movements[311] and proprioceptive stimulation with passive wrist movement, which induced a delayed increase in corticospinal excitability of the forearm muscles.[238]

Cortically Induced Silent Period

Cortically applied TMS induces a cortical silent period (CSP) of the voluntarily contracted target muscle ipsilateral to the side of stimulation (see Chapter 9-5),[74,170,174] presumably on the basis of transcallosal inhibition, mediated by the anterior half of the trunk of the corpus callosum, which develops after the age of 5 years.[145] Accumulated evidence indicates that TMS activates the excitatory and inhibitory networks differently. These include appearance of CSP without a preceding MEP,[45] a lower threshold to activate CSP than MEP,[431] plateauing of MEP amplitude before CSP duration with increasing stimulus intensity,[166] and different modulation of MEP and CSP by subthreshold conditioning stimulus.[404] The duration of CSP depends on the intensity of TMS pulse but remains relatively unaffected by the level of ongoing muscle activity. Thus, the use of the ratio (CSP duration)/(MEP size) reduces intersubject variability, eliminating TMS pulse type differences.[298]

Voluntary contraction reduces transcallosal inhibition induced by a conditioning subthreshold TMS applied to the hemisphere ipsilateral to the muscle activity at short interstimuli of up to 6 ms.[315] Thus, voluntary drive seems to suppress cortical inhibitory circuits that project to the spinal motoneurons subserving the activated muscle. Vibration prolongs CSP in an antagonistic muscle presumably by enhancing inhibitory network at a supraspinal level.[27] In a patient with dystonia,[367] intrathecal baclofen infusions induced a marked increase of CSP, showing no hemispheric asymmetry.[78] Adolescents with diplegic cerebral palsy showed no transcallosal inhibition,[146] whereas patients with generalized epilepsy had prolonged CSP, possibly reflecting an increased intracortical inhibition.[236]

In the upper limb, H reflexes, markedly suppressed early in the TMS-induced CSP, return to baseline before the end of this period.[421] In contrast, the H reflexes in the lower limb either remain unchanged or show facilitation throughout CSP, which, therefore, must result from cortical, rather than segmental, mechanisms.[53] A normal R1 component of the blink reflex seen during CSP also suggests cortical origin of this inhibition in the facial muscles.[220] Conversely, cortically applied TMS may also inhibit the brainstem motoneurons per se.[220] For example, TMS reduces masseter motoneuron pool excitability by descending corticobulbar activity, showing no inhibition attributable to cortical mechanisms.[373]

Conditioning and Testing Paradigm

Repeated trials of TMS show a high degree of variability in the amplitude of evoked response, which in part results from spontaneous fluctuations in corticospinal excitability,[209,430] although magnetic resonance imaging (MRI) guided stimulation results in improved spacial precision.[132] In paired pulse (PP) paradigm, the first, conditioning stimulus modifies the response to the second, test stimulus, which reveals a series of excitability changes depending on the stimulus intensities employed.[30,200,246] The conventional PP paradigm using subthreshold conditions and suprathreshold test stimulus reveals an intracortical inhibition at intervals of 1–4 ms and facilitation at 8–12 ms.[450] Direct recording of corticospinal volleys also shows triphasic changes of motor cortex excitability, inhibition at 2.5 ms, facilitation at 25 ms, and second inhibition at 100–200 ms after a conditioning stimulus.[182,183,287]

The initial inhibition called short-latency intracortical inhibition (SICI), depends on the proportion of spinal motoneurons activated by corticospinal input.[216,336,427] Those excitability changes, probably mediated by inhibititory interneurons and facilitatory interactions between I waves, show no interhemispheric asymmetry or

intra-individual variability.[241] The second inhibition, called long-latency intracortical inhibition (LICI), may help elucidate cortical involvement in various conditions such as Parkinson's disease[86] and limb immobilization.[60] Continuous theta burst stimulation administered at a low stimulus intensity can reduce the excitability of SICI network without affecting the facilitatory intracortical motor networks involved in the MEP.[95] Transcranial direct current stimulation over the motor association cortex also induces plastic changes in the ipsilateral primary motor and somatosensory cortices.[196]

Variations of PP paradigm have demonstrated a wide range of interaction between conditioning stimuli and test MEP, based on excitability changes at cortical or spinal level. A conditioning stimulus over the cerebellum reduces the size of responses evoked by test stimulation given over the scalp 5–7 ms later.[418] Trigeminal sensory input elicited by electric or magnetic stimulation also interferes with the central motor drive to the intrinsic hand muscles.[366] Vibration of the target muscle enhances a cortically activated response by altering the excitability of alpha motoneurons.[64,368] Electric stimulation of the index finger about 80 ms earlier facilitates MEP recorded from lower limb.[51] A conditioning, motor threshold stimulation applied to the median nerve at the wrist enhances the MEP probably on the basis of muscle afferent input.[207] Stimulation of cutaneous afferents also induces modulation of upper-limb MEP. Activation of A-δ fibers initiates a spinal reflex causing MEP amplitude reduction in muscles involved in reaching and grasping, and MEP amplitude facilitation in muscles involved in withdrawal.[202] Whole-hand mesh-glove electrical stimulation increased motor cortical excitability lasting for at least 60 minutes.[130] Single TMS of Brodman area 44, or the caudal part of Broca area, produces MEP from hand muscle and can easily interrupt target-oriented hand movements.[422]

Cortical stimuli can also change the size of H reflex and F wave. Motor threshold[253,423] or subthreshold cortical volleys[16,278] coinciding with the Ia input potentiate the H reflex elicited in the upper and lower limb. Similarly subthreshold motor volley arriving at the anterior horn cells concomitantly with antidromic impulse facilitate the F wave.[256] Conversely, suprathreshold motor volley preceding the Ia input suppress the H reflex.[121,452] Alterations in the TMS-conditioned F wave and H reflex reflect the time course of excitability change of the spinal motoneuron population liminally or subliminally activated by descending central drive.[167]

Repetitive Transcranial Stimulation

Repetitive transcranial magnetic stimulation (rTMS) produces lasting excitability changes on corticospinal descending activity[92] and neural networks at near as well as distant locations, depending on the stimulation paradigms.[54,117,175] At frequencies of 5 Hz or higher, it enhances cortical excitability beyond the time of stimulation.[303,353] If given at 1 Hz, however, it induces lasting decrease in cortical excitability.[52] In general, high-frequency stimulation exceeding 5 Hz yields excitation, whereas lower frequencies or irregular patterns induce inhibition.[73,124,156] Low-frequency stimulation, which does not induce long-term potentiation (LTP) by itself, suppresses consecutive LTP by occlusion.[82] In one study,[124] which confirmed the general trends of low- and high-frequency rTMS, cluster analysis revealed the presence of two distinct groups of subjects with opposite responses at the same frequency of stimulation. In another study, 5 Hz rTMS in a standard block design induced facilitation, whereas a continuous protocol using the same number of pulses caused inhibition.[333] Contralateral rTMS also induces interhemispheric enhancement of somatosensory cortical excitability.[255] Inhibitory rTMS induces less excitability change in advanced age compared to younger population.[396]

Like single-pulse TMS, rTMS over the cerebellum affects corticospinal excitability by cerebellar and peripheral mechanisms. In one study,[125] rTMS over either the right cerebellum or the right posterior neck facilitated MEP in the hand and forearm muscles ipsilaterally for up to 30 min after the end of the train. Subthreshold low-frequency rTMS depressed cortical excitability beyond the duration of the train, presumably by selective cortical disfacilitation.[323] Subthreshold prefrontal rTMS[319,372] depressed intracortical inhibition by

reducing the excitability of inhibitory interneurons or altering the facilitatory neurons for I waves.[275] Focused high-frequency rTMS helps localize the unexposed primary motor cortex during brain tumor surgery.[318]

As a variant of rTMS, paired-pulse TMS (PPS) applied over the medial frontal cortex in a certain time window can enhance pain perception of acute, electrically induced, Aδ fiber–mediated pain.[285] Repetitive paired-pulse TMS (rPPS) delivered at an I-wave periodicity of 1.5 ms for 30 min facilitate the cortical MEP to a single TMS, without affecting concomitantly recorded F-wave excitability.[393] During this facilitation, lasting up to 10 min after the cessation of the intervention, an MEP elicited by TMS applied to brainstem remains unaltered.[134] These findings suggest that rPPS delivered at 1.5 ms intervals affects the motor cortex per se, rendering a sustained excitability change. In some studies, rPPS markedly increased the corticospinal excitability,[93,393] which improved patient disability scales during recovery from acute ischemic stroke.[189] Quadro-pulse conditioning stimulation induced motor cortical plasticity more effectively than paired pulse.[135]

Other reported results of rTMS in humans include a long-lasting increase in cortical excitability,[192] sustained enhancement of the inhibitory mechanisms responsible for CSP,[59] reduction of blink reflex excitability,[79] restoration of finger movement by releasing the contralateral motor cortex from transcallosal inhibition,[199] improved hand function by reducing interhemispheric inhibition in chronic subcortical pediatric stroke,[197] reduction of essential blepharospasm by functional inhibition of the medial frontal area [211] and reduction in pain provoked by laser stimulation.[219,284] Muscle vibration can counter rTMS-induced inhibition of the corticospinal system.[320]

The use of rTMS has become a noninvasive tool to study plasticity of the human cortex, but any therapeutic implication for this modulation of cortical excitability remains undetermined. The disorders tested in this regard include depression,[272,279] Parkinson disease,[113] chronic pain syndrome,[218,321] phantom limb pain,[399] writer's cramp,[142,347] Tourette syndrome [282] and ALS.[90,451] Overall, rTMS causes infrequent and generally mild adverse effects, although more serious complications include seizures and instances of psychotic symptoms reported infrequently.[240]

Paired Associative Stimulation

Repetitive stimulation of either a pair of peripheral nerves,[314] muscle motor point and motor cortex,[254] or peripheral nerve and motor cortex[375] induces reorganizations within the human motor cortex. These results confirm the importance of associative input for the induction of cortical plasticity.[313] For example, repetitive paired stimulation, coupling a single electric stimulus delivered on a peripheral nerve with a single TMS, gives rise to changes in the excitability of the motor [376,440] and sensory cortex.[441]

These interventions, called paired associative stimulation (PAS), produce a long-lasting cortical excitability change. The test MEP shows a decrease in amplitude after a short-interval PAS of 10 ms and an increase in amplitude after a longer interval PAS of 20 ms. The PAS-related excitability changes evolve rapidly within 30 min and last longer than 60 min, showing good intraindividual reproducibility.[119] Clinical studies of motor cortical plasticity using this technique revealed a partial loss of expected physiologic change and its restoration by administration of dopamine in patients with Parkinson's disease[409] and age-related decrease in the elderly.[111] Biological basis of PAS for inducing neural plasticity may relate to repetitive pairing of two types of afferent stimulation. To support this notion, repetitive pairing of TMS applied to the right and, after a 15 ms time interval, the left motor cortex produced an associative long-term potentiation-like effect, facilitating MEP for up to 20 minutes.[203]

7. OTHER TECHNIQUES FOR MOTION PHYSIOLOGY

Movement-Related Cortical Potentials

Movement-related cortical potentials comprised at least eight separate components.[290,357] Those preceding the onset of movement include a symmetric early negative shift called Bereitschafts potential

(BP); intermediate shift (IS); negative slow wave (NS) maximal over the contralateral precentral region; P-50 or premotion positivity (PMP); and N-10 or motor potential (MP). Components occurring after the onset of movement include N+50 or a sharp negative wave over the contralateral frontal region; P+90; N+160; and P+300 or a widely distributed large positivity maximal over the contralateral precentral region (Fig. 20-11).

In the clinical domain, patients with Parkinson's disease show abnormal topography of premotion slow negativity, or a BP/NS complex, with reduced amplitude on the side of the affected basal ganglia.[80,362] This component also undergoes a predictable reduction of amplitude in patients with cerebellar ataxia in general and in those with myoclonic epilepsy, ragged red fiber (MERRF) syndrome in particular, presumably

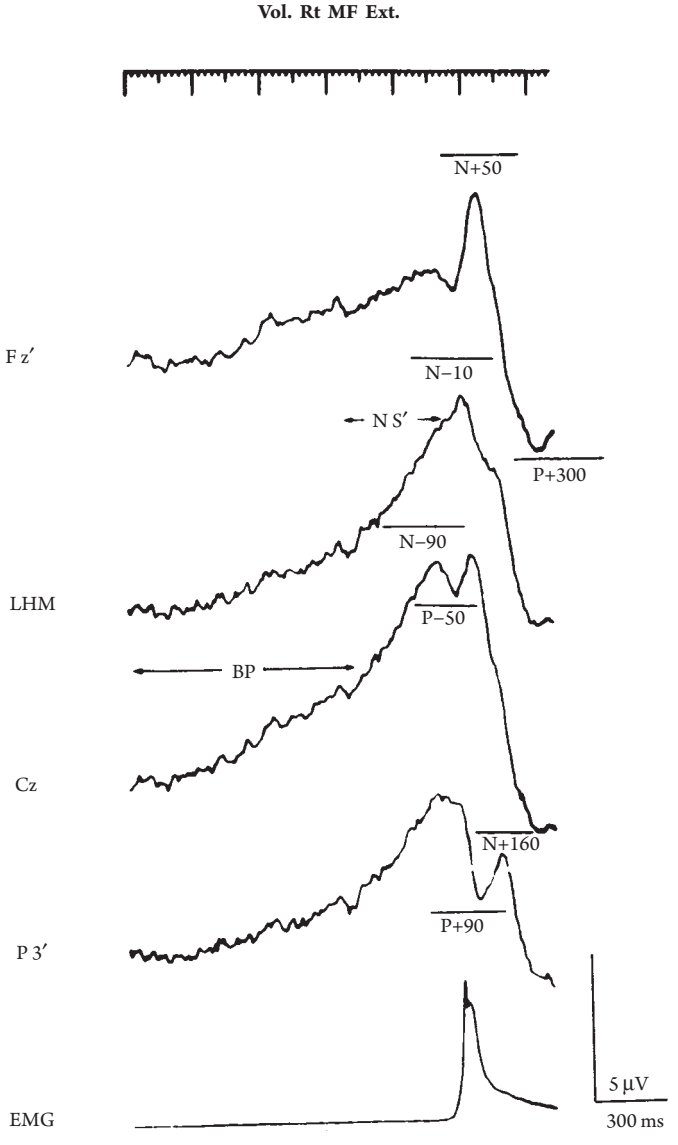

FIGURE 20-11 Terminology of each component of cortical potentials associated with voluntary, self-paced middle finger extension. The record shows a grand average in l4 healthy subjects, 200 trials for each subject. (Modfied from Shibasaki, Barrett, Halliday, et al.[354,355])

reflecting the dysfunction of the cerebellofugal or dentatothalamic pathways.[362] Reduction of the late BP amplitude may also serve as a surrogate marker for dysfunction of the cerebello-dentato-thalamo-cortical projection in essential tremor.[231] The increase in electromyographic (EMG) amplitude and slope, and MP amplitudes suggest a possible link between the control signal originating in the motor cortex and activity level of the α-motoneuron pool as a function of progressive muscle fatigue.[172]

Cortical slow negativity similar to the BP/NS precedes choreic movement in patients with chorea-acanthocytosis but not in those with Huntington's disease.[361] In patients with Gilles de la Tourettes syndrome, voluntary jerks but not spontaneous tics accompany a premotion negativity despite their apparent resemblance. Patients with mirror movement may show an abnormal topography of NS that appears bilaterally, indicating unintended participation of the opposite motor cortex.[359] Slow premovement cortical potentials do not reflect the degree of improvement after therapy in writer's cramp.[447]

Jerk-Locked Averaging

Jerk-locked backward averaging of the scalp EEG helps identify cerebral events time-locked to a voluntary or involuntary muscle contraction. With this technique, rectified electromyography (EMG) signals serve as the trigger for averaging the cerebral activity, preceding the movement by means of a delay line (Fig. 20-11).[208] A number of investigators have used the method in assessing movement-related cortical potential,[21,217,355,356] mechanisms of synkinesis,[359] and the pathophysiology of myoclonus,[357] parkinsonism,[94] other involuntary movements,[361] and voluntary or involuntary muscle relaxation.[358,390,391]

Averaging the EEG time-locked to a myoclonic discharge helps identify the responsible cortical spike and determine cortical excitability after myoclonus.[163,271,364] The EEG correlates of myoclonus established by this means resemble the giant early cortical component of the SEP in waveform, topography, and time relationship to spontaneous myoclonus.[363] Cortical reflex myoclonus shows relatively enhanced cortical excitability for 20 ms just after the myoclonus, followed by a suppressed postmyoclonus period thereafter.[360] In such cortical reflex myoclonus, cortical spikes precede movement of the upper limb by 6–22 ms. In contrast, periodic synchronous discharges start 50–85 ms before the myoclonus in patients with Creutzfeldt-Jakob disease. Patients with Alzheimer's disease and those with Down's syndrome also demonstrate a focal, negative cerebral potential over the contralateral central region antecedent to the myoclonic jerks.[435]

8. CLINICAL APPLICATION

Clinical Practice and Safety Issues

To record a MEP after TMS, the muscles modestly facilitated in the range of 10%–20% of maximal contraction yield the best response. A weaker effort causes small inconsistencies in latency, whereas a very strong attempt gives rise to excessive noise, making measurement of onset latency difficult. Moderate contraction of the homologous contralateral muscle also reduces latency and increases amplitude without obscuring a response. In a slightly contracted muscle, neither a wide range of stimulus intensity nor the position of the stimulating coil within an area of 6 cm^2 over the vertex alters the onset latency substantially. We choose the shortest onset latency and largest response from a series of four or five consecutive trials, expressing the amplitude in percentage of the maximal muscle response evoked by peripheral nerve stimulation. The size difference between peripherally and transcranially induced responses, at least in part, results from physiologic temporal dispersion and phase cancellation (see Chapter 11-5). Assessments should include waveform complexity, trial-to-trial variability, and corticomotor threshold.[267] Late muscle responses sometimes recorded after the cortically evoked short-latency primary potential probably reflect startle effect from the scalp stimulus.[153]

A reduction in amplitude indicates either a block or degeneration of corticospinal fibers or a dispersion of the response. The rate-dependent conduction failure characteristic of demyelination may block trains of I waves, which would have fired the spinal motoneurons. Reduced

amplitude may also result from depressed spinal excitability or presynaptic inhibition of corticospinal terminals. For these reasons, identical abnormalities may result from different disorders, showing limited specificity for pathophysiologic processes. Changes seen in a wide range of neurologic disorders thus imply no single disease process, despite some findings considered more typical of one than another. The technique may occasionally demonstrate subclinical motor abnormalities, although more often it confirms known deficits detected by clinical examination. The numerous physiologic variables affecting the descending volley in the corticospinal tract alter the central conduction time (CCT) by a few milliseconds. Thus, the role of magnetic brain stimulation for quantification of abnormalities and for follow-up purposes remains undefined, although, in one study, TMS induced a reproducible tibialis anterior MEP in healthy subjects.[42]

We have experienced very few adverse effects of single TMS other than minor discomfort of the stimulated scalp and short-lasting dull headache. In one series of 30 healthy subjects, EEG and cognitive and motor tests remained unchanged before and after TMS. Except for a slight decline in serum prolactin level, biochemical studies showed no correlation between the test results and the extent of stimulation.[34] In the cat, a repeated series of high-intensity stimuli resulted in no adverse consequences as tested by cortical electrical activity and blood flow, blood pressure, or heart rate.[109] Although not reported in the literature, magnetic stimulation could theoretically dislodge intracranial metallic objects such as aneurysm clips and shunts. The heating of metal electrodes during rapid rate magnetic stimulation constitutes a possible safety hazard, but temperature does not usually increase to the degree high enough to induce a skin burn.[332]

A train of high-frequency stimuli at a rate of 3 Hz or more could kindle the motor cortex to induce epileptic foci. Initially expressed concern of the theoretical risk of kindling, however, seems very remote with the single or repetitive stimuli now in use.[349] Although many thousands of patients have undergone cortical stimulation, only isolated reports of focal seizures during or after the procedure have appeared, often in patients under treatment with drugs that potentially lower the seizure threshold.[61,112] No published or empirical evidence suggests more than minimal risk of TMS applied to children.[128] Low-frequency rTMS of the posterior fossa, however, induced reproducible symptoms of nausea, which lasted for about 10 minutes after the end of the procedure in 2 of 8 healthy subjects.[344] In the monkey, based on positron emission tomography, rTMS induced a long-term effect on motor-related regions and distant limbic-related area.[143]

Magnetic stimulation capable of painless excitation of the motor system has an obvious advantage over electrical stimulation. One must, however, bear in mind the possibility of adverse effects with the clinical use of any newer applications of TMS techniques. For now, we exclude patients with epilepsy, those with a cardiac pacemaker, and those with a history of brain surgery. A published guideline describes the use and safety of an rTMS[244,327,328] and a standard safety questionnaire to screen individual subjects for risk of adverse events.[187]

Normal Values

Table 20-1 shows normative data for conduction to abductor digiti minimi using magnetic cortical stimulation with a facilitatory background contraction and electrical stimulation of the cervical roots.[283] The normal central motor conduction time to the voluntarily contracted tibialis anterior averages 12.5 ms after magnetic stimulation of the motor cortex.[62] Values for proximal lower-limb muscles (mean ± SD) reported in one study performed in 100 healthy subjects consisted of mean MEP latency (20.6 ± 1.99 ms), CCT (10.1 ± 1.29 ms), and MEP/M amplitude ratio (60.0 ± 15.75%).[6]

Factors important in determining normative data for central motor conduction studies include the location of the target muscle, coil position, coil size, direction of current flow, and stimulus intensity in relation to the threshold. The choice of electrical or magnetic stimulation makes relatively little difference. Total conduction time shortens with a voluntary contraction. Surface

Table 20-1 Normative Data (n = 36 SIDES)

MEASUREMENT	MEAN	SD	RANGE	MEAN + 2.5 SD
Conduction time C7/Tl to ADM (ms)	13.60	1.35	10.9–16.9	16.3
Conduction time C7/Tl to wrist (ms)	11.18	1.19	8.7–13.8	13.56
Conduction time scalp to ADM (ms)	19.73	1.25	17.5–23.1	22.23
Central conduction time (ms)	6.13	0.89	4.5–7.7	8.35
R/L difference in onset latency (ms) (n = 12)	0.69	0.58	0–1.8	2.14
Amplitude as % of amplitude from wrist	—	—	18.6–96.6	—

ADM, abductor digiti minimi; R/L, right/left. (From Mills,[260] with permission).

stimulation of the motor roots yields a shorter peripheral conduction time than an estimation using F waves. The formula used to calculate conduction velocity holds only if cortical and spinal stimulation activates the same group of motor fibers. If cervical but not cortical stimulation activates the large fast-conducting spinal motoneurons, this discrepancy will erroneously increase the calculated value of CCT. In one study of 40 normal subjects, the body height showed a linear correlation to cortical and spinal latencies by electrical stimulation, but not to CCT, obtained as the difference between the two.[413]

In normal subjects maintaining a small voluntary contraction, magnetic stimulation, with intensity 20% above threshold for relaxed muscles, evokes an MEP of at least 18% of the maximal response elicited by electrical stimulation of the nerve (Fig. 20-2). Therefore, any response reduced to a level below 15% of the maximum CMAP suggests conduction block along the central or peripheral pathways (see Chapter 20-5).[260] In one study,[249] latency comparison between cortical and spinal stimulation yielded a conduction velocity of 48 m/s from cortex to cervical spinal cord and 47 m/s from cortex to lumbosacral enlargement. The cortex-to-hand latency of 22.5 ms obtained by this method slightly exceeded that of 18–21 ms after stimulation of the exposed human cortex during neurosurgical procedures.[270] Combined studies of M response, patellar T reflex, and MEP may facilitate clinical evaluation of corticospinal and peripheral conductions to proximal lower-limb muscles.[6,405]

Prolonged central motor conduction usually implies demyelination or transmission via small myelinated fibers or by some other oligosynaptic pathways after degeneration of fast-conducting corticospinal fibers. Any reduction in the descending volley through loss of fibers or conduction block will diminish temporal and spatial summation at the alpha motoneurons, or the final common path, delaying their excitation. In general, the CCT shows a correlation to voluntary phasic force and twitch force, most likely reflecting the degree of conduction block and temporal dispersion rather than the delay in conduction per se.[424] Normal MEP studies of apparently weak muscle support, but do not necessarily confirm, the suspicion of a functional basis for symptoms. In contrast, an absent or delayed response rules out an entirely functional weakness, if suspected on clinical grounds.

Multiple Sclerosis

In early studies, electrical stimulation of the brain and the spinal cord revealed markedly prolonged CCT in patients with multiple sclerosis.[264,330] Later reports confirmed these findings with magnetic stimulation, showing a much lower incidence of absent responses compared to electrical stimulation.[23,35] Paired TMS may reveal a substantial delay of the conditioned response and no increase in MEP size normally seen at short interstimulus intervals, suggesting defective generation of I wave.[152] The upper-limb MEP equals the visual evoked potential (VEP) and surpasses the

upper-limb SEP and brainstem auditory evoked potential (BAEP) in detecting conduction abnormalities of multiple sclerosis, but MEP studies uncover subclinical lesions less often than VEP or SEP studies. A paraspinal MEP after TMS also detects absent or delayed responses in patients with multiple sclerosis.[140]

A number of other motor system diseases, such as Balo's concentric sclerosis,[230] and radiation myelopathy[371] show similar conduction abnormalities along the central motor system. Therefore, these findings by no means offer a specific diagnosis, although other conditions rarely cause an extreme CCT prolongation characteristic of demyelination.[260] Other abnormalities seen in patients with multiple sclerosis include postexercise facilitation and depression of MEP, suggesting an intracortical motor dysfunction.[293,306]

Clinical signs showing a good correlation with conduction abnormalities include weakness of the target muscle, pyramidal signs in the limb, brisk finger flexor reflexes,[149] and Babinski sign.[169] One study showed a delay of responses recorded in small hand muscles on one or both sides in 72% of 83 patients.[149] Most patients with a prolonged conduction time also showed reduced amplitude and variability of the recorded response (Figs. 20-12 and 20-13). Brain stimulation commonly fails to evoke muscle action potentials in the lower limb but rarely in the upper limb. The onset latency variability may occasionally constitute the only abnormality.[36] Studies reveal subclinical deficits in 20%–24% of neurologically normal limbs.[99] Serial MEP studies may uncover changes in CCT consistent with clinical remission and relapse[179] or with therapeutic effect of corticosteroid administration.[340] This technique, therefore, serves usefully in quantificating motor disability when monitoring the course of the disease. One study[178] showed a good correlation between MEP and MRI and clinical measures.

Motoneuron Disease

Patients with MND have a high incidence of abnormality,[100,350] which typically shows a small amplitude and a slight delay in latency. Some patients have subclinical deficits,[158] whereas others show normal findings despite clinical evidence of central motor involvement.[350] In general, CCT abnormalities do not appear to correlate with physical signs.[269] In one study,[100] almost all of the 40 patients had abnormalities in at least one recording from three upper-limb muscles, and 75% showed deficits in small hand muscles. Patients with prominent pseudobulbar features usually had no recordable response despite the normal bulk and strength of the target muscle. In one study,[84] TMS detected the involvement of multiple cranial muscles, showing abnormalities of central motor circuits, cortical excitability threshold, intracortical inhibition, and CSP. In another study of seven primary lateral sclerosis (PLS) patients,[40] four had no response in either upper- or lower-limb muscles, whereas three had a grossly prolonged CCT.

In one series of 121 patients with motoneuron disease,[402] TMS showed progressive inexcitability of central motor pathway and loss of the physiologic CSP. In contrast, patients with pure motor neuropathy tend to have normal CSP and amplitude ratio.[11] In early stages, patients with sporadic ALS have a reduced TMS threshold of the motor cortex,[267,446] a shorter CSP [309] and reduced intracortical inhibition,[445,454] all possibly reflecting cortical hyperexcitability. A study using a peristimulus time histogram showed dysfunction of the corticomotoneuronal projection system.[13,204,434] In a subgroup of familial ALS with superoxide dismutase 1 (SOD1) mutation, TMS studies revealed an abnormality of intracortical or intraspinal inhibition.[300] In one series of 30 patients with solely lower motoneuron signs, 63% had upper motoneuron abnormalities detected by TMS, 63% by MR spectroscopy, and 46% by both techniques.[186]

Compared to conventional TMS, TST and CSP testing may prove more useful in the diagnosis of subclinical upper motoneuron involvement in ALS.[14,206] In one study of cortical excitability, ALS patients showed significantly reduced SICI, increased intracortical facilitation, and reduced duration of CSP.[428] Other studies of interest include mapping of cortical muscle representation in ALS[77] and transcranial direct-current stimulation, which induces

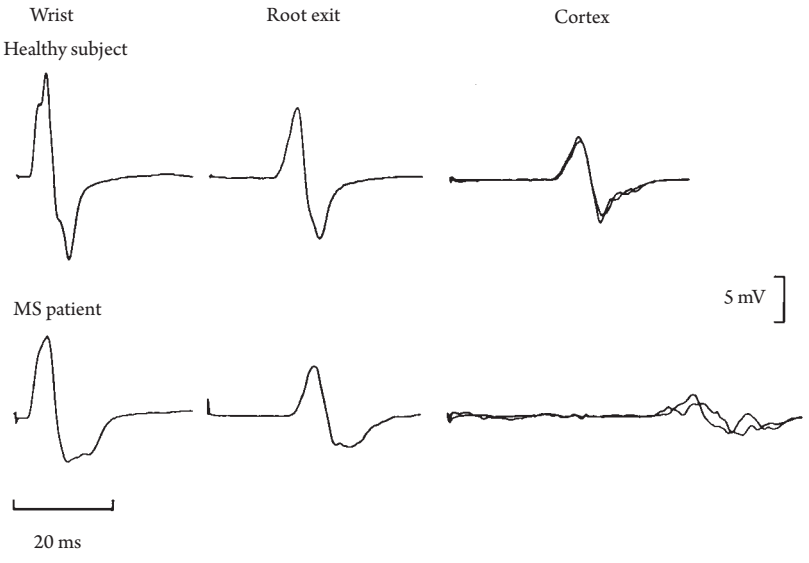

FIGURE 20-12 Recordings from the right abductor digiti minimi muscle. After supramaximal stimulation of the ulnar nerve at the wrist (left traces), the C7-T1 roots by a high-voltage electric stimulator placed over the cervical spine (middle trace) and the motor cortex with a circular magnetic coil centered at the vertex. The normal subject (top) had a central motor conduction time of 5.8 ms and the CMAP amplitude of about 50% compared to the ulnar nerve stimulation. The patient with multiple sclerosis (bottom) had a small, temporally dispersed response with a delayed conduction time of 35 ms. (From Mills,[262] with permission.)

changes in intracortical excitability in normals but not in patients with ALS. [310]

Epilepsy

A high-frequency stimulation of the brain carries the theoretical risk of kindling an epileptic focus, although, based on animal studies, this poses little or no concern with a commonly employed train of stimuli at low rates. Magnetic stimulation has occasionally induced focal seizures in patients with ischemic lesions of the cortex and in those with multiple sclerosis.[154,180] A study of patients with partial or generalized epilepsy found no change in seizure pattern or in the EEG following TMS.[387] Rapid train of magnetic stimulation to the cortex could induce a motor seizure, although it may[157] or may not[85] specifically activate the preexisting epileptic focus. Anticonvulsant medication probably raises cortical threshold.[252] One report describes a prolonged CSP in untreated patients with idiopathic generalized epilepsy.[236]

In a patient with focal epilepsy and myoclonus, stimulation on the affected side induced a shorter CSP and reduced corticocortical inhibition, indicating asymmetry in cortical excitability.[168] An increased CSP duration observed in patients with partial epilepsy involving the primary motor cortex may reflect compensatory mechanisms.[58] In patients with myoclonic epilepsy, but not in healthy subjects, TMS at the foramen magnum elicited long loop reflex (see Chapter 9–5) via the ascending tracts in addition to direct response via the descending tracts.[419] Of the two, the long loop reflex required less stimulus intensity to activate probably because the large-diameter muscle afferents carry the ascending volley.

Stroke

Several studies have found abnormalities of central motor conduction in patients with cerebrovascular diseases.[24,154,179] The paretic muscle often shows no response to brain stimulation or increased threshold intensities.[1] Motor responses may predict functional outcome better than clinical assessment,[400,403] especially when combined

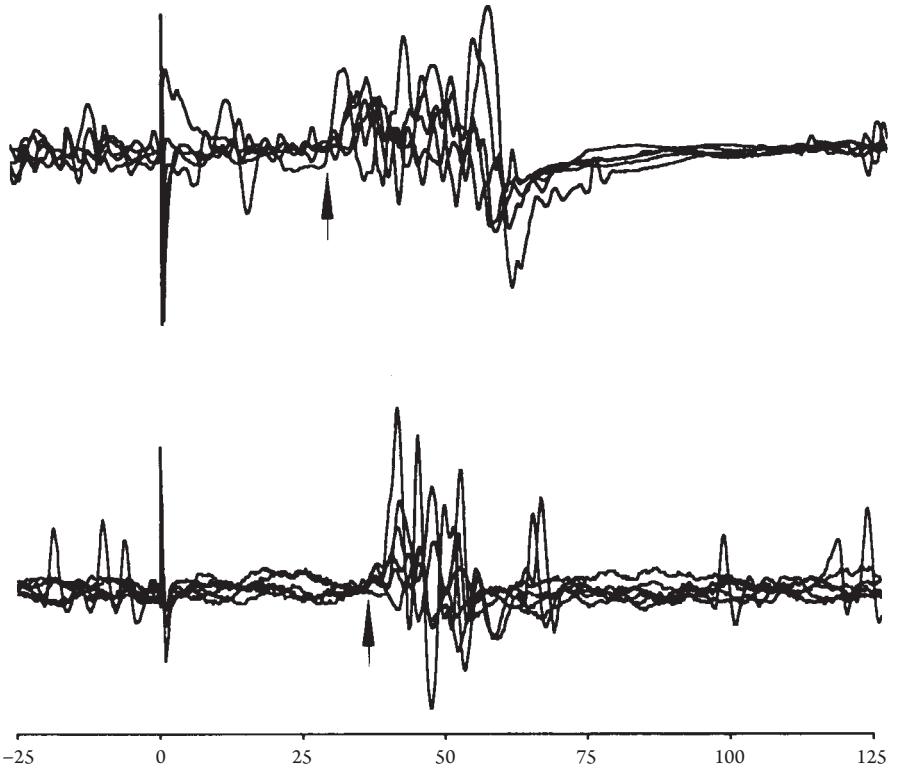

FIGURE 20-13 Abnormalities of motor evoked potentials in two patients with clinically definite multiple sclerosis. The upper traces show a cortex-to-muscle latency of 28 ms with a calculated central motor conduction time of 14.2 ms, and the lower traces, a total latency of 38 ms with central conduction time of 22.7 ms. Superimposed traces in each example illustrate the marked variability and pathologic dispersion of the wave form. (From Mills,[262] with permission.)

with SEP studies.[235] After pure motor stroke, MEP changes may persist despite complete clinical recovery.[305] The presence of an ipsilateral MEP elicited by TMS applied to the unaffected cortex in acute stroke patients suggests facilitation of the usually latent ipsilateral corticospinal tract.[46,274] In one study,[188] five daily sessions of rTMS delivered at 1 or 3 Hz over the unaffected hemisphere enhanced recovery of acute stroke patients at the 3-month time point. In another study,[102] rTMS at 1 Hz and 5 Hz produced sustained improvement in motor function and disability after ischemic stroke. Other aspects of MEP studies reported in stroke include CSP changes,[48] cortical excitability by paired TMS,[71] effects of subcortical lesions,[392] motor output reorganization,[57,81,118] motor disinhibition in the unaffected hemisphere,[223] rTMS in childhood stroke [198] and the effects of PAS on knee extensor motor excitability of poststroke patients.[317]

Movement Disorders

In Parkinson's disease, magnetic stimulation may show an abnormally large MEP [99,181] with normal CCT.[23] Patients with parkin gene (*PARK2*), however, tend to show a prolonged CCT.[307] In one study,[44] patients with asymmetric disease had a lower threshold to cortical stimulation for the hemisphere contralateral to the side of rigidity than the uninvolved side or normal controls. Paired-shock study revealed L-dopa-responsive impairment of cortical excitability to TMS delivered after the end of CSP.[25] In Parkinson's disease, dopaminergic drugs restore facilitatory premotor-motor interactions as tested by MEP after premotor rTMS.[273]

Some, but not all, patients with progressive supranuclear palsy had abnormalities of CCT, suggesting functional damage to the corticospinal tracts.[2] In healthy subjects, a single dose of dopaminergic drugs enhanced inhibition, whereas antidopaminergic counterparts reduced it as tested by TMS.[453] Thus, these two agents seem to serve as inverse modulators of motor cortex excitability. In patients with movement disorders, repeated TMS can result in long-term plastic changes in the motor system, which has led to increased interest in its possible therapeutic applications.[97] In patients with dystonia, deep brain stimulation with electrodes implanted in the globus pallidus internus influences motor cortex excitability by a rapid modulation of the thalamocortical outputs.[213] In patients with deep brain stimulators, hand motor responses ipsilateral to TMS may result from a subcortical activation of corticospinal fibers via the implanted electrode in the other hemisphere.[214]

Huntington's chorea or dystonia shows no MEP abnormalities [98,115] except for a prolonged CSP.[276] Patients with Wilson's disease may[259] or may not[56] have prolonged CCT. The shortening of CCT seen in patients with Rett syndrome implies unique cortical hyperexcitability corresponding to the characteristic overactivity of motor function.[292] In some patients with congenital mirror movement, a reversed relationship between the direction of current flow for stimulation and hemispheric activation suggests ipsilateral projections,[36] although in others, unilateral stimulation elicits bilateral small hand muscle responses.[425] In one study,[210] rTMS modulated blepharospasm. Patients with essential tremor have normal cortical motor area excitability.[322] In myoclonus, the lack of late inhibition usually induced by interhemispheric interaction suggests deficiency of inhibitory interneurons.[138]

Ataxia

Patients with a cerebellar or cerebellothalamocortical lesion have an abnormal reduction in the physiologic suppression of cortically elicited MEP by preceding TMS applied over the cerebellum.[251,412] In contrast, this suppression remains normal in those with MFS or with lesions in the afferent pathway to the cerebellum.[418] Studies also provide useful information in the differentiation of spinocerebellar atrophy (SCA) subtypes. In one study,[348] CCT exceeded 10 ms in all cases of SCA I compared with an upper limit of normal at 8.5 ms. In contrast, SCA III patients often had a normal value. Another study[444] also showed an increased MEP threshold and prolonged CCT in SCA I but not in SCA II or III, indicating the value of this technique in differential diagnosis of ataxia. Other studies revealed dispersed low-amplitude upper-limb responses with a delayed latency in most patients with Friedreich's ataxia and to a lesser extent in those with other ataxic disorders.[63,70] Application of TMS can partially normalize the prolonged reaction time and abnormal excitability rise in cerebellar patients[222] and may alleviate truncal ataxia in some cases of SCA.[365]

Myelopathies

A few studies elucidated a slowing or block of corticospinal conduction in radiation myelopathy[371] or cervical cord trauma.[394] Patients with hereditary spastic paraplegia had absent or very small responses in the lower limb with only minor prolongation in latency, and normal responses in the upper limb despite clear clinical signs of spasticity.[65] These findings suggest length-dependent degeneration of the corticospinal tracts. Several studies documented prolonged CCT in cervical spondylotic myelopathy [49,242,388] and after spinal cord injury.[75]

Mild cases of cervical spondylotic myelopathy[384] without pyramidal signs may have abnormal MEP despite normal SEP.[369] In patients with corticospinal tract lesion above C5, prolonged trapezius MEP latencies provided functional correlates to the radiological and clinical findings.[50] In one study of transcranial electric stimulation,[288] conduction block and attenuation of spinal cord evoked potential recorded intraoperatively at C6–7 resulted in prolongation of CCT. This finding supports the view that CCT prolongation in this disorder usually implies a corticospinal conduction block rather than a delay.[185] Impaired temporal summation of multiple descending potentials may produce a delay of TMS-induced

motoneuron firing, which contributes to the mechanism of CCT prolongation.[185] In compressive cervical myelopathy, neck extension may prolong the CCT by increasing MEP latency.[144]

Other disorders showing CCT abnormalities include Behcet's disease,[377] adrenoleukomyeloneuropathy,[151] cerebrotendinous xanthomatosis, HTLV-1-associated myelopathy, tabes dorsalis,[414] and Pelizaeus-Merzbacher disease.[291] Patients with cauda equina and lumbosacral cord lesions[94] may show a prolonged CCT and an additional slowing of the peripheral motor pathway, indicating a myelopathy associated with radiculopathy.

Neuropathies and Radiculopathies

In patients with Charcot-Marie-Tooth disease Types I and II (CMT I and II), MEP studies in the upper limb show a normal CCT if corrected for slowing of the proximal motor roots. Abnormalities of CCT abound, however, in patients with CMT V characterized by pyramidal features such as extensor plantar responses.[65] Some cases of acute or chronic demyelinating polyneuropathies may have similar abnormalities unilaterally or bilaterally.[382] Although MEP changes seen in these disorders mostly reflect abnormalities in the proximal motor nerve,[164,165] reversible increase of CCT seen in some patients with MFS suggests corticospinal tract abnormality.[228] Patients with multifocal motor neuropathy (MMN) have a normal CCT.[277] In one study,[4] high-voltage electrical stimulation of the cauda equina revealed proximal lesions in multifocal motor neuropathy better than F-wave studies or magnetic stimulation.

Some investigators advocate the use of magnetic stimulation in the diagnosis of lumbosacral radiculopathy[28,105,226] and lumbosacral spinal stenosis.[137] The technique, however, suffers from inherent limitation of not clearly localizing the site of stimulation. Paravertebral magnetic stimulation at proximal and distal cauda equina while recording from muscles of the foot, shin, and thigh may help subdivide the demyelinating neuropathy spectrum.[233] Application of TMS to the cauda equina at the L1 spine elicits an MEP in the external anal sphincter.[380] In one study, pudendal nerve latency (mean ± SD) showed a significant increase in patients with idiopathic neurogenic fecal incontinence (7.3 ± 0.7 ms) compared to normal subjects (5.6 ± 0.6 ms). The proximal conduction between the L1 and L4 vertebral levels, however, showed no difference between the two groups.[17,380] Clinical application of MEP as a diagnostic procedure for these disorders, however, waits further clarification.

Other Disorders

This technique has found its way to test many other entities, although its value as a clinical tool still remains uncertain. These include Alzheimer's disease,[87] brachial plexus injury,[68] cervical spondylotic myelopathy,[406] chronic pain,[225] cortical tremor,[155] Cretuzfeldt-Jakob disease,[438] fatiguing muscle exercise,[352] head trauma,[55] hereditary spastic paraparesis,[289] Huntington's disease,[229] leg cycling after spinal cord injury,[381] migraine,[281] myopathy,[224] pain perception,[191,383] plasticity and sleep,[66] spastic paraplegia,[171] spinal cord injury,[370] and tinnitus.[248,426]

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21

Intraoperative Monitoring

Abbreviations: CMAP—compound muscle action potential, EMG—electromyography, MEP—motor evoked potential, NCS—nerve conduction studies, SEP—somatosensory evoked potential, TES—transcranial electrical stimulation

1. INTRODUCTION

The same basic principles apply to monitor peripheral nerve function during surgery as routine studies conducted in the electrophysiology laboratory. Intraoperative examination serves a variety of purposes: to characterize the nerve injury, to elucidate the mechanism and severity of the lesion, and to determine prognosis for recovery. Such evaluation can also warn the surgeons if a tissue considered for dissection contains neural elements and guide them to take an appropriate course of action.[84]

Sources of artifact abound in a surgical environment, complicating electrophysiologic recording. In particular, 50 or 60 Hz noise may arise from operating lights, medication delivery systems, blanket warmers, microscope, and video equipment. Other operational concerns include high-electrode impedance, interference from cautery devices, and movement artifacts in the operating suite. Inadvertent use of neuromuscular blocking agent reduces or eliminates compound muscle action potentials (CMAPs). Ischemia may also obliterate responses from nerve and muscle. Logistic barriers to avoid contamination of the sterile surgical field may preclude useful recording from the particular nerve of interest.

Despite these limitations, intraoperative monitoring, conducted by experienced technologists under direct supervision of a trained clinical electrophysiologist, offers much needed information to improve surgical outcome.[1,93,94] Although visually monitoring a muscle twitch during surgery can confirm the integrity of motor system, recording a CMAP provides surgeons with a more accurate, quantitative assessment.

Electrodiagnostic techniques available for this purpose comprise nerve stimulation technique and electromyography (EMG) to monitor peripheral nerve function. The same electrophysiologic principles apply to any intraoperative monitoring as it pertains to different surgical exploration for peripheral and central nervous system.

Common procedures requiring such intraoperative monitoring include release of tethered spinal cord, pedicle screw placement, and selective dorsal rhizotomy. In addition, spinal cord surgery utilizes far-field somatosensory evoked potential (SEP), segmental recording of spinal conduction, and motor evoked poential (MEP).

2. GENERAL PRINCIPLES

The procedure follows simple principles, although the special environment of operative suites gives rise to many technical challenges. Thus, it takes a dedicated and skilled team of clinical neurophysiologists and technologists to acquire and interpret electrophysiologic data rapidly and accurately. A good working relationship with the surgeons and anesthesiologists helps to maximize the efficacy and utility of the study. Preoperative study often elucidates the location, degree, and type of involvement of the nerve lesion, which would dictate the surgical approach. Monitoring the integrity of the roots, plexus, and nerves assists the surgeon in the overall approach to the operative intervention.[15]

Technical problems in intraoperative monitoring include low body temperature, which causes slowing of conduction velocities, and low systemic blood pressure, which reduces SEP and MEP amplitudes. In addition, electrical noise originates from surgical instruments, beds, machine, fluorescent lights, electrical motors, and cautery devise.

Effect of Anesthetic Agents

Anesthesia with inhalational agents such as nitrous oxide, halothane, enflurane, and isoflurane suppresses the descending impulse via the spinal interneurons and motoneurons.[140] Isoflurane, halothane, and narcotics, however, interfere with the procedure minimally even with bolus doses, which achieves high anesthetic effects. Isoflurane serves better for this purpose than halothane, requiring lower concentrations during stimulation. A generally preferred anesthetic regimen for SEP monitoring comprises intravenous narcotic and propofol combined with a medium acting neuromuscular blocking, followed by low-level halogenated agent. Inhalation agents reduce cortical excitability, thus suppressing scalp-recorded SEP more than cervical or nasopharyngeal potentials.

Neuromuscular blocking agents, though desirable for studying nerve action potentials and SEPs, precludes recording muscle contraction in response to electrical stimulation of neural tissues. Thus, inhalation anesthesia or intermediate-acting nondepolarizing muscle relaxants used for intubation must wear off before initiating EMG monitoring. Partial neuromuscular blocking up to 75%, however, does not necessarily abolish neurotonic discharges.[48]

Stimulation Technique

The equipment used for regular nerve conduction studies (NCSs) suffices for both sensory and motor fibers, with application of a bipolar or monopolar stimulator directly to the surgically exposed neural elements. Hook electrodes may help to lift and separate the nerve from the surrounding wet tissue. Bipolar stimulation, with the cathode and anode separated by 10–20 mm along the nerve, produces a localized flow of current without much spread to adjacent nerves.[125] Shock intensities necessary to activate a healthy nerve range from 0.2 to 2.0 mA for a pulse of 0.05 ms in duration. Injured nerves with fibrosis may need a much higher level of stimulation up to 20 to 25 mA.[88] Averaging several responses helps elucidate small nerve action potentials. In the absence of an expected response or a twitch from the muscle, recording from a normal nerve or muscle located nearby would help establish the integrity of the amplifier and the connecting cables.

Stimulus artifact related to the usual intraoperative environment poses a major technical difficulty in recording nerve action potentials. A number of precautions help minimize this problem, which may interfere with proper recordings.

These include using an adequate stimulus lowest in intensity and shortest in duration, increasing the distance between the stimulation and recording sites, lifting electrodes out of a wet surgical field, and, if possible, orientating the line connecting the cathode and anode to dissect the line connecting E1 and E2 perpendicularly, which would equalize the surface spread of current to the two electrodes.

Mixed Nerve Action Potential

We use the same amplifier setting for intraoperative recording as the routine nerve conduction studies, 5 to 10 Hz for low-frequency (high-pass) filter and 5 to 10 KHz for high-frequency (low-pass) filter, and a gain of 20 to 50 μV per division. Sweep speed depends on the nerve length under study, with the usual setting of 0.5 to 1.0 ms per division. To record mixed nerve action potentials directly from a nerve, the surgeon may place sterile recording electrodes within the operative field away from the stimulating electrodes. Shock artifacts predominate for interelectrode distances of less than 5 cm. Successful monitoring, therefore, calls for adequate surgical exposure to assure a sufficient distance between stimulation and recording sites.[45,125] The amplitude, as a measure of axon density, normally exceeds 1–2 mV, but it may not reach 20 μV in regenerating nerve fibers, depending on their maturity.

In studying nerve action potentials, placing an active electrode (E1) at least 4 cm from the cathode minimizes the stimulus artifacts. With the reference electrode (E2) located 1 to 2 cm further away from the cathode, the recorded response has an initially positive triphasic waveform. With a longer separation of the two recording electrodes, the traveling waves pass completely under E1 before passing under E2, making the response larger, although extraneous noise, including stimulus artifacts, also increases. Lifting the recording segment of the nerve out of excessive fluid in the surgical field avoids the shunting effect. The same set of electrodes work for stimulation or recording by switching the connection between the amplifier and the stimulator, although pointed electrodes tend to serve better for stimulation and curved hook electrodes, for recording. A flat medal plate placed under the patient serves as the ground electrode, separate from the ground used for cautery.

Compound Muscle Action Potential

Intraoperative recording of a CMAP helps distinguish neural from nonneural structures and identify nerve or nerve roots supplying a particular muscle. The equipment, though requiring a less amplification, has, otherwise, the same settings as those used for monitoring nerve action potentials. The procedure consists of stimulating a nerve or root in the surgical field and recording a distant muscle response with a pair of surface electrodes or monopolar needle or wire placed subcutaneously or intramuscularly. Recording a CMAP using surface electrodes, as in routine nerve conduction studies, assesses the total number of functional motor axons. In contrast, subcutaneous or intramuscular needle or wire electrodes register only from a fraction of the stimulated axons but have the advantage of clearly identifying the muscle supplied by the neural tissue in question.

Typical applications include lumbar spine surgeries, tumor resection of the cauda equina or conus medullaris, and tethered cord release. A multichannel system allows simultaneous recording from several key lower-limb muscles and anal sphincter. A reproducible response in any of the channels implies the presence of functional neural components in the stimulated tissue. Conversely, failure to evoke detectable potentials in any of the channels with a high level of stimulation documents the absence of neural elements, giving a rationale for its surgical resection. In general, use of stimulus intensity greater than 4.0 mA reduces the risk of misidentifying neural elements for nonneural tissue.

Intraoperative monitoring also uses muscle action potentials to evaluate clinically incomplete peripheral nerve injury. Short segmental stimulation every 1 cm can localize the exact site of a focal lesion by abrupt shift in waveform, amplitude, latency, or stimulation threshold (see Chapter 11-7). The criteria for abnormality include latency changes at least twice that of adjacent segments, although a sudden waveform change usually provides a more sensitive measure.

Chronic nerve injury may elevate the threshold of stimulation to a level much higher than expected.

Electromyography

A pair of intramuscular needles or wire electrodes placed prior to the procedure permits continuous monitoring of EMG to warn the surgeon of potential harm to neural elements in the operative field.[48] Recording settings typically comprises band pass of 10 Hz to 10 KHz, sensitivity of 200–500 μV per division, and sweep speed of 20–200 ms per division. For localization of the source, each channel should ideally represent a separate source with both recording electrodes placed in the target muscle. Placing them into two nearby muscles, like E1 in the medial gastrocnemius and E2 in the tibialis anterior, however, would help limit the number of required channels while achieving the need to identify irritated axons, the tibial and peroneal nerves, for example.

Like nerve stimulation technique, EMG also gives rise to relatively stable signals even during general anesthesia. Various types of spontaneous discharges include endplate activity, fibrillation potentials, positive sharp waves, and fasciculation potentials, all of which continue even after infusion of a short-acting neuromuscular blocking agent adjusted to produce at least 25% of the baseline CMAP.[10,70] As the rule, an MUP, recorded with incomplete relaxation, discharges semiregularly or as continuous bursts if many different units fire simultaneously. Artifacts associated with electrode movement or produced by surgical instruments, unlike physiologic potentials, typically produce irregular triangular waves often accompanied by a popping sound. In addition to video display of waveforms, monitoring the auditory patterns through a loudspeaker helps identify various discharges by their characteristic sounds.

This type of monitoring in free running mode also helps identify abnormal activity such as neurotonia, indicating irritation to the axons.[39,65] Mechanical stimulation of peripheral nerve membrane triggers such discharges as a warning of pending nerve injury. They consist of a high-frequency burst of 1–10 MUP trains, firing at frequencies of 50 to 200 Hz. Each train usually lasts several milliseconds, though it may sustain up to 1 minute, probably depending on the degree of irritation. The trains of activity, although frequently described as "neurotonic," usually fire at a somewhat slower range than classically defined neurotonia or neuromyotonia. Nonetheless, these discharges, unlike semirhythmic 10–30 Hz motor unit activity seen with a lightened level of anesthesia, fire rapidly and irregularly, producing a characteristic sound similar to neuromyotonia induced by hyperexcitable axons. Their appearance as multiple repetitive bursts usually signals mechanical manipulations of the nerve by touching or rubbing, or with tractions.[42]

Neurotonic discharges may provide immediate information on surgical maneuver destined to cause nerve injury, alerting the surgeon of potential harm to the nerve under scrutiny. Despite its utility as a sensitive indicator of nerve irritation, neurotonic discharges do not necessarily imply nerve damage and their absence does not always exclude a nerve injury.[33] Spontaneous EMG activities registered from the 76 facial muscles during microvascular decompression for trigeminal neuralgia, for example, did not always lead to a postoperative facial palsy.[101] Also, neurotonic discharges usually do not occur with sharp transection of a nerve as compared to mechanical manipulation, appearing more commonly with healthy nerves as compared to damaged nerves.[89]

3. PERIPHERAL NERVOUS SYSTEM

Cranial Nerves

The electrophysiologic monitoring can assess functional integrity of the cranial nerves and prevent injury to the neural elements from intraoperative trauma or ischemia. The electrodiagnostic techniques used for this purpose include nerve stimulation, EMG, and various evoked potentials. Circuitous course, delicate epineurium, and small size make the cranial nerves more susceptible to injury than the limb nerves.[43] The pathologic conditions such as tumors, which necessitate the surgery, may displace the target nerve, increasing the risk of intraoperative damage.

During the procedure, mechanical, electrical, or metabolic stimuli can activate motor and sensory potentials, providing immediate feedback for the functional status of the specific cranial nerves. Thus, intraoperative EMG monitoring comprises continuous recording of muscle activity, primarily looking for neurotonic discharges or intermittent or continuous MUP bursts.[108] These findings guide the surgeon to alter the procedure, if feasible, to prevent further compromise. It also helps predict the nature and severity of postoperative deficits and prognosis for recovery. Monitoring facial nerve function during posterior fossa surgery, for example, reduces the incidence and severity of postoperative facial nerve palsies. In one study,[56] however, spinal accessory nerve monitoring in posterior fossa surgery did not serve the purpose as well as expected because of commonly detected false-positive neurotonic discharges. Besides, the need for a high-stimulation intensity up to 3 mA to excite the nerve did not necessarily predict a bad outcome, as anticipated. The use of intraoperative monitoring of recurrent laryngeal nerve may[18] or may not[16] decrease vocal cord paralysis as a complication of thyroid surgery.

Electrical stimulation of the nerve in the surgical field allows recording a CMAP from one or more muscles as a measure of functional loss occurring to the motor axons during surgery.[35,112] Stimulus intensity required for cranial nerve activation ranges from 1 to 5 mA with pulse duration of 0.05 to 0.1 ms. Damaged, distant, or insulated nerve usually requires a higher intensity, which increases the risk of unintended excitation of adjacent tissue by current spread. Hand-held sterile stimulators used intraoperatively come in various sizes. Because of their location, small electrodes are better suited for stimulating the cranial nerves. Exposing only 1 to 3 mm of the electrode tip minimizes current shunting for selective stimulation of the target nerve. Bipolar stimulators with cathode and anode separated by 1 to 20 mm along the nerve tend to produce a localized flow of current without spread to adjacent nerves. Monopolar stimulators with the cathode on the nerve and the anode placed several centimeters away carry the risk of current spread to other nerves.

The size of a surface-recorded CMAP or nerve action potential elicited by supramaximum stimulation relates linearly to the number of functional motor or sensory axons. Thus, stimulating the cranial nerve proximal to the site of surgical dissection at regular intervals allows the surgeon to assess the degree of functional loss resulting from the operative procedure.[35] Even though this immediate change cannot distinguish between the conduction block and transection of the axons, a proximally elicited response, if full, gives assurance that surgical manipulation caused no nerve damage. A partial loss of response warns the surgeons to alter operative approach for preservation of the remaining function. Absent or markedly reduced response predicts the severity of immediate cranial nerve deficit and a poor long-term prognosis.

In contrast to EMG and nerve stimulation technique, visual[54,135] and trigeminal nerve evoked potentials[41,87] have inherent susceptibility to anesthetics. In addition, the lack of clear criteria for abnormalities makes these procedures less effective as a monitoring tool.[43]

Limb Nerves, Plexus, and Roots

Intraoperative monitoring helps identify the peripheral nerve in question, localize the lesion along the course of the nerve, determine the degree of functional continuity, assess the possibility of root avulsion, specify the optimal site for nerve biopsy, and prevent unintended intraoperative damage.[11,19,44,114,116] The same principles apply to any type of surgery, but commonly reported procedures include decompression of the ulnar[58] and common peroneal nerves from entrapment[59] and dissection of nonneural or neural sheath tumors of the peripheral nerve.[59,60,61]

The monitoring procedure comprises direct stimulation of the surgically exposed nerve and recording of a nerve action potential or a CMAP peripherally and spinocortical potentials centrally. A bipolar stimulator, held in place by the surgeon with the cathode closer to the recording sites, allows selective activation of the intended segment. The intraelectrode distance ranges from 3 to 10 mm, depending on the size of the nerve under consideration. A less preferred monopolar stimulation utilizes the cathode placed on the nerve and the anode elsewhere, which tends to

increase the current spread to unintended nerves in the vicinity. Tripolar stimulation consists of a single cathode flanked by two anodes, which further focuses the site of activation and minimizes the stimulus artifact.[125] Most surgeons prefer special stimulating electrodes with very small pointed tips or hooks, which help elevate the nerve out of the surgical field to avoid contact with excessive fluid. Stimulating electrodes made of a silver solder alloy withstand gas sterilization and autoclaving for use in subsequent surgical procedures.

The nerve length between stimulating and recording sites dictates the latency, which averages 0.2 ms per 1 cm, assuming a conduction velocity of 50 m/s. The inching technique consists of stimulating the nerve in short increments and recording the action potential across the involved segment (see Chapter 11-7). A nonlinear shift in either latency or waveform documents the site of the lesion.[11] The presence of only a few large myelinated axons can produce a response with a relatively normal conduction velocity when assessing for continuity. Amplitude of the recorded nerve action potential serves as a better measure of the number of surviving axons across a lesion. The presence of a nerve action potential recordable across the site of the lesion usually proves the existence of over 4000 functioning, medium-sized myelinated axons.[63]

Intraoperative monitoring of nerve action potentials plays an important role in early assessment of the injuries and the type of surgical intervention to promote recovery. Even if nerve injury spares the epineurium, a neuroma may still develop with intraneural fibrosis and misdirected fibers. It takes weeks to months to identify EMG evidence of reinnervation, depending on the length of the axons, which usually regenerate toward the muscle at a rate of 1 mm/day. In contrast, recording nerve action potentials across the neuroma can identify nerve fibers long time before they reach the intended target. The presence of regenerating axons calls for neurolysis, whereas the absence of functioning axons signals the need for a repair with grafting. Intraoperative recording of nerve action potentials also helps monitor resection of a peripheral nerve tumor or dorsal nerve roots responsible for radicular pain syndrome, such as postherpetic neuralgia.

The presence of an SEP recorded over the scalp or cervical spine indicates the continuity of dorsal roots in cases of suspected avulsion.[46,96] Similarly, the presence of an MEP indicates continuity of the ventral roots, whereas its absence implies root avulsion assuming the integrity of the peripheral nerve.[128] The loss of the ventral root as a grafting vehicle will necessitate transposition procedures exploiting other territories.[110]

Tethered Cord

The tethered cord syndrome results from any form of spinal dysraphism that prevents the conus medullaris from normal upward movement during development.

Mechanically stretching or distorting the tethered cord can lead to progressive neurologic, urologic, or orthopedic dysfunctions through vascular compromise. An abnormal "tethering" usually involves the lumbosacral region, but it can also develop in other levels of the spinal canal in a variety of conditions. The tethered cord syndrome gives rise to a characteristic combination of clinical and radiologic findings of progressive neurologic deficits and orthopedic deformities in infants and children with a bony defect.

The symptoms may appear abruptly after mechanical stress imposed by hyperflexion of the spine, flexion at the hip, lithotomy position, or other trauma. Following the first prophylactic surgery, pain will completely resolve with or without improvement in function or scoliosis. At least 10% of patients, however, experience retethering and require additional surgery. Radiographic diagnosis consists of magnetic resonance imaging (MRI), to demonstrate a posterior and caudal displacement of the cord, and ultrasonography, to determine the presence or absence of cord pulsations. Surgical release of a tethered cord improves not only mechanical distortion known to cause tearing of neuronal membranes but also oxidative metabolism impaired by ischemia from acute and chronic traction.

Monitoring for tethered spinal cord surgery helps minimize inadvertent damage to neural elements during laminectomy for the release or resection of the filum terminale, lipoma, dermoid, or scar tissues.[57] Free-running EMG can monitor neural irritation or injury with subdermal needle or wire

electrode placed in vastus lateralis, tibialis anterior, gastrocnemius, semitendinosus, and gluteus maximus.[50] A brief unsustained neurotonic discharge suggests a minor trauma, whereas sustained activity may signal a greater, possibly irreversible injury.[85]

Recording muscle action potentials provides more accurate information than visual observation of the muscle contraction through surgical drapes. A multichannel monitoring system allows simultaneous display of evoked muscle action potentials from a number of sites pertinent to tethered cord surgery (Fig. 21-1). These include tibialis anterior, triceps surae, and quadriceps femoris.[50] The operative field in the lumbosacral area also necessitates careful monitoring of bowel and bladder function. Correct insertion of a needle electrode into the external urethral sphincter poses considerable difficulty, especially in infant girls. Fortunately, studying the muscle action potentials from the external anal sphincter serves as a monitor of the pudendal nerve, which also innervates the external urethral sphincter.

Normal nerve roots require less than 1 V for activation and stimulation of the spinal cord usually takes less than 10 V.[66] Some authors advocate the use of high current intensities up to 100 V

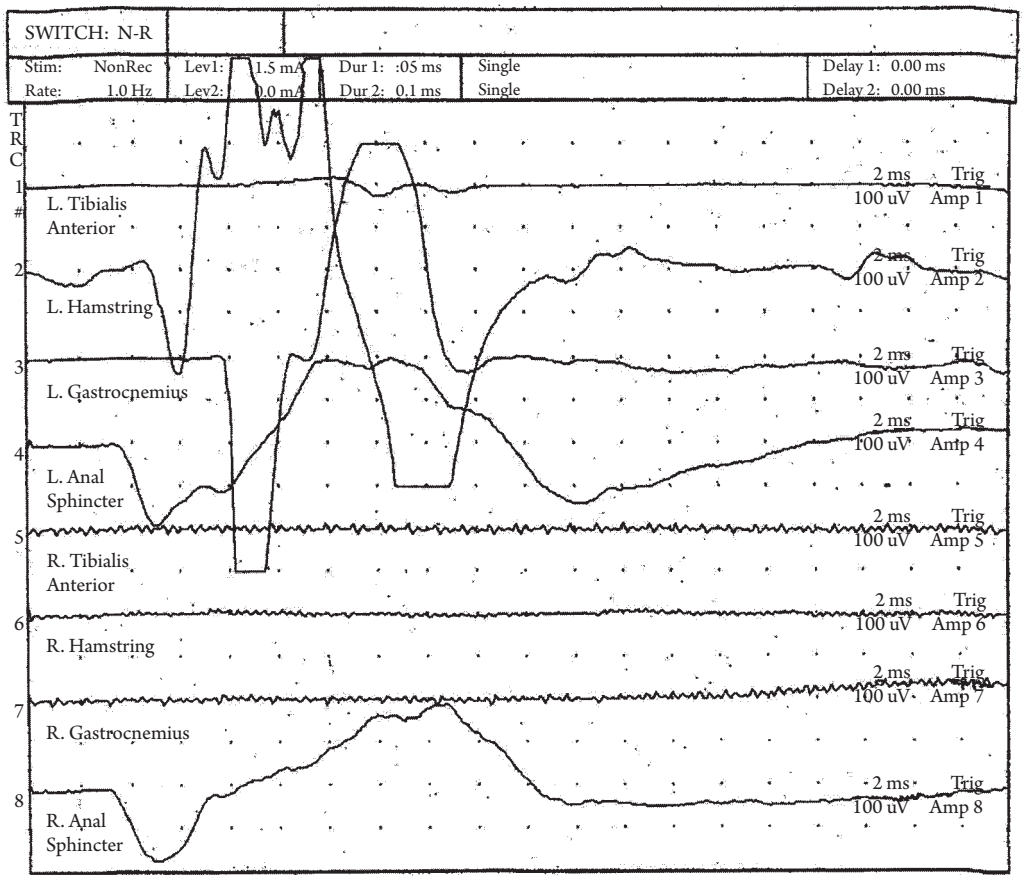

FIGURE 21-1 Intraoperative monitoring studies performed to evaluate lower lumbar and sacral nerve roots during tethered cord procedure in a 4-month-old boy. The tracings show simultaneous recording from the left (first 4 channels) and right (last 4 channels) tibialis anterior, hamstring, and gastrocnemius by a pair of monopolar needle inserted in each muscle, and the anal sphincter by an intramuscular wire lead and a reference electrode placed on the surface. Electric shocks with duration of 0.05 ms and intensity ranging from 1.0 to 20 mA, delivered from a pair of hook electrodes, identified neural elements by eliciting muscle responses in the left hamstring and gastrocnemius (2nd and 3rd channel) and both sides of anal sphincter (4th and 8th channels).

when identifying neural element in the filum terminale, before sectioning it.[102,133] An increase in the motor response threshold after surgical release of tethered cord syndrome indicates possible worsening of clinical symptoms.[51] Spinal cord stimulation during tethered cord surgery may help predict neurologic outcome.[52]

Measuring the vesical pressure serves as a monitor of the detrusor muscle innervated by the pelvic nerve. The need of high-frequency stimulation exceeding 10–30 Hz for sufficient pressure elevation, however, limits its use during surgery. Thus, this method, slower and less sensitive than muscle action potentials, falls short of fulfilling a role as an intraoperative monitoring. Somatosensory evoked potentials (SEPs), widely used for spinal monitoring, also have a limited value for tethered spinal cord syndrome, in which potentials rarely change before injuring neural elements. In contrast, recording muscle action potentials following stimulation of the tissues provides an easy method to identify the motor fibers.

Pedicle Screw Placement

Pedicle screw fixation of the lumbar spine, an accepted maneuver for spinal fusion, provides rigidity of the vertebral segment. Orthopedic instrumentation surgeries often use the pedicle for spinal stabilization in patients with spondylolisthesis, spinal stenosis, segmental instability, and scoliosis. The screws intended to lie entirely within the bone may pass through the pedicle wall into the spinal canal. These misdirected metal pieces, if uncorrected, may irritate the roots postoperatively, causing radiculopathy. Direct stimulation of the pedicle screw intraoperatively helps determine whether such misplacement has developed. Recording an SEP, once advocated to monitor lumbosacral nerve root, does not improve the sensitivity and specificity for detecting single nerve root dysfunction, masked by overlapping innervation by normal adjacent roots.

Multichannel recording strategy works well for monitoring application of pedicle screw used to attach spinal instrumentation to the vertebrae. Constant current or voltage stimulation of the screw placed in the pedicle allows monitoring of evoked muscle activity from the lower limb. The correctly placed screw fully surrounded by bone has high impedance to electrical current. In contrast, a current flows through the bone defects leading to excitation of the nearest nerve root at a stimulation intensity of about 20 V. In case of a bridge, therefore, a low-level stimulation evokes potentials in the lower-limb muscles or anal sphincter. Repositioning the pedicle screw and retesting its integrity reduce the risk of postoperative neurologic deficits. Thus, intraoperative monitoring helps successful placement of the pedicle screw without compromising the nerve root.

Selective Dorsal Rhizotomy

Carefully chosen patients may benefit from selective dorsal rhizotomy or subdivision and sectioning of portions of dorsal nerve roots to reduce spasticity commonly in children with cerebral palsy, but this is also sometimes performed in adult patients with multiple sclerosis, spinal cord injury, or brain trauma.[115] Controversies still prevail about the efficacy of monitoring this procedure electrophysiologically.[72,82,98,117,129,138] Some believe monitoring multiple muscles helps avoid sectioning many normal rootlets that subserve important function. Others concede monitoring does not necessarily alter the final outcome of rhizotomy.

Propofol may facilitate intubation by depressing pharyngeal and laryngeal reactivity, although its use has proven unsatisfactory to prevent the cause of muscle spasms during stimulation. The procedure consists of exposing the L2 to S1 nerve roots and selectively sectioning hyperexcitable subsets of the dorsal roots, or rootlets, as guided by monitoring. At each level, rootlet stimulation with single pulses of 20–50 Hz train normally activates the stretch reflex, which produces motor responses in the lower limbs.[141] The normal pattern elicited by sensory rootlet stimulation comprises a brief twitch of the appropriate muscles to the first train of stimulation, but no response to a subsequent train presumably by inhibitory feedback activated by high-frequency inputs.

In contrast, types of abnormal responses include repetitive firing in the appropriate muscles, dissemination of the response to other muscle groups, sometimes in the contralateral limb or the arms, and sustained discharges after

cessation of the stimulus train. Hyperactive rootlets also give rise to an abnormal spread of motor responses, as judged by observation of lower-limb movement and EMG recording from various muscle groups (Fig. 21-2). The muscles selected for monitoring, usually covering L2 to S1 nerve roots, vary depending on the clinical condition under study. These include the adductor longus, medial gastrocnemius, hamstring, and gluteus maximus muscles. Presurgery assessment optimizes the selection of the muscle groups to gain maximal information during the surgical procedure.

Stimulation of the normal motor root also exhibits no inhibition, showing responses similar to those elicited by stimulation of abnormal sensory roots. A complete relaxation at the cessation of stimulation, however, helps identify the ventral roots. Sensory rootlets generally require 2.5–5.9 mA to activate an electrophysiologic response as compared to 0.1–0.5 mA current used for motor roots. Thus, the intensity of stimulation necessary to activate the action potential also can theoretically differentiate between the abnormal sensory rootlet and the normal motor rootlet. This may not hold during surgery,

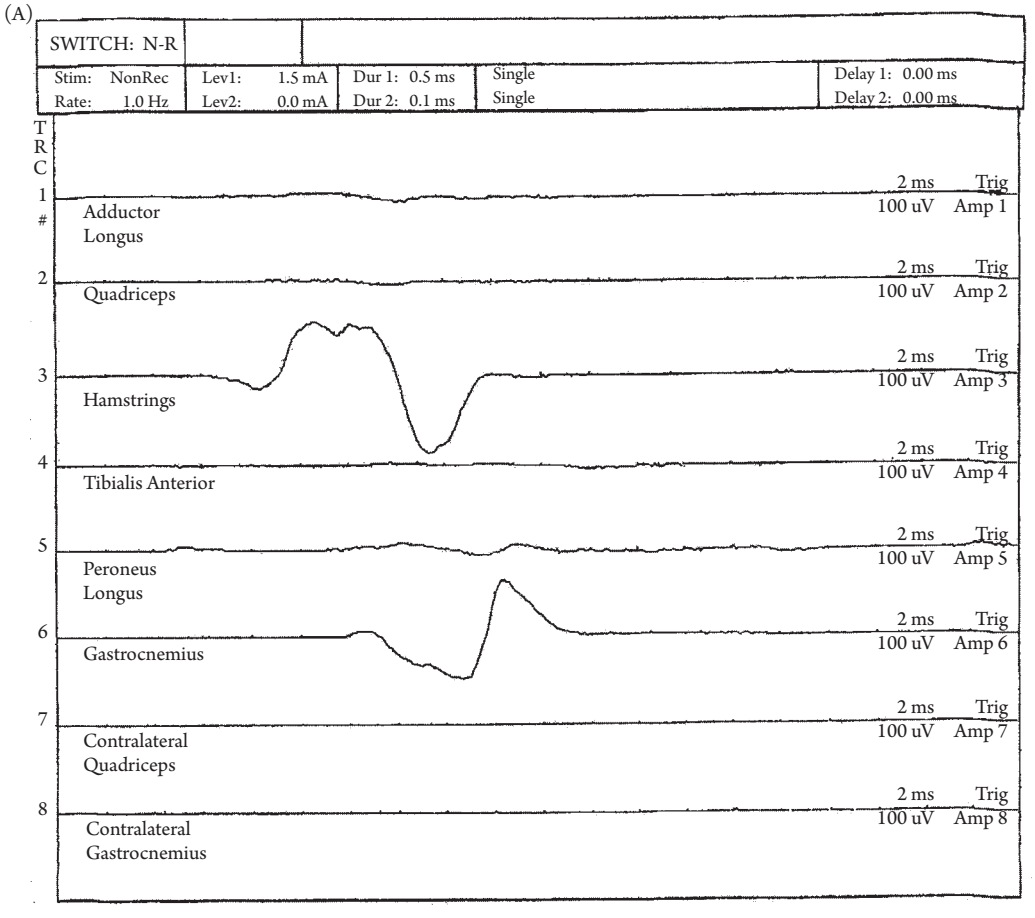

FIGURE 21-2 Intraoperative monitoring of dorsal rhizotomy comprises placing monopolar needle electrode pairs in the ipsilateral adductor longus, quadriceps (vastus lateralis), medial hamstring, tibialis anterior, peroneus longus, and medial gastrocnemius, and contralateral quadriceps and gastrocunemius, and stimulating individual dorsal rootlets from L2 through S2 levels. A: Determination of threshold intensity. An electric shock with duration of 0.05 ms and intensity of 1.5 mA, delivered from a pair of hook electrodes, elicited muscle responses of ipsilateral hamstring and gastrocnemius (3rd and 6th channels).

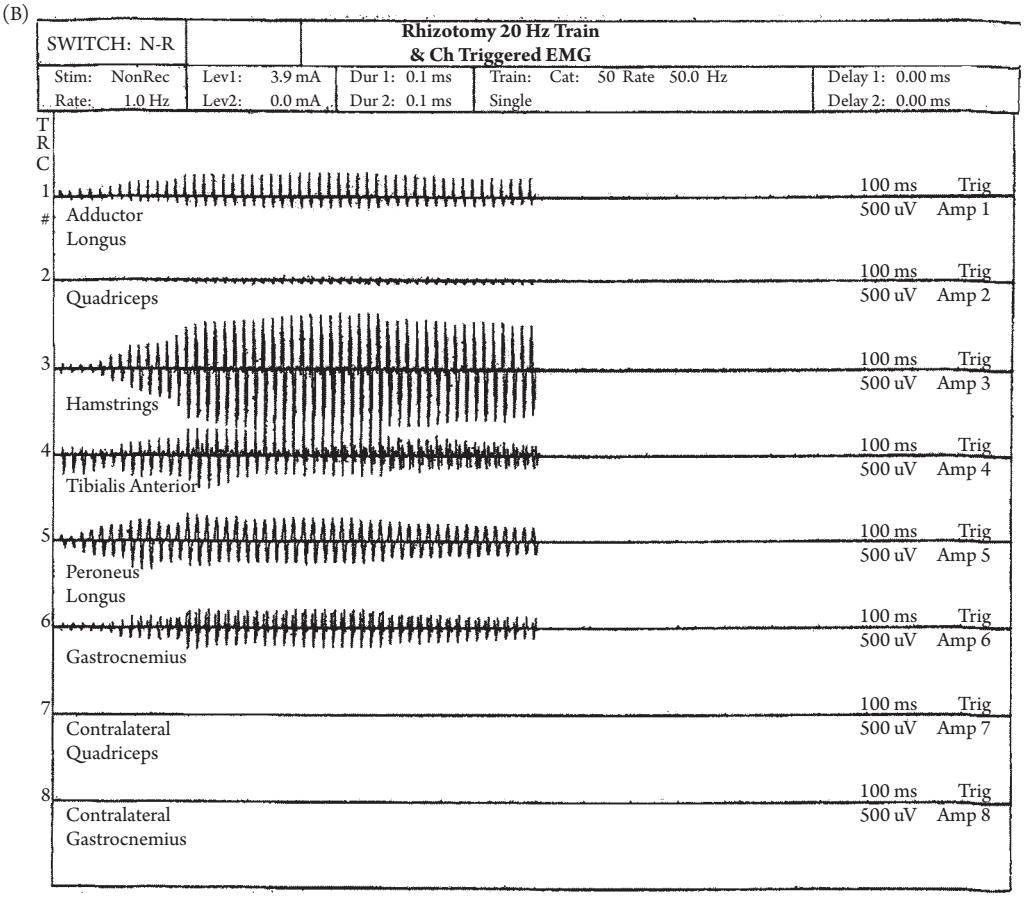

FIGURE 21-2 (*Continued*)

B: Distribution and duration of motor response. The decision whether to preserve or transect the rootlets depends on the muscle responses elicited by 50 Hz frequency stimuli of 1 second duration at threshold intensity defined as producing a constant motor response, if given individually (see Figure A). For each rootlet, the usual sites of recording include, in addition to all the ipsilateral muscles, the contralateral quadriceps and gastrocnemius.

however, where gentle dorsal root retraction and dissection can cause areflexia.[73] Indeed, the majority of motor responses evoked by apparent dorsal rootlet stimulation may result from ventral rootlet costimulation in the setting of intraoperative areflexia.[72,74]

Factors used in the decision to transect or preserve specific rootlets include clinical patterns of muscle contraction, electrophysiologic responses monitored through multichannel recordings, and presurgery assessment to define a desired outcome for the strength and quality of responses. If a single root contains fibers connecting to both normal and abnormal types, its surgical division into rootlets usually determines the sources of the excessive response. This select-and-cut approach leaves rootlets associated with normal responses intact, minimizing the loss of sensory input transmitted to the central nervous system. The dorsal root neurons have collaterals that give rise to ascending branches with synapses to the spinal anterior horn cells at many levels. Thus, dividing lumbar posterior rootlets may reduce motoneuron excitability not only at the lumbar segments but also at higher levels. This may account for commonly reported postoperative improvement of spasticity, muscle tone, mobility, posture, balance, and mass reflexes not only in the lower but also upper limbs.

4. SPINAL CORD SURGERY

Cortical Somatosensory Evoked Potential

During scoliosis surgery or removal of a spinal cord tumor, general or local anesthesia precludes clinical examination of spinal cord function. In contrast, a tibial or peroneal nerve SEP, though slightly reduced in amplitude, persists under halogenated inhalational anesthesia.[107] Thus, one of the important applications of SEP (see Chapter 19-6) relates to its use as an intraoperative spinal cord monitoring.[20,36,55,91,109] Most initial studies dealt with cortical potentials evoked by peripheral nerve stimulation. This type of recording shows, as a major disadvantage, inherent variability in amplitude, reflecting the fluctuating levels of excitability during anesthesia.[8,76] The uses of far-field potentials, which remain stable under anesthesia, circumvent this difficulty as a preferred measure for spinal cord monitoring (Fig. 21-3). Selection of appropriate derivations with a high signal-to-noise ratio helps improve reproducibility for rapid surgical feedback.[2,3,14,79]

Other factors of importance dictating the SEP latency and amplitude include blood pressure, body temperature, and administration of various medications.[67] In one patient, hemorrhagic hypotension caused SEP changes only with systolic pressures in the low 40s.[134] Hypothermia, induced for surgical repair of the aorta, abolished the cortical SEP at about 20°C and subcortical components at lower temperatures.[37] Intravenous loading of diphenylhydantoin at serum levels around 30 μg/ml induced a reversible delay of synaptic transmission in spinal and central somatosensory structures.[81] An amplitude loss also occurred by subdural gas collections during surgical procedures preformed with the patient in the semisitting position.[137]

Intraoperative monitoring of both cranially and spinally recorded SEP can provide means to assess details of functional integrity and prognosis for recovery of the spinal cord near a space-occupying tumor.[53] A large multicenter study has shown that SEP monitoring reduces postoperative paraplegia by more than 50%–60%.[92] Application of time-frequency analysis may improve reliability of SEP for intraoperative means of spinal cord function.[49] Monitoring of upper-limb SEP also has the added value of detecting brachial plexus injury induced by inappropriate position of the patient.[68]

Although SEP monitoring has acceptable sensitivity for detecting neurologic damage,[136] postoperative neurologic deficits may ensue despite an unchanged intraoperative SEP.[28,99] Thus, a normal SEP offers no guarantee for the integrity of the spinal cord. Conversely, inability to induce intraoperative SEP may not necessarily lead to consequent postoperative motor deficits,[17] although a markedly distorted or delayed response usually signals a warning for an impending risk. In particular, the cortical response tends to fluctuate as a function of neuromuscular status and procedural factors. In fact, it could abate entirely without a major change in the concentration of the anesthetic agent or surgical manipulation of the cervical cord.[131]

A scoliosis Research Society poll[95] provided a wealth of support for the use of SEP during spinal deformity surgery. Findings included a 50% decline in a major neurologic deficit since the introduction of intraoperative neuromonitoring, an estimated SEP sensitivity of 92% and specificity of 99%, and half the rate of neurologic deficits by participation of experienced, as compared to inexperienced, monitoring teams. Unfortunately, a false-positive finding occurs commonly relative to true-positive findings with a predictive value of only 42%. More important, false-negative cases may also occur as an indicator of motor function, even with the use of spinally elicited peripheral nerve responses.[86]

A pair of surface electrodes placed over the neck and scalp registers P14 and P31 after stimulation of the median and tibial nerve (Fig. 21-3) (see Chapter 19-3). In addition to N37,[78] these FFP peaks, showing less effect to anesthesia compared with cortical potentials, serve as a useful intraoperative measure. If peripheral nerve stimulation fails to elicit a FFP of adequate amplitude, cauda equina stimulation produces considerably higher evoked potentials, permitting reliable monitoring of spinal cord function.[29]

Spinal Somatosensory Evoked Potential

Compared to a cranial SEPs, spinal cord potentials show less variability when recorded either from

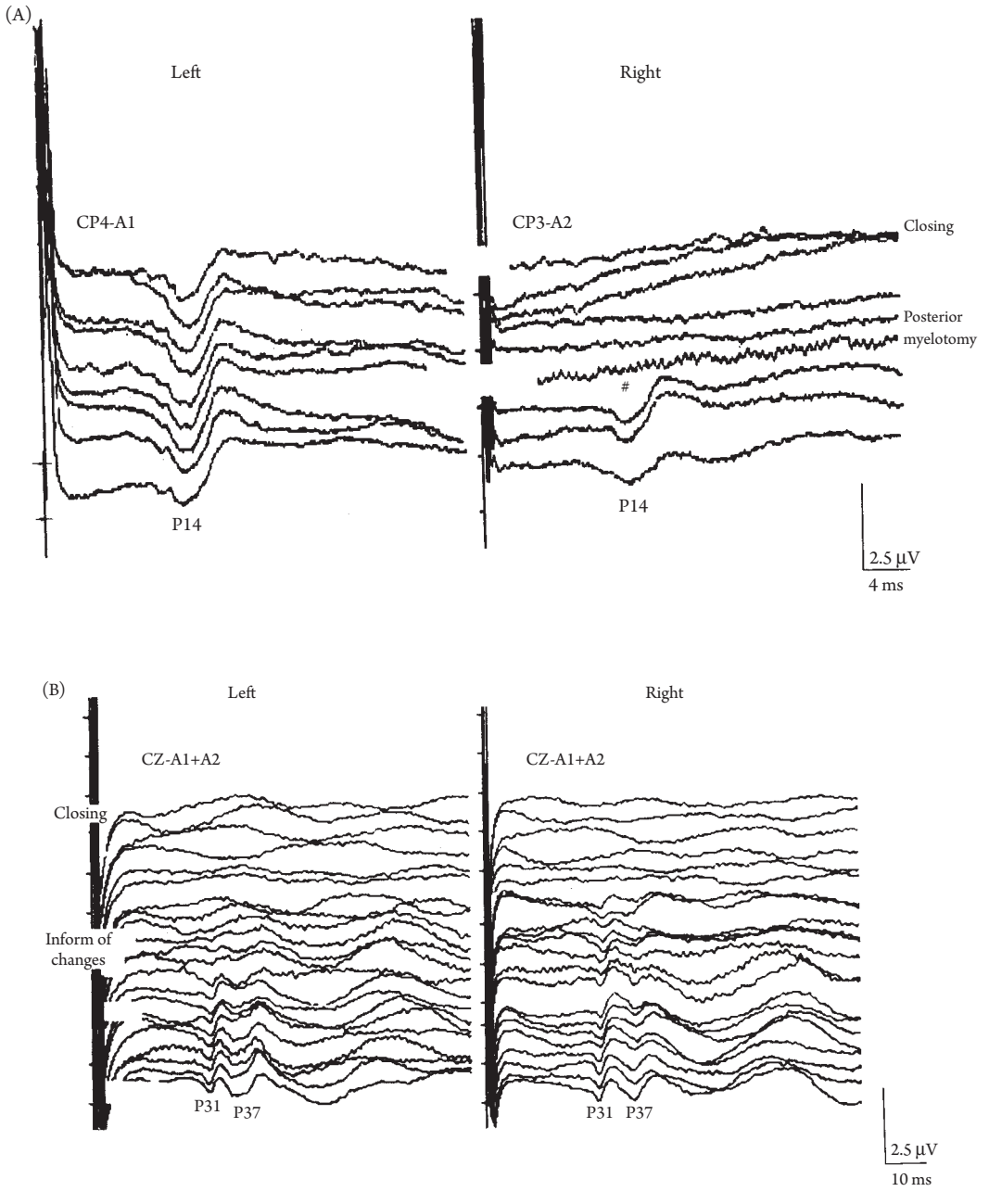

FIGURE 21-3 (***A*** and ***B***) Median (patient *A*) and tibial nerve (patient *B*) somatosensory evoked potential (SEP) to monitor a surgical resection of a cervical and lower thoracic intramedullary cord tumor. In both cases, continuous recording from bottom to top identified a sudden loss of subcortical potential, P14 and P31, on right-sided stimulation, which persisted postoperatively. The patient *A* developed a severe loss of proprioceptive sense in the right arm with preservation of motor strength. The patient *B* had a paraparesis with a sensory level at T9 cord level.

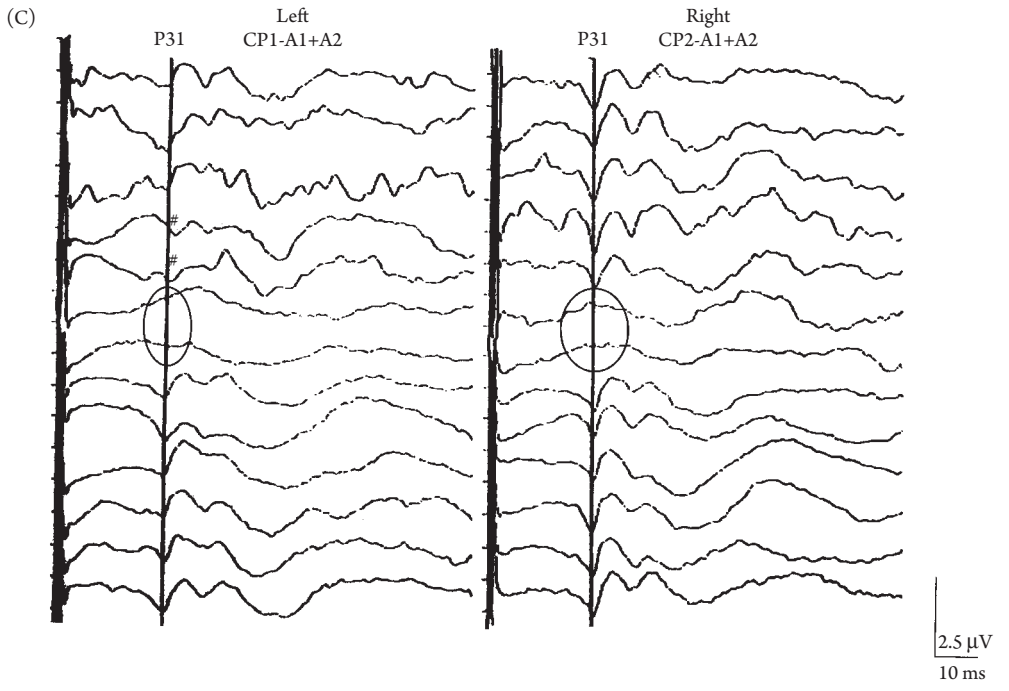

FIGURE 21-3 (*Continued*)

(***C***) Tibial nerve SEP (patient *C*) to monitor scoliosis surgery. Continuous recording from bottom to top revealed a sudden loss of P31 on both sides as verified by two consecutive trials (oval). A wakeup test confirmed the loss of motor function involving the lower but not upper limbs. Immediate lessening of spine distraction resulted in a quick return of P31 on both sides. The patient developed no neurologic deficits postoperatively (***A***: Modified from Yamada, Tucker and Husain,[139] ***B*** and ***C***: Modified from Galloway.[34])

Kirshner wire electrodes inserted in the spinous processes or from needles in the interspinous ligament. Spinal evoked potentials recorded by epidural electrodes serve as a means of monitoring spinal cord surgery.[62,111] Stainless-steel wire electrodes inserted into the epidural space register two to three negative potentials after stimulation of the peripheral nerve in humans (Fig. 21-4). Estimated conduction velocity ranges between 65 and 80 m/s for the fastest activity and 30 and 50 m/s for the slower waves.[80] In animals, spinal evoked potentials also consist of two negative peaks after direct cord stimulation.[121] Transection of the lateral column attenuates the first peak; and that of the posterior column, the second peak. The subsequent polyphasic waves probably result from slower conducting ascending sensory pathways.

Epidurally applied shock to the spinal cord yields better spinal or scalp potentials than surface stimulation of the peripheral nerve. Spinal potentials elicited by this means consist of two major negative peaks, NI and NII, and subsequent multiple smaller components (Fig. 21-5).[80] Individual variabilities in the waveform and amplitude of the spinal potential reflect inconsistency in the placement of the stimulating or recording electrodes.[122,124] Precise positioning of electrodes at optimal locations would minimize this difficulty by selective stimulation of, or recording from, the spinal pathway in question (Figs. 21-6 and 21-7). The facilitatory or inhibitory effect on

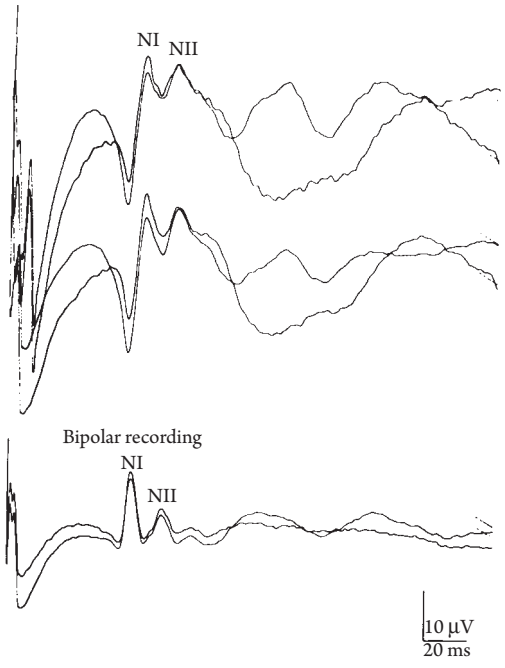

FIGURE 21-4 Comparison of monopolar and bipolar recording of spinal cord evoked potentials. Two top tracings show monopolar recordings from E1 and E2 placed 1 cm apart at the level of the T2 spinal process referenced to another electrode placed on the paraspinal muscle. The bottom tracing represents a bipolar derivation between E1 and E2 used for the top montage. Bipolar recording yielded a better defined, more stable potential with fewer technical problems such as muscle artifacts or stimulus-related baseline shift. (Modified from Machida, Weinstein, Yamada, et al.[80])

the spinal motoneurons, however, may spread many segments below the level of the cathode.[40]

The same spinal stimulation also elicits a CMAP in the lower limb, although this does not necessarily measure motor function if descending impulses of the sensory rather than motor tracts activate the anterior horn cells.[22] Direct stimulation of the spinal cord allows recording of peripheral nerve action potentials at the popliteal spaces under maximum neuromuscular blockade, which obliterates CMAP. Again, significant evidence indicates that spinally elicited peripheral nerve response probably results from sensory rather than motor pathway of the spinal cord, despite the commonly used designation, neurogenic motor evoked potentials.[86,126]

Transcranial Electric Stimulation

Various neurophysiologic techniques monitor the functional integrity of motor pathway intraoperatively.[13,80,97,120] Transcranial stimulation may substitute stimulation of the spinal cord with needle electrodes inserted into spinous processes (see Chapter 19-6),[5] providing an intraoperative means for monitoring the corticospinal and corticobulbar tracks.[31] For this purpose, an electrical shock has an advantage over magnetic stimulation because focal activation, induced by smaller electrodes, overcomes the effect of sedation. A short train of transcranial electric stimuli (TES) elicits D waves even in anesthetized patients,[27] who benefit little from the lack of pain with magnetic stimulation.

The refractory period limits the frequency of repetitive TES used for intraoperative monitoring. Submaximal intensity calls for a long interval of 4 ms, whereas supramaximal intensity produces fast recovery, making shorter interstimulus interval effective.[90] Under the anesthetic condition used in one study,[6] the optimal stimulus characteristics comprised a train of five stimuli, each 50 μs in duration and 500 V in intensity. Accumulated evidence supports the validity of intraoperative monitoring using spinal epidural recording of the D wave after single-pulse TES as well as MEP elicited by multiple TES.[28,118]

Of these, D waves specifically assess the descending volleys from direct activation of the fast-conducting corticospinal tract. The most accepted use of this method includes monitoring surgery for an intramedullary spinal cord tumor.[105,106] A 50% drop in amplitude serves as the standard criteria to stop the procedure and wait for its recovery before taking further surgical steps.[104] Its drawbacks include invasiveness, inability to monitor lesions lower than T11, and some limitations in its application for surgeries of scoliosis[130] and purely ischemic spinal cord lesion.[21,77]

Recording an MEP elicited by TES also enables the assessment of motor pathways intraoperatively.[6] In fact, it serves as a widely accepted, reliable means to predict motor outcome, despite the lack of consensus for the standard criteria used to interrupt surgery.[69] Compared to D waves, the MEP involves various

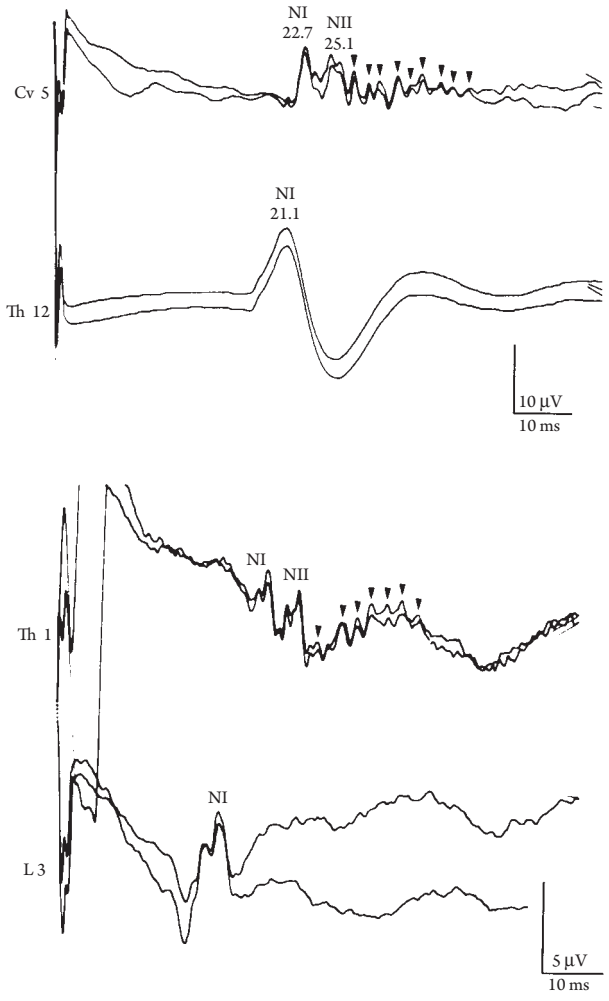

FIGURE 21-5 Spinal evoked potentials in two subjects recorded from an epidural electrode placed at the rostral and caudal spine after stimulation of the tibial nerve. The response recorded at the T12 spine level consisted of a single diphasic potential with the initial negativity. The waveform varied considerably when recorded at the L3 spine level or further caudally. In both cases, polyphasic waves followed the major negative peaks, NI and NII, when recorded at a more rostral level. (Modified from Machida, Weinstein, Yamada, et al.[80])

motor pathways, and as such, provides less specific evaluation of the corticospinal tract.[23,127] Monitoring motor potential directly from the spinal cord may reveal abnormalities even in the face of a normal SEP.[9,71]

Fast charge delivery yields a higher stimulation efficiency to improve the performance of intraoperative monitoring.[12,47] Continuous EMG recording may detect suprasegmental spinal motor tract injury during extradural spinal cord decompression.[7,113] A train of cutaneous conditioning stimuli may induce a spacial facilitation of the cortically elicited response in monitoring spinal surgery.[4] Despite the clinical validity of this technique that generally prevails, some patients with a preserved MEP until the end may show a new motor deficit, and conversely, others with worsened response intraoperatively may develop no new motor deficits.

Summary

Optional intraoperative monitoring during scoliosis surgery entails both SEP and MEP

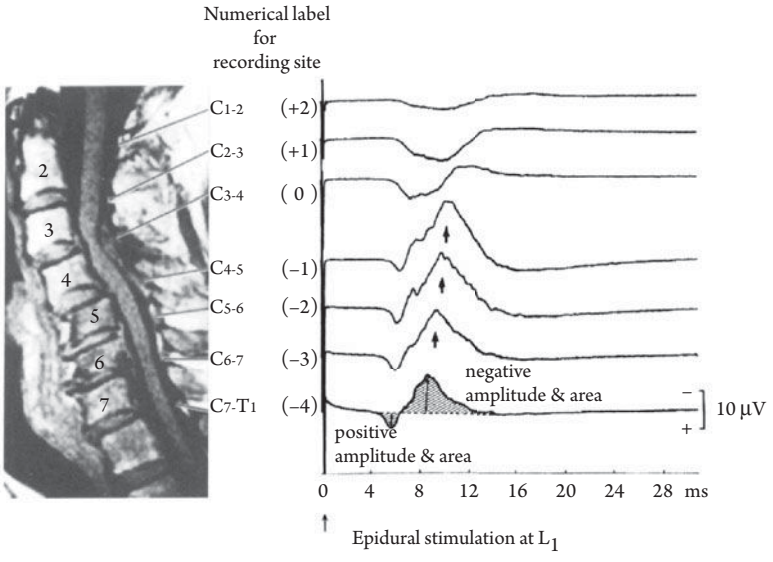

FIGURE 21-6 A T1-weighted magnetic resonance (MR) image (left) and spinal evoked potentials (right) recorded unipolarly from the ligamentum flavum of C7-T1 through C1-2 after epidural stimulation at L1 in a 69-year-old patient with cervical spondylotic myelopathy. Note the progressive increase in size of the negative component (arrows pointing up) from C7-T1 (–4) through C4-5 (–1) followed by the abrupt reduction at C3-4 (0) and a monophasic positive wave at C2-3 (+1). The "0" level corresponds to the site of a marked cord compression seen on the MR image. (Modified from Tani, Ushida, Yamamoto, et al.[123])

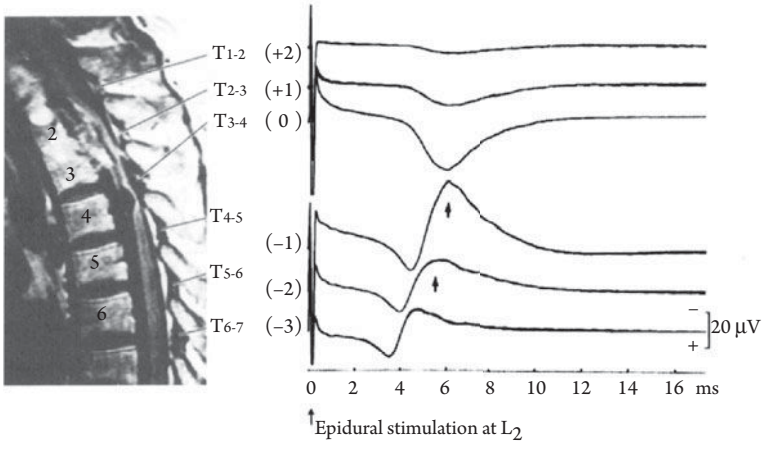

FIGURE 21-7 A T1-weighted magnetic resonance (MR) image (left) and spinal evoked potentials (right) recorded unipolarly from the ligamentum flavum of T6-7 through T1-2 after epidural stimulation at L2 in a 63-year-old patient with thoracic myelopathy and ossified posterior longitudinal ligament. Note the progressive increase in size of the negative component (arrows pointing up) from T6-7 (–3) through T4-5 (–1) followed by a monophasic positive wave at T3-4 (0). The "0" level corresponds to the site of a marked cord compression seen on the MR image. (Modified from Tani, Ushida, Yamamoto, et al.[123])

recordings, a combination of which offers a more complete assessment of spinal function.[83] A generally accepted set of criteria for SEP abnormality comprises a 50% loss of amplitude relative to the baseline and a 10% increase in latency of the monitored signal. In contrast to the SEP, the MEP elicited by TES shows a considerable intertrial variabilityo.[139] Thus, the criteria for MEP

abnormality may utilize not only a percentage reduction of amplitude[100] but also the presence or absence of CMAP as all-or-none phenomenon.[64] To minimize the cases of false-negative or false-positive results, the various recording techniques described here complement one another in the assessment of spinal cord function in the operating room.[100]

5. CORTICAL AND SUBCORTICAL MAPPING

A cortical SEP recorded with subdural electrodes shows an initially positive postrolandic potential with a latency (mean ± SD) of 22.3 ± 1.6 ms and an initially negative prerolandic potential with a latency of 24.1± 2.7 ms, thus delineating the central sulcus.[30] The phase reversal of N20-P20 serves as a simple and reliable method to locate the perirolandic gyri, although the presence of a tumor in the postcentral region may mask the clear identification.[103] A change in a median nerve SEP noted while monitoring carotid endarterectomy usually signals cerebral ischemia and the need for a shunt during the surgery.[32,38] The use of electrophysiologic monitoring improves intraoperative management of intracranial aneurysms and helps predict unfavorable outcomes.[75]

The issue of subcortical mapping has also emerged for a functional approach to the surgery of gliomas to avoid injuring white matter tracts. The short train of stimuli delivered using a monopolar derivation to elicit a muscle response allows both cortical and subcortical mapping through a handheld probe with a strip electrode overlying the motor cortex.[24,119] Recording from the cricothyroid and vocal muscles also enables intraoperative monitoring of the corticobulbar tract using similar methodologies.[25,26]

6. CONCLUSION

Intraoperative peripheral nerve monitoring through NCS and EMG can help improve surgical outcome by characterizing nerve injuries, identifying neurologic structures, and preventing unintended surgical trauma to neural tissues. In operative release of the spinal cord, cauda equina, and spinal nerves tethered by fibrous band, for example, monitoring helps detect any nerve elements that the surgeon needs to preserve. The use of EMG monitoring also provides a sensitive measure for detecting malpositioned pedicle screws, as a source of neurologic complication. Some surgeons advocate intraoperative monitoring to guide their decision in choosing the rootlets for section during a selective dorsal rhizotomy to reduce spasticity. This procedure may allow preservation of sensory innervation useful to maintain appropriate motor function of the affected muscle group. Short-latency, far-field SEP peak, not affected by anesthetic agents, serves as a stable intraoperative measure of spinal cord function. Segmental recording of spinal conduction by a series of electrodes placed along the cervical spine also helps surgeons to decompress the appropriate level by precisely localizing the site of conduction block, which imagery studies often fail to document. Recording SEP continues to retain clinical value for assessing the integrity of the dorsal column as a supplement to MEP studies, now considered the gold standard for spinal cord monitoring.[28]

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PART VII

Disorders of Spinal Cord and Peripheral Nervous System

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22

Diseases of the Spinal Cord

Abbreviations: AIDS—acquired immunodeficiency syndrome, ALS—amyotrophic lateral sclerosis, BSMA—bulbospinal muscular atrophy, CCT—central conduction time, CK—creatine kinase, CIDP—chronic inflammatory demyelinating polyneuropathy, CJD—Creutzfeldt-Jakob disease, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CRD—complex repetitive discharge, CTS—carpal tunnel syndrome, DMD—Duchenne muscular dystrophy, EEG—electroencephalogram, EMG—electromyography, EPP—endplate potential, FSH—fascioscapulohumeral, FVC—forced vital capacity, HAM—HTLV-I associated myelopathy, HSP—hereditary spastic paraplegia, HTLV-I—human T-lymphotropic virus I, IFCN—International Federation of Clinical Neurophysiology, MEP—motor evoked potential, MG—myasthenia gravis, MMD—multifocal motor neuropathy, MND—motoneuron disease, MUNE—motor unit number estimation, MUP—motor unit potential, MVV—maximal voluntary ventilation, NCS—nerve conduction studies, NMT—neuromuscular transmission, PBP—progressive bulbar palsy, PLS—primary lateral sclerosis, PMA—progressive muscular atrophy, PPB—progressive bulbar palsy, PPF—paired-pulse facilitation, PPI—paired-pulse inhibition, SBMA—spinobulbar muscular atrophy, SCA—spinocerebellar atrophy, SEP—somatosensory evoked potential, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy, SNAP—sensory nerve action potential, SOD—superoxide dismutase, TMS—transcranial magnetic stimulation, TRH—thyrotropin-releasing hormone, TSP—tropical spastic paraparesis, TST—triple stimulation technique, WFN—World Federation of Neurology

1. INTRODUCTION

Degenerative diseases of the anterior horn cell rank first among the wide range of disorders of the spinal cord commonly seen in an electromyographic (EMG) laboratory. Of various classifications proposed, those based on clinical and genetic features have proved most satisfactory, pending the elucidation of the basic etiology. Classic motoneuron disease (MND) characteristically shows a combined involvement of the upper and lower motoneurons. This group of diseases comprises progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), and amyotrophic lateral sclerosis (ALS), and its variant, primary lateral sclerosis (PLS). In contrast, the patients with spinal muscular atrophy (SMA) have genetically determined degeneration of the anterior horn cells without corticospinal tract involvement.

A number of other conditions, infectious or toxic in nature, affect the motoneurons selectively or in conjunction with the corticospinal tracts. Despite the advent of a vaccine in the 1950s, poliomyelitis still prevails in the tropics. With diminishing public awareness of the need for vaccination, new epidemics may develop. The residual of old poliomyelitis, although relatively common, may escape detection unless clinically suspected. Polio-like symptoms may develop in other viral disorders such as Western Nile encephalitis. Syringomyelia, another classical neurologic disorder, also involves the spinal cord. The disease often mimics MND, especially if cutaneous touch sensation remains completely normal. Careful sensory examination will, however, reveal a selective loss of pain perception in the cervical or lumbosacral dermatomes in question.

Amyotrophy may occur as a feature of familial multisystem atrophies such as familial MND and familial spastic paraplegia. Some subtypes of spinocerebellar atrophy (SCA) such as Machado Joseph disease (SCA3) also have clinical and EMG evidence of lower motoneuron disease as a major finding. Other systemic disorders associated with amyotrophy and denervation includes Parkinson's disease, Huntington's chorea, Pick's disease, and xeroderma pigmentosum. Juvenile SMA with hexosaminidase deficiency also resembles an MND.

Electrophysiologic studies help characterize these disease entities and localize the lesion site. Reduced recruitment suggests a loss of motoneurons during early stages. Fibrillation potentials appear a few weeks after the onset of illness. Large-amplitude, long-duration motor unit potentials (MUPs) develop later as the consequence of reinnervation. Reinnervation of denervated muscle fibers by sprouting tends to normalize the size of compound muscle action potentials (CMAPs) despite loss of motor axons. Nonetheless, clinical severity of the disease correlates approximately with the degree of reduction in amplitude of CMAP, but not necessarily with the magnitude and distribution of fibrillation potentials. Despite reduced amplitude of muscle potential and slowed motor conduction, sensory action potentials remain normal in the vast majority of cases. This section discusses certain diseases of the anterior horn cells as they pertain to EMG and nerve conduction studies (NCS).

2. MOTONEURON DISEASE

Etiology and Pathogenesis

Together with parkinsonian syndrome and Alzheimer's disease, MND constitutes a triad of degenerative disorders of the aging nervous system.[104,194,253,345] In this entity, selective vulnerability of a special set of cells leads to primary degeneration of the upper and lower motoneurons. In addition to common sporadic cases, 5%–10% have familial incidence with an autosomal dominant pattern of inheritance. Patients with PMA develop only lower motoneuron impairment, whereas those with PLS have prominent corticospinal tract signs without lower motoneuron involvement. Patients with ALS have features of both upper and lower motoneuron lesions. In comparison, patients with PBP show the combined features of brainstem dysfunction and spasticity. The various syndromes, although described as separate nosologic entities, may represent a disease spectrum showing varying sites of maximal neuronal damage.

Attempts to isolate a virus or other causative elements have consistently failed despite clinical resemblance to transmissible Creutzfeldt-Jakob

disease and immunologic reactivity against certain infectious agents. An unidentified virus might have caused an MND with the clinical and pathologic appearance of ALS in a woman severely bitten by a cat.[170] A number of patients developed a progressive MND after an electrical injury.[172,179] In one case, the onset of the disease involved the limb through which the shock entered.[328] In some members of the families with recessively inherited MND,[99,254] hexosaminidase may fall to a very low level as seen in their relatives with Tay-Sachs disease. Some patients show a reduced level of glutamate and aspartate as well as elevated glutamate dehydrogenase activity in the spinal cord.[234] Disorders reported in conjunction with a typical ALS include chronic inflammatory demyelinating polyneuropathy (CIDP).[101,300] Diabetes mellitus Type II may delay the onset of motor symptoms in ALS.[183]

Amyotrophic Lateral Sclerosis

GENERAL FEATURES

The adjective *amyotrophic* implies muscle wasting as a result of an anterior horn cell disorder. The term in other contexts, however, may refer to any neurogenic atrophy, including those resulting from radicular lesions or localized injuries of the peripheral nerve. The disease has a prevalence rate of 2 to 7 and an incidence rate of 1.0 to 1.9 per 100,000 populations[7,118] with a higher incidence in men than women.[4] Analysis of a Cuban population[398] indicates a reduced frequency of ALS in an ethnically mixed population. Etiologic possibilities include genetic,[299,379] toxic [92,326] including smoking,[381] immunologic,[112] environmental,[53,65,90] traumatic,[239] and premorbid habitus such as weight, body mass, and physical activity,[315] although none has shown definite proof.[9]

The siblings and children of ALS patients have an about 10-fold risk for ALS compared with the reference group.[114] Familial cases, accounting for 10% of patients,[74] usually show a dominant pattern. Of these, one-fourth have missense mutation in the antioxidant enzyme copper/zinc superoxide dismutase (*SOD1*) gene on chromosome 21.[133,135] This finding supports the hypothesis that oxidative damage plays a role in the pathogenesis of ALS. Many patients with this mutation have the signs restricted to those of lower motoneuron by clinical and postmortem examination.[309,314] Linkage studies have also found other gene mutations in familial ALS: TDP-43, FUS, and VCP.[121] Patients with FUS mutation, another not uncommon cause of familial ALS, manifest earlier development of symptoms, a higher rate of bulbar onset, and shorter duration of symptoms than those with *SOD1* mutations.[395]

The essential pathologic and functional change consists of relatively selective degeneration of the motor cells in the spinal cord, brainstem, and, to a much lesser extent, the cortex typically, although not universally, sparing Onuf's nucleus.[81,193] The most extensive cellular damage occurs in the cervical and lumbar levels, primarily affecting the large motor cells. Studies of the ventral spinal root reveal axonal degeneration of the large myelinated fibers. In the brainstem, histologic changes predominate in the motor nuclei of the 10th, 11th, and 12th cranial nerves and, less frequently, in those of the 5th and 7th nerves. Rarely, the pathologic changes involve the nuclei of the 3rd, 4th, and 6th cranial nerves.[117,320] The cellular damage consistently involves the corticospinal tracts in the lateral and ventral funiculi of the spinal cord. Indeed, autopsy studies reveal these pathologic alterations even if the patient had no clinical signs of upper motoneuron lesions in life.

Disputes continue regarding the primary neurons involved in ALS. Some postulate initial involvement of the cortical motoneuron or the local circuit interneurons that inhibit its activity[104,108] without subsequent confirmation.[79] Others hypothesize retrograde transport of pathogens from neuromuscular junctions with the spread of the disease process monosynaptically from the lower to the upper motoneuron.[59] Still others[14] conclude, based on transcranial magnetic stimulation (TMS) studies to characterize motor units over time, that cortical and spinal motoneurons degenerate independently. The body region with the highest upper motoneuron involvement at onset also has the highest frequencies of lower motoneuron signs.[204] The well-known heterogeneity of motor phenotype may thus result from contiguous spread of a focal

process through the upper and lower motoneuron levels.[302] In one study,[79] MUP analyses showed the same degree of changes in the trapezius receiving contralateral corticospinal innervation and sternocleidomastoid with bilateral innervation. This finding suggests spinal as compared to cortical factor as the cause of lower motoneuron degeneration.[94] Although the anterior horn cells and the corticospinal tracts undergo most severe degeneration, a wide spectrum of changes affects the entire spinal cord.

Degeneration of the anterior horn cells results in denervation of muscle fibers. Collateral sprouts from surviving motoneurons then reinnervate the affected motor units. Reinnervation, as a relatively active process, sufficiently makes up for the progressive loss of motoneurons until more than 50% of them have died.[36] Histochemical studies of fresh frozen specimens thus show characteristic denervation atrophy with fiber grouping that represents a compensatory mechanism. Myopathic changes also appear presumably as part of the denervation process, although most biopsies show relatively intact intermyofibrillar network and cellular architecture of the fibers. Type I grouping correlates with the best prognosis, whereas a high density of atrophic fibers implies a rapid progression. A needle biopsy obtained at the time of initial diagnosis may predict the rate of disease progression.[207] According to a quantitative study of the terminal innervation ratio and fiber type grouping, collateral reinnervation occurs less in ALS than in the more slowly progressing Charcot-Marie-Tooth disease (CMT).[353] Motor nerve biopsy also shows less density for regenerative clusters of small myelinated fibers in ALS compared to motor neuropathy.[62]

CLINICAL FEATURES

Symptoms usually begin at a fairly definable point in time[84] in the fifth to seventh decades. Distal weakness commonly develops as an early symptom, although both central and peripheral factors contribute in muscle fatigue.[192] Despite asymmetric initial manifestations, at times limited to only one limb, the disease progresses rapidly to involve muscles of the trunk and those innervated by the cranial nerves. Spasms and cramps of the leg muscles occur early in the course of the disease, often appearing at night or after exercise. This onset may mimick a more benign entity called cramp, muscle pain, and fasciculation syndrome.[84] Bulbar involvements tend to appear late in the course but dysarthria, dysphagia, vocal cord dysfunction,[367] and rarely respiratory failure[57] may constitute the initial symptoms.

Although patients commonly complain of aching and other vague sensory complaints, they have no clear objective loss of sensation. Pathologic examination of the peripheral nerves also shows some involvement of sensory axons but not as an essential part of the disease. A reduction in epidermal nerve fiber density in the distal calf muscles in patients as compared to control supports the concept of distal axonopathy in ALS.[387] The disease may affect the autonomic nervous system.[188] A neurogenic bladder, although rare at the onset, may develop terminally. Pathologic laughing and crying spells signal a pseudobulbar manifestation at some stage of the illness.

Clinical signs include widespread atrophy affecting the limb and facial muscles, usually in proportion to the degree of weakness that primarily results from lower as opposed to upper motoneuron loss. Some patients develop a dropped head syndrome usually within the first 1 to 2 years of onset.[142] The sparing of the extraocular muscles stand in sharp contrast to the frequent involvement of the tongue. Most patients have hyperreflexia, some with ankle clonus and extensor plantar responses. Fasciculations occur almost universally at some stages, although some patients may not notice spontaneous muscle twitching. A paucity of fasciculations may suggest slow progression of the illness, but their abundance does not necessarily imply a worse prognosis. Benign fasciculations, not uncommonly seen in healthy subjects, usually involve the eyelid, calf, or intrinsic hand muscles, especially after strong contraction. Unlike the patients with ALS, these subjects develop neither muscle weakness nor atrophy, and EMG studies show no evidence of denervation.[27]

The signs and symptoms may wax and wane, with an apparent improvement presumably after reinnervation from collateral sprouting. Despite a fluctuating course, the disease usually progresses without remission clinically or as tested

by combined physiologic measures.[82,231] On the average, it leads to death in 2 to 4 years,[91,335] most often from respiratory failure.[138] The most frequently reported negative prognostic indicators in ALS include older age at onset, bulbar onset, short delay to diagnosis, and executive dysfunction from frontotemporal dementia.[109]

Longer survival in younger patients probably reflects their greater neuronal reserve.[106] Perhaps as many as 20% of all patients have a more favorable course with survival in excess of 5 years. The "benign" form lacks bulbar signs in the early stages but otherwise shares the same clinical features with the classical variety. Other indicators for shorter survival include greater age, lower predicted forced vital capacity, lower serum chloride level, which signals respiratory acidosis, a shorter interval from symptom onset to diagnosis of ALS, and greater weight loss.[70] Body mass index, not dyslipidemia, may serve as an independent predictor of survival in ALS.[189,275] In one series,[271] about 4% of patients, mainly younger men, experienced unusually long courses with milder paralysis. Although very rare, some patients with symptoms closely suggestive of ALS recovered completely 5 to 18 months after onset.[361,362]

Clinical diagnosis depends on the combined features of widespread muscular atrophy, weakness, fasciculations, and evidence of damage to corticospinal and bulbar tracts. Differential diagnoses include any conditions associated with diffuse muscle atrophy. A syndrome clinically resembling ALS may appear in association with compressive lumbar myelopathy,[196] organochlorine insecticides,[125] lead intoxication,[31] chronic mercurialism,[187] chronic copper deficiency,[386] multifocal motor neuropathy (MMN),[257,284,369] delayed radiation-induced bulbar palsy,[139] Allgrove syndrome,[21,139] and proximal motor neuropathy.[49] In addition, cervical spondylosis and developmental anomalies in the region of the foramen magnum sometimes simulate the disease closely, with presenting symptoms of muscular weakness in the upper limbs and evidence of spasticity in the lower limbs. When an MND and cervical or lumbar spondylosis coexist, sensory symptoms of radiculopathy alter the picture of pure motor dysfunction.

A myelogram helps distinguish these diagnostic possibilities caused by structural abnormalities. Muscle enzyme levels may reach two or three times the normal value in about half of the patients with MND. Infrequent and mild pleocytosis and oligoclonal bands seem to have no clinical importance in well-established cases of ALS.[270] Mass spectroscopy identified cystatin C and transthyretin as biomarkers, which predicted ALS with an overall accuracy of 82%.[312] Fractional anisotropy seen in diffusion tensor magnetic resonance imaging (MRI) reflects functional abnormality of the intracranial corticospinal tracts.[178] Neuromuscular ultrasound demonstrates nerve and muscle atrophy.[45]

Therapeutic regimen includes, in addition to multidisciplinary supportive care,[246,355] administration of riluzole, which may prolong life by a few months without tracheostomy.[247] High-dose methylcobalamin may slightly retard muscle wasting in some patients.[184] One study[24] showed beneficial effect of 3–4 diaminopyridine. Drugs proven ineffective include lithium carbonate.[58,280] Drug trials must rely on clinically defined endpoints that measure disease progression.[69] These include questionnaire-based ALS Functional Rating Scale and examination-based Appel ALS scores.[372]

In testing muscle strength, manual muscle testing shows a greater reproducibility than maximal voluntary isometric contraction, an effect largely accounted for by the number of muscles tested.[144] The rate of change of MUNE and CMAP amplitude may serve to divide ALS patients into groups of different progression rate.[228] A series of quantitative tests designed to monitor pulmonary function includes sternocleidomastoid[288] and phrenic nerve motor response[221,289–291] in addition to forced vital capacity (FVC), maximal voluntary ventilation (MVV), and sniff nasal pressure as an abbreviated alternative.[123] In one series,[148] ALS patients reported high usefulness with all bathroom adaptive devices. Ocular muscles resist for a longer period time as potential targets to establish a fruitful patient–computer communication to access the caregivers.[75,262]

PHYSIOLOGIC CHARACTERISTICS

Motor nerve conduction studies typically show a reduced CMAP amplitude recorded from distal

muscles,[83] often involving abductor pollicis brevis and first dorsal interosseous more severely than abductor digiti minimi.[211] Electrophysiologic studies also reveal a reduced number of motor units with a higher average amplitude than normal (see Chapter 14-5), greater variability of motor unit responses than normal to electrical stimulation of different intensities,[159] abnormal excitability of motor axons (see Chapter 10-4), and a slight slowing of motor conduction, reflecting a loss of the fast fibers.[205,265] The maximal conduction velocity, however, rarely falls below 70% to 80% of the normal lower limits with some studies indicating little or no change. These findings suggest at least partial preservation of the fastest fibers for a long time with no evidence of their preferential loss. Pathologic slowing of normally slow fibers may increase the scatter of velocities.

Characteristic EMG abnormalities found during various stages of the illness reflect the sequence of pathologic changes in the muscle. Diffuse denervation gives rise to widespread fibrillation potentials and positive sharp waves (see Fig 14-8B in Chapter 14). Fasciculation potentials, as a nonspecific but characteristic feature of ALS, imply motoneuron irritability in an appropriate clinical context.[163,248,249] These abnormalities typically have an asymmetric distribution particularly during early stages. The presence of large and small fibrillation potentials suggests both recent and chronic denervation. Additional physiologic findings include increased fiber density and jitter values as well as intermittent blocking determined by single-fiber electromyography (SFEMG).[339] These abnormalities, seen consistently in fasciculating motor units, reflect the degree and the recency of collateral reinnervation.[181] Muscles showing no abnormalities, either clinically or by conventional needle examination, may have subtle signs of reinnervation and immature motor nerve terminals. Despite active reinnervation, which only compensates for up to 50% loss of the total pool, progressive denervation produces a deteriorating clinical course.

A typical MUP has large amplitude and polyphasic waveform, some with late components. A peristimulus time histogram study indicated abnormalities of corticospinal drive, which contribute to the generation of double discharges in ALS but not in Kennedy's disease.[373,385] The surviving motor units, reduced in number, recruit poorly and discharge rapidly, producing a less than full interference pattern (see Figs. 13-8B and 13-9B in Chapter 13). Motor unit number estimate (MUNE) (see Chapter 10-2) can document functional motoneuron loss[10,86] and may serve as an outcome measure in ALS.[325] In one estimate, population halved in each 6-month period of the first year and then diminished more slowly thereafter.[71] Enlarged units contribute less twitch force[370] and fatigue more easily[321] than normal units, showing mechanical inefficiency.

Near nerve recording may detect subtle abnormalities in the sensory action potential in some patients.[324] In most cases sensory nerve action potentials (SNAPs) remain normal in amplitude and onset latency,[298] although some studies revealed their slight but significant reduction in up to one-third of patients.[152] Any substantial abnormalities in sensory conduction, however, suggest another disorder. Spectral analysis of heart rate variability[292] and studies of pseudomotor function[16] may reveal subclinical involvement of the autonomic nervous system.

The common complaint of easy fatigability suggests impairment of neuromuscular transmission (NMT) with a small unstable MUP showing temporal amplitude variability (see Fig. 14-13 in Chapter 14). In many patients with a rapidly progressive form of the disease, slow repetitive nerve stimulation shows a decrement of CMAP.[380] In one series,[95] 67% of 55 patients had an abnormal response, especially in the atrophic or fasciculating muscles. As in myasthenia gravis (MG), local cooling or administration of edrophonium (Tensilon) normalizes the findings, and exercise induces a posttetanic potentiation and exhaustion (see Chapter 18-5).

Cortical stimulation reveals a number of abnormalities, including the absence of responses, increased central delay,[250] corticomotor hyperexcitability,[263,363] changes in cortical muscle representation [78,199] (see Chapter 20-8), and initially reduced and later raised thresholds for cortical excitation of single motor units.[107] Analysis of amplitude ratio established by triple stimulation technique (TST) (see Chapter 20-5)

may detect upper motoneuron involvement in ALS better than regular TMS.[202]

Cathodal transcranial direct current stimulation (see Chapter 20-6) induces a consistent decrease in corticospinal excitability in healthy controls, but not in ALS.[260] Firing patterns of single motor units tested by TMS suggest sprouting of corticospinal axons, which may characterize surviving motoneurons.[13] Studies by TMS also demonstrated a reduction in paired-pulse inhibition (PPI) and paired-pulse facilitation (PPF).[44,397,401] A therapeutic trial with riluzole partially restored deficient PPI, leaving PPF unchanged, indicating that attenuation of glutamate-related excitotoxicity contributes to its beneficial effect.[341]

Upper motoneuron dysfunction may antedate clinical weakness in familial ALS patients, although this finding does not necessarily imply cortical onset of the disease.[87,375,377] Additional factors other than simple *SOD1* mutation expression triggers cortical hyperexcitability and neurodegeneration in familial ALS.[377] Very slow central conduction time (CCT) seen in patients homozygous for the CuZn-SOD mutation may result from selective loss of fast-conducting large pyramidal cells.[384]

Studies of laryngeal movement and EMG during sequential motor swallowing revealed dysfunction of the central pattern generator as the cause of dysphagia.[15] Increased excitability of the spinal motoneuron pool results in a higher amplitude of the H reflex in the soleus muscle after stimulation of the tibial nerve. Unlike in normal persons, stimulation of the ulnar or median nerve also elicits an H reflex in the intrinsic hand muscles. Similarly, stimulation of the peroneal nerve reflexively activates the extensor digitorum or tibialis anterior muscle. Although patients may experience few or no paresthesias during ischemia of the arm and after its release, the changes in axonal properties in ALS differ from the ischemia resistance seen in diabetes mellitus (see Chapter 10-4).[256]

DIAGNOSTIC CRITERIA

A variety of focal or diffuse neuropathic disorders may mimic ALS. A set of traditional electrophysiologic criteria proposed early to avoid falsely diagnosing this fatal disease included the following[213]: (1) fibrillation and fasciculation potentials in at least two muscles innervated by different nerves and roots in each of three limbs, or in two limbs and the head; (2) reduction in number and increase in MUP amplitude and duration; (3) normal electrical excitability of the surviving motor nerve fibers; (4) motor fiber conduction velocity within the normal range in nerves of relatively unaffected muscles and not less than 70% of the average normal value according to age in nerves of more severely affected muscles; and (5) normal excitability and conduction velocity of afferent nerve fibers even in severely affected limbs.

Although specific disease-modifying therapy has not evolved, symptomatic treatments provide considerable benefit.[37,40] It has thus become increasingly more important to diagnose ALS early in the natural history of the disease to initiate the best management when a large population of motoneurons still remains viable. In this context, more recent studies have raised some concern that the classical diagnostic criteria may preclude earlier acceptance of many ALS patients into therapeutic trials.[18] To accommodate this need, the World Federation of Neurology (WFN) established El Escorial criteria in 1994[55,232,392] and its revision, Airlie House criteria, in 1998 primarily using clinical findings. To incorporate electrodiagnostic characteristics in the existing clinical document, the International Federation of Clinical Neurophysiology (IFCN) more recently sponsored a consensus conference, which convened on Awaji Island in Japan.[76,77]

While adhering to the general principles[72,213] established by the El Escorial and Airlie House criteria,[41] the panel made a new initiative to equate the EMG changes of denervation to clinical features of neurogenic change. In this modification, abnormalities may come from either clinical or neurophysiological studies within a single limb, to fulfill the requirement as set out in the general instructions (Table 22-1). This interpretation would render obsolete the imprecise category previously called "Laboratory Supported Probable ALS." Furthermore, in the absence of fibrillation potentials and positive sharp waves, the presence of fasciculation potentials should serve as evidence of ongoing

Table 22-1 Awaji-Shima Consensus Recommendation for the Application of Electrodiagnostic Test to the Diagnosis of Amyotrophic Lateral Sclerosis, as Applied to the Revised El Escorial Criteria

1. PRINCIPLES (FROM THE AIRLIE HOUSE CRITERIA)
The diagnosis of amyotrophic lateral sclerosis (ALS) requires *(A) the presence of* (1) evidence of *lower motor neuron (LMN) degeneration* by clinical, electrophysiologic examination (2) evidence of *upper motor neuron (UMN) degeneration* by clinical examination, and (3) *progressive spread of symptoms or signs* within a region or to other regions as determined by history, physical examination, or electrophysiologic tests *(B) the absence of* (1) *electrophysiologic or pathologic evidence of other disease processes* that might explain the signs of LMN and/or UMN degeneration, and (2) *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiologic signs
2. DIAGNOSTICS CATEGORIES
Clinically definite ALS is defined by *clinical or electrophysiologic* evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions. *Clinically probable ALS* is defined on *clinical or electrophysiologic* evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs *Clinically possible ALS* is defined when *clinical or electrophysiologic signs of* UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded

(From de Carvalho, Dengler, Eisen, et al.[76])

denervation in muscles showing evidence of chronic neurogenic change. This agreement would obviate the need for the often difficult search for spontaneous single muscle fiber discharges in patients with clinically evident features of ALS, in particular, in cranial-innervated muscles of normal bulk and strength, which may or may not show fibrillations potentials and positive sharp waves.

The Awaji criteria incorporate the WFN principle to divide the body into bulbar/cranial, cervical, thoracic, and lumbosacral regions. Electrophysiologic tests should establish a combination of active and chronic denervation in one, two, and at least three of the four parts for possible, probable, and definite diagnosis of ALS. The criterion calls for abnormalities of at least two muscles innervated by different roots and peripheral nerves when testing the cervical or lumbosacral region. The evidence of denervation of one muscle suffices for the other parts, for example, the tongue or trapezius[332] for the bulbar/cranial region and paraspinal or abdominal muscles[394] for the thoracic region. The presence of fasciculation potentials counts as evidence of denervation if found in conjunction with neurogenic MUPs. Their absence should raise doubts, although it does not rule out the diagnosis. This proposal has since gained general acceptance based on a number of critical assessments to test

whether the new criteria facilitates the early diagnosis of ALS.[19,29,56,75,77,85,98,127,206,252]

Typical cases have asymmetric and multifocal abnormalities. The involvement of upper and lower limbs serves to differentiate this entity from a syrinx or spondylosis with segmental lesions. Optimal selection of the muscles can minimize the ambiguity especially when studying cranial involvement.[295] In the limbs, examining the flexor pollicis longus rather than the thenar or hypothenar muscles circumvents the possible effect of compressive neuropathies, such as the carpal tunnel syndrome (CTS) or tardy ulnar palsy. Similarly, denervation of the extensor digitorum brevis may result from nerve entrapment by a tight shoe. Assessment of thoracic paraspinal muscle helps to distinguish this entity from other disorders such as combined cervical and lumbar spondylosis.[79,233] Studies should include EMG, sensory and motor NCS, as well as the assessment of muscle strength using a standard tool. Sparing of the sensory nerves provides an important clue, especially if demonstrated in one of the weaker limbs. When appropriate, tests of NMT with either repetitive stimulation or SFEMG help establish recent reinnervation and immature endplates, which tend to indicate an active disease process and a poor prognosis.

Progressive Muscular Atrophy

In the rare PMA, or syndrome of Aran-Duchenne, clinical signs and symptoms suggest a selective disorder of the anterior horn cells, although pathologic studies often show some changes in the corticospinal tract as well.[175,310] Compared to common cases that occur sporadically, familial forms, reported in a small percentage, have a more benign course. Atrophy and weakness of the muscles develop without accompanying features of spasticity or other evidence of upper motoneuron involvement. The patients initially have asymmetric wasting and weakness of the intrinsic hand muscles. They then develop atrophy of the shoulder girdle, bulbar, and lower-limb muscles. Less commonly, the clinical signs may resemble CMT disease or peroneal nerve palsy, with preferential involvement of the anterior leg compartment in early stages. Diaphragmatic paralysis, although rare, may cause respiratory insufficiency as a prominent presenting symptom. Despite generalized wasting and weakness, the stretch reflexes usually remain normal or only slightly decreased. The disease runs a slower course than the classic ALS. Nonetheless, unremitting and progressive symptoms and signs lead to eventual demise, often from aspiration pneumonia.

Progressive Bulbar Palsy

Signs and symptoms that predominantly involve the bulbar muscles justify the name *PBP*. The presence of disease in siblings suggests an autosomal recessive form of inheritance.[20] The disease usually begins in the fifth or sixth decade with initial symptoms of progressive dysarthria and dysphagia. The tongue becomes atrophic with visible fasciculations. Troublesome signs include pooling of saliva, nasal regurgitation of fluids, and inability to chew or swallow. Most patients eventually develop signs of pseudobulbar palsy from lesions affecting the brainstem at higher levels or cerebral cortex. Despite often localized initial symptoms, widespread motoneuron involvement ensues in the terminal stage. Thus, the diagnosis usually denotes merely the bulbar onset of ALS in many instances,[271] unlike adult-onset Hallervorden-Spatz syndrome, which mimics PBP without progression of symptoms.[368]

Primary Lateral Sclerosis

Patients with PLS with an ascending progression of symptoms form a distinct clinical subgroup.[400] Serial studies of MRI findings[329] and pathologic studies[327] in typical cases show selective loss of the corticospinal and corticobulbar tracts sparing the anterior horn cells. The clinical signs include spasticity, diffuse hyperreflexia, Babinski signs, and pseudobulbar palsy. The degree of severity and manner of progression vary between genetic types and between different families with the same genetic abnormalities.[120] In some cases of PLS, TMS may reveal a markedly prolonged CCT.[209] Neither EMG nor motor or sensory NCS discloses clear abnormalities. These negative findings and slow clinical course distinguish PLS from other types of MND as a distinct entity.

In the conspicuous absence of atrophy and weakness of distal musculature, the disease may simulate cord compression with a spastic paraparesis. Hereditary spastic paraplegia, which also mimics PLS, comprises a heterogeneous group of neurodegenerative disorders, characterized by slowly progressive weakness and spasticity of the lower limbs.[198] In one series,[140] ALS patients, initially diagnosed as PLS, inevitably developed EMG findings of denervation, which occurred within 4 years of symptom onset in 77%. A 4-year span of EMG studies, therefore, can usually differentiate clinically pure PLS from upper motoneuron dominant ALS. Reported cases of PLS seen in *SOD1*-negative familial ALS kinship also suggest possible pathophysiological link between these two entities.[42]

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) includes a group of inherited disorders in which axons of the corticospinal tract either fail to develop normally or undergo progressive degeneration. Electrophysiologic evaluation shows diffuse central nervous system involvement, sparing the peripheral nerves.[236] In one series,[215] TST revealed normal value for corticospinal projection to the upper limbs in all 15 patients with pure HSP. The subgroups include autosomal dominant HSP,[241,318] autosomal recessive HSP with thin corpus callosum,[46] and infantile ascending HSP.[220]

Familial Disorders with Geographic Predilection

Geographic foci of MND described in the literature include the island of Guam,[38] Kii Peninsula of Japan,[212] and Ryukyu Island south of Japan.[203] Epidemiological studies have revealed a number of other smaller clusters.[63] The Guamanian cases in the Chamorro population[134] show a high familial incidence. Nearly 10% of the adult population on the island died of the disease. The parkinsonian-dementia complex affects the same population, but the two entities have no etiologic relationship. Other reported associations with familial MND include presenile dementia[255] and colonic neoplasia.[322]

Early studies may have underestimated the incidence of familial cases of juvenile and adult onset with variation of penetrance.[391] Some of these kindreds have a mixed pattern of amyotrophy such as motoneuron involvement with pyramidal signs[89] and upper-limb amyotrophy, spastic paraplegia, and pseudobulbar palsy.[151] In contrast to the age-dependent incidence of sporadic cases, familial ALS[54] has an age of onset distributed about a mean of 46 years.[343] Genetic analysis initially suggested a role for free radicals in relation to one gene, *SOD1*, in the disease process. Other mechanisms examined to explain selective motoneuron death include cellular homeostasis of copper and calcium in the context of oxidative stress, protein aggregation, glutamate excitotoxicity, and apoptosis.[153]

3. SPINAL MUSCULAR ATROPHY

Of all the genetically determined neurologic disorders of childhood, SMA, characterized by degeneration of anterior horn cells, has one of the most devastating outcomes.[201] In a series of 108 patients seen in the Mayo Clinic between 1955 and 1975, the mortality rate reached 31% with a mean age of 65 months at the time of death.[210] Only 35% of these patients could walk unassisted. Classifying childhood SMA into Types I, II, and III has now gained wide acceptance[261]: SMA I with onset in the first month of life, SMA II by 18 months, and SMA III thereafter. In addition, SMA IV denotes adult onset after age 30 years (Table 22-2).

The disease shows an autosomal recessive trait with deletion of the telemetric survival motoneuron gene 1 (*SMN1*) on chromosome 5q13 in more than 95% of infantile cases.[64,111,266] Some adult-onset cases have the same deletion. Patients retain at least one copy of the centrometric form, survival motoneuron 2 (*SMN2*), which differs from *SMN1* by a single point mutation in axon. Although the *SMN2* copy number could provide prognostic indications, clinical discrepancies still exist among patients.[285] Apart from this well-defined entity, SMA forms a clinically and genetically heterogenous group of disorders, including adolescent SMA with

Table 22-2 Distinguishing Features of the Various Forms of Proximal Spinal Muscular Atrophy

TYPE		AGE (USUAL)		ABILITY TO SIT	FASCICULATIONS	SERUM CREATINE KINASE
		ONSET	SURVIVAL			
I	Infantile	<9 months	<4 years	No	+/–	Normal
II	Intermediate	3–18 months	>4 years	Yes/No	+/–	Normal
III	Juvenile	>2 years	Adulthood	Yes	++	Elevated
IV	Adult	>30 years	50 years +	Yes	++	Elevated

(Modified from Kloepfer and Emery.[197])

calf hypertrophy,[396] distal SMA, also known as spinal-type Charcot-Marie-Tooth (CMT) disease,[371] and dominant SMA with lower-limb predominance.[156] Thus, in addition to SMN, other genes may cause or influence the SMA phenotype. No consensus has emerged whether various subdivisions represent independent entities or a spectrum of the same disorder.

Typical features (Table 22-2)[197] separate Type I, rapidly progressive infantile Werdnig-Hoffmann disease; Type III, relatively benign late childhood or juvenile Kugelberg-Welander syndrome; and Type IV, midadult form with the onset after 30 years old. An intermediate form between Types I and III constitutes Type II. Despite an overlap in onset, the infantile, juvenile, and intermediate forms have different time courses of the disease and age of death. Other clinically identifiable syndromes include scapuloperoneal and facioscapulohumeral (FSH) SMA, juvenile progressive bulbar palsy, or Fazio-Londe disease, and arthrogryposis multiplex with anterior horn cell disease. The distribution of affected muscles distinguishes ALS with distal weakness from the adult form of SMA with more proximal involvement.

Morphometric analysis of intramuscular nerves showed less marked loss of myelinated nerve fibers and more effective reinnervation compared to ALS.[308] Various types of SMA share the same or similar EMG findings consisting of fibrillation potentials, positive sharp waves, fasciculation potentials, and a large rapidly firing MUP with a late recruitment and reduced interference pattern. In a progressing infantile SMA, needle studies suggest a mixture of denervation and regeneration with a small, temporally varying MUP.

Infantile Spinal Muscular Atrophy

Infantile SMA, first described by Werdnig[388] and Hoffmann,[164] shows an autosomal recessive trait. Parents of affected children have a significantly higher rate of consanguinity than controls. The estimated incidence ranges from 1 in 15,000 to 25,000 live births in Britian.[282] One-third of the affected children have the disease already manifest at birth with decreased fetal movements or congenital arthrogryposis.[283] In the remainder, symptoms begin usually by 3 months, and certainly before 6 months, after birth with delayed developmental milestones and, in some cases, with respiratory distress.[147] In many cases, the infant dies of pneumonia often before the first birthday and usually by the age of 3 years, although not all cases of neurogenic muscular atrophy in infancy follow this acute course. In chronic SMA of childhood, clinical signs first appear at about 6 months but occasionally as late as 8 years of age, with the median age of death later than 10 years.

The clinical features comprise progressive muscle weakness, atrophy of the trunk and extremities, hypotonia, and feeding difficulties. The infants characteristically lie motionless with limbs abducted in the frog-leg position. They cannot hold their head up or sit, having difficulty with any type of locomotion with the loss of previously developed motor skills. About half of the patients have fasciculations in the tongue and, much less frequently, in the atrophic muscles of the limbs. Children with the

chronic form of SMA may develop kyphoscoliosis, contractures of the joints, and dislocation of the hip as the disease progresses. Bulbar signs appear later in the course of the rapidly progressive illness. The facial muscles, often unaffected or affected only mildly, give the infant an alert expression, despite severe generalized hypotonia with reduced or absent stretch reflexes. The patients have normal sphincter functions and intact sensory systems even in the terminal stages of illness.

Muscle biopsy reveals sheets of round atrophic fibers intermixed with clumps of hypertrophic Type I fibers. The chronic form shows fiber type grouping with large Type II fibers and elevated levels of serum creatine kinase (CK). Ultrastructural findings include massive muscle cell elimination by apoptosis and numerous immature muscle fibers. This finding raises the unlikely possibility that muscle cell damage results in secondary death of motoneurons that no longer have the peripheral target.[119]

The incidence of fibrillation potentials and positive sharp waves depends on stage, progression, and severity of the disease. It reached 100% in one study[157] but considerably less in another.[210] Fasciculation potentials occur infrequently, if at all. A late MUP recruitment reflects the loss of anterior horn cells. The maximal effort produces an incomplete interference pattern with a limited number of potentials discharging at a rapid rate. In extreme instances, only one or two motor units fire at 40–50 Hz. As expected from collateral sprouting and a high fiber density, a quantitative survey shows a high-amplitude, long-duration MUP. Regenerating axons, however, may also give rise to low-amplitude, short-duration potentials. In advanced stages, EMG shows either abnormally large or small units,with nothing between the two extremes.[157] The temporal variability of their waveform suggests instability of NMT. Although MUNE (see Chapter 10-2) fell below the control range, it showed no correlation with the severity of weakness.[131]

In general, NCS shows normal or nearly normal velocities with a reduced amplitude of CMAP. In one study,[210] 94% of the patients showed reduction of amplitude to less than 50% of the normal means. Mildly slowed conduction velocities result from the loss of fast-conducting axons. In one study,[222] CMAP had excellent test-retest reliability and moderate to strong correlation with modified Hammersmith Functional Motor Scale. Repetitive stimulation of the nerve at either slow or fast rates causes a decreasing muscle response during ongoing reinnervation, suggesting defective NMT. In contrast to the motor responses, sensory nerve studies usually reveal normal amplitudes and velocities, although occasional patients may have minor electrophysiologic or histologic abnormalities.[311] Rare cases of infantile neuronal degeneration clinically resemble infantile SMA, but NCS, showing marked slowing, helps distinguish this entity as a demyelinative neuropathy with widespread extensive neuronal degeneration.[342]

Juvenile Spinal Muscular Atrophy

The juvenile form of SMA, or Kugelberg-Welander syndrome inherited in an autosomal dominant or recessive fashion, begins with proximal muscle weakness and atrophy in the lower limbs. Two thirds of the patients have a family history. The disease progresses more slowly with less predilections for proximal muscles in the dominant variety than in the recessive type. Compared with the infantile form, it has a later onset throughout childhood or adolescence, but most commonly between the ages of 5 and 15 years. The symptoms initially involve the extensor muscles of the hip and knees and later, the shoulder girdle muscles. Age-related loss of motor function results primarily from loss of muscle strength.[244] Handheld dynamometry provides a reliable measure for longitudinal studies.[245]

The patient has a characteristic lordotic posture with protuberant abdomen, hyperextended knees, hypertrophic calves, and rare involvement of the cranial musculature. One-half of the cases have fasciculations in the proximal muscles. This abnormality affects the legs more than the arms, sparing the distal muscles and the tongue except in the advanced stages. Examination usually reveals hyporeflexia with atrophy but occasionally hyperreflexia and Babinski signs. The disease follows a relatively benign course with frequent surviva l into adulthood, usually necessitating the use of a wheelchair by the mid 30s. A 6-minute

walk test demonstrates motor fatigue as a standardized measure.[258,348] Some patients develop chronic neurogenic quadriceps amyotrophy as a forme fruste of this entity.[28,129] The differential diagnoses otherwise include myositis, muscular dystrophy, and a long-standing cord lesion affecting motor fibers selectively as described in a case of schwannoma.[122]

A modest elevation of serum enzymes remains nearly constant as the disease progresses. This stands in contrast to Duchenne muscular dystrophy (DMD), in which an initially very high level of CK gradually declines later. Muscle biopsy specimens show fascicular atrophy and fiber type grouping characteristic of a neurogenic disorder with occasional mixture of myopathic features. Biochemical and immunocytochemical analyses may help classify chronic SMA, identifying the maturational stage of the muscle at the age of disease onset.[150] A quantitative study using ultrasound has the potential of serving as a measure of disease severity.[393]

An overall incidence of fibrillation potentials ranged from 20% to 40% in one series[158] and 64% in another.[210] More severely affected patients have an even higher percentage, although it does not match the level seen in the Werdnig-Hoffman disease. Complex repetitive discharges (CRDs), if present, suggest a late stage. Spontaneous activities first involve the lower more than upper limbs and proximal more than distal muscles.[158] Voluntary contraction gives rise to a high-amplitude, long-duration MUP, which increases in percentage as the disease progresses, showing a poor recruitment even at maximal effort. Late components indicate the presence of slow-conducting regenerating axons. In advanced cases, small polyphasic potentials also appear, suggesting secondary changes of atrophic muscles. These potentials show constant configuration, unlike the varying waveforms seen in more rapidly progressive infantile cases.[210]

Motor and sensory NCSs, although usually normal, may reveal a moderate reduction in CMAP amplitude. As in Werdnig-Hoffman disease, this abnormality shows a strong correlation to the functional capacity related to the motor system. In one series,[210] bedridden patients constituted 54% when the amplitude fell below half of normal, compared to only 7% in the remainder. The modified Hammersmith Functional Motor Scale serves well in testing children with SMA for clinical trials and follow-up studies.[208]

Juvenile Progressive Bulbar Palsy

Slowly progressive bulbar palsy characterizes this very rare disorder of Fazio-Londe inherited as an autosomal recessive trait. The diagnostic criteria based on a review of 24 children[242] consist of clinical features of a pure motoneuronopathy affecting the bulbar nuclei, exclusion of other causes of progressive bulbar paralysis and neurogenic changes seen in EMG or muscle biopsy. Characteristic findings include ophthalmoplegia, facial diplegia, laryngeal palsy, and other cranial nerve involvements with onset in early childhood. Facial diplegia, if present at birth, suggests other entities such as infantile myotonic dystrophy, infantile FSH muscular atrophy, and Möbius syndrome. Progressive ophthalmoplegia and dysphagia may also develop as late manifestations in some cases of juvenile SMA but not as the presenting signs. Prominent EMG abnormalities seen in bulbar and pontine muscles consist of fibrillation potentials, positive sharp waves, and impaired MUP recruitment.

Scapuloperoneal Spinal Muscular Atrophy

As indicated by the name, a unique pattern of muscular weakness distinguishes this type of SMA from the rest.[93] A form of muscular dystrophy also exhibits the same distribution of weakness with features often indistinguishable from muscular atrophy, prompting some to propose the term *scapuloperoneal syndrome* to include both neurogenic and myogenic forms. Similarly, patients with CMT I may also present as scapuloperoneal atrophy associated with distal sensory loss.[173] In addition to sporadic cases, familial incidences occur showing an autosomal dominant trait. One family had both Werdnig-Hoffmann disease and chronic distal SMA with apparent autosomal dominant inheritance.[34]

This variety of muscular atrophy slowly progresses after its usual onset in early adulthood. Atrophy and weakness initially affect the anterior

tibial and peroneal muscles and later the musculature of the pectoral girdle, producing winging of the scapulae. Some patients develop laryngeal palsy.[93] In most cases, EMG studies demonstrate a low-amplitude, short-duration MUP, fibrillation potentials, and positive sharp waves, whereas NCSs reveal normal motor and sensory responses. Muscle biopsies usually show a mixture of neuropathic and myopathic pattern.

Facioscapulohumeral Spinal Muscular Atrophy

Like the scapuloperoneal SMA, FSH atrophy has a unique distribution of weakness similar to its counterpart, FSH muscular dystrophies. When inherited, it follows an autosomal dominant pattern. Atrophy primarily affects the muscles of the face and pectoral girdle musculature. The weakness begins in early adult life, showing a slowly progressive course. Clinical features resemble those of FSH dystrophy (see Chapter 27-2). As a descriptive term, *FSH syndrome* is used in some cases to suggest an inability to distinguish between the neurogenic and myogenic forms.

Distal and Asymmetric Spinal Muscular Atrophy

Distal SMA resembles CMT I and II except for preservation of stretch reflexes, relative sparing of the upper limbs, and a normal sensory examination. Some of these patients have peroneal muscular atrophy, whereas others suffer from cramps and fasciculations of the calves, showing true neurogenic hypertrophy.[146] In one study of 34 patients,[155] motor and sensory NCS revealed no abnormality. Another study reports three patients from a large family, who had an autosomal dominant scapulohumeral form of SMA.[182] Thedisease progressed rapidly without corticospinal tract dysfunction, leading to death from respiratory failure.

Chronic asymmetric SMA typically shows neurogenic atrophy involving one or more limbs without evidence of pyramidal tract or bulbar dysfunction.[154] Patients with this disease have no evidence of generalized neuropathy, although motor NCS may show a slight slowing associated with muscle wasting. Other entities include chronic segmental SMA of upper limbs either as a familial or a sporadic form[349] and a predominantly cervical form of SMA.[143,227]

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita comprises congenital contractures of at least two different joints and major muscle wasting not associated with a progressive neurologic disorder. The condition may result from a number of different neuromuscular and bony disorders, causing immobilization of the limbs at the time of the embryonic formation of joints.[126] One study describes a dominantly inherited lower MND as the cause of arthrogryposis present at birth.[124] Disorders of the motoneuron probably predominate, although different investigators postulate myogenic or neurogenic origins.[60] In some cases, EMG studies showed the presence of spontaneous discharges such as fibrillation potential and CRD, and reduced number of motor units, which fire rapidly, but no NCS abnormalities.

Focal Amyotrophy

Distal amyotrophy of the upper limb develops in a heterogenous group of disorders.[97,276,281] Those reported from Japan and, to a lesser extent, elsewhere as Hirayama disease[141,162,169] have distal and segmental muscular atrophy of juvenile onset with atopic tendency in some cases.[195] The clinical features include male preponderance, localized atrophy uniquely affecting the hand and the forearm, and sparing the lower limbs and cranial nerves. The disease primarily involves C7, C8, and T1 myotomes, showing characteristic mechanovascular changes in flexion MRI of the cervical spine.[110] Some series include bilaterally symmetric form of the disease.[132,294] The age of onset, distribution of atrophy, and benign course, despite initially rapid progression, distinguish it from MND. Needle studies show a large-amplitude and long-duration MUP, which recruits poorly. Abnormalities of SFEMG, if found over both arms and legs, suggest a more generalized disturbance than would appear

clinically.[52] In one study,[230] motor NCS revealed reduced CMAP amplitudes primarily affecting the ulnar as compared to median nerve distribution, making the amplitude ratio between the two smaller than normal. This stands in contrast to a reverse pattern of hand muscle involvement seen in ALS. In one study,[293] median and ulnar nerve somatosensory evoked potentials (SEPs) showed peripheral and segmental spinal abnormalities.

Rare, monomelic amyotrophy with similar clinical features may follow trauma and immunization in children.[277] Atrophy involving part of the body may not necessarily justify the diagnosis of a focal MND without first excluding other possibilities. Alternative diagnoses include spinal cord tumors, neurofibromatosis,[358] radiculopathy, plexopathy, and mononeuropathy. Sensory abnormalities, if identified clinically or by electrophysiologic means, help differentiate these conditions from MND. In benign monomelic amyotrophy reported in India and elsewhere, patients typically develop involvement confined to one leg without progression over many years.[259,273]

Spinobulbar Muscular Atrophy (Kennedy's Disease)

In male patients with X-linked recessive spinobulbar muscular atrophy (SBMA) or neuronopathy,[191] disease severity correlates with the size of the tandem CAG repeat in the androgen receptor gene. Heterozygous women show no symptoms, whereas homozygous patients may have occasional muscle cramps and twitches.[317] Clinical features in men consist of mild facial weakness, facial fasciculations, severe atrophy of the tongue, postural hand tremor, hyporeflexia, testicular atrophy, gynecomastia, and a high serum CK level.[50] Most patients have slowly progressive clinical course with proximal limb weakness, although some families may have an early onset and rapid deterioration, requiring assisted ambulation before age 30.[102] Some patients may develop jaw drop, which superficially resembles that of MG,[344] but a rare association between these two disorders has also occurred.[35] In some cases, laboratory tests reveal hyperlipoproteinemia, hypobetalipoproteinemia,[382] and hyperestrogenemia.[366] Autopsy studies show marked depletion of the spinal and brainstem motoneurons with the exception of the 3rd, 4th, and 6th cranial nerves.[331]

Electrophysiologic abnormalities include fibrillation potentials, CRD, a large MUP firing rapidly, reduced values of MUNE as tested by modified statistical method,[218] and absent or low-amplitude SNAP despite relatively preserved sensation in clinical testing.[243] These abnormalities indicate a very slowly progressive disease of motoneurons associated with a sensory neuronopathy, sometimes mimicking an acquired process.[116] Selective sparing of jaw-jerk, relayed by mesenchalic nuclei located in the central nervous system, stands in contrast to markedly affected other trigeminal reflexes as expected from a trigeminal ganglionopathy. In one study,[8] laser evoked potential showed marked abnormality indicating involvement of pain pathways. In another study,[235] quantitative sensory studies and sweat tests showed severe abnormalities of tactile thresholds and mechanical pain perception. These together with severe reduction of sweat drops confirm the extensive involvement of large- and small-size sensory neurons. In one study,[374] TST and threshold tracking TMS studies reiterated normal corticomotoneuronal function.

Despite the clinical resemblance, this entity carries a much better prognosis than an MND. In one series, 2% of patients initially diagnosed as having an ALS showed the CAG repeat expansion, underscoring the importance of genetic screening.[278] Differential diagnoses also include syringobulbia, amyloidosis,[303] Tangier disease,[274] Sjogren's syndrome, basilar meningitis, Sandhoff disease, or hexosaminidase A and B deficiency,[354] various motoneuronopathies,[2] autosomal dominant form of SMA with gynecomastia,[174] and sporadic bulbospinal muscular atrophy (BSMA).[176,376]

4. CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease (CJD)[66,180] has proven its infectivity both in humans and chimpanzees.[137]

The transmissible pathogen, called prion to distinguish it from viruses, produces no immune response and resists the action of enzymes that destroy RNA and DNA. The conversion of the normal cellular protein to the infectious form involves a conformational change in the protein structure.[297] Accidental inoculation occurred after a corneal transplant[100] and a surgical procedure with contaminated stereotactic electrodes.[23] Brain tissue from dying patients also causes scrapie like encephalopathy in goats.[149] The pathologic features resemble those of kuru, a transmissible disease seen in New Guinea,[136] and consist of widespread spongiform degeneration with loss of nerve cells in the cortex, basal ganglia, and spinal cord.

The disease may have a sporadic or familial form.[279] It affects both sexes equally with onset in middle age or later. Following vague prodromal symptoms, the patient develops mental deterioration, anxiety, depression, memory loss, and confusion. A variety of neurologic disturbances indicate cortical degeneration and upper and lower motoneuron involvement. The most commonly encountered features include weakness, rigidity, spasticity with hyperreflexia, muscular atrophy, incoordination, tremor, and visual loss. Muscle wasting and fasciculations during late stages of illness mimic the typical appearance of MND. The patient usually has two types of negative myoclonus usually in the early stages, one associated with a characteristic electroencephalographic (EEG) abnormality of high voltage sharp and slow complex, and the other, induced by electrical stimulation as cortical reflex.[238] The disease follows a rapidly progressive course, leading to severe dementia, blindness, lethargy, and eventually coma and death within a year after onset. The evidence of denervation indicates muscular atrophy with involvement of motor cells in the medulla and spinal cord. Motor and sensory NCS reveals no abnormalities unless the patient has a compressive or diffuse nutritional neuropathy in chronic stages.

Electromyographers have increasing concern about the risks involved in examining patients with CJD, necessitating the use of double gloves. With this disease, in contrast to the acquired immunodeficiency syndrome (AIDS), exposure to saliva, nasopharyngeal secretions, urine, or feces should cause no special alarm. After such contact, recommended procedures consist of thorough washing of hands and other exposed parts with hospital detergent or ordinary soap and discarding the needle electrodes used for study after incineration (see Chapter 3-2)

5. POLIOMYELITIS AND POLIO-LIKE SYNDROME

Poliomyelitis no longer prevails as summer epidemics in developed countries, but sporadic, mostly vaccine-associated cases still occur throughout the year.[73,330,352] Pediatric monomelic amyotrophy still suggests a wild-type poliovirus myelitis, "polio-like" virus myelitis or vaccine-associated paralytic poliomyelitis.[240] Most clinical illness results from infection by Type I virus, but at times also by Types II and III. The intestinal and respiratory tracts initially invaded by the virus transmit the agent to the nervous system via the bloodstream. Affected anterior horn cells in the spinal cord and brainstem undergo degenerative changes, causing an inflammatory reaction in the meninges. Isolation of the poliomyelitis virus confirms the diagnosis in about 90% of patients with paralytic illness.

The clinical features of systemic infection include flulike symptoms such as fever, general malaise, diarrhea, and loss of appetite. Only a small percentage of patients with meningeal irritation complain of headaches, a stiff neck, and vomiting. In some cases, paralytic illness follows the prodromal symptoms. It progresses over a period of several days to a week, affecting one or more limbs or, in a small number of children, bulbar musculature. Respiration weakens with the involvement of the diaphragm and intercostal and abdominal muscles, necessitating assisted ventilation in advanced cases. Neurologic examination shows widespread atrophy, diminished or absent stretch reflexes in the affected limbs, and a normal sensory system. Some survivors of polio may have sensory derangement evidenced by SEP studies.[296] The spinal fluid examination reveals mild pleocytosis.

During the acute phase of poliomyelitis, EMG initially shows only a reduced recruitment pattern.

Fibrillation potentials develop as the axons degenerate, and then diminish concomitant with the appearance of a large-amplitude, long-duration MUP, signaling reinnervation. Patients with a history of restricted clinical weakness usually show widespread chronic, partial denervation involving clinically unaffected muscles.[39,390] Similarly, clinically involved spinal segments often show a large MUP bilaterally even in cases with the history of unilateral weakness. If small atrophic muscle fibers survive despite inadequate reinnervation, low-amplitude fibrillation potentials persist many years after an acute episode. A motor NCS reveals normal velocities but a reduced CMAP amplitude approximately in proportion to the degree of muscle atrophy. Electrical stimulation of the arm nerves may produce muscle response in the atrophic thigh muscles, suggesting abnormal spinal circuit.[113]

Considerable recovery takes place even if severe generalized weakness develops. An excessive use of remaining motor units leads to Type I muscle fiber dominance, presumably as the result of muscle fiber transition from Type II.[32] Even clinically unaffected muscles show increased jitter and fiber density as well as a large macro MUP, indicating pronounced, and often unstable, reinnervation to compensate for the loss of motoneurons.[103,229,237] The results of MUNE (see Chapter 10-2) provide a more sensitive measure of lost motor units than the summated CMAP amplitude.[334] Weak muscles may have only a few extremely large units. A sequential evaluation using macro EMG revealed up to a 20-fold increase in MUP amplitude before exceeding its capacity.[145] A supervised resistance training program can lead to improved dynamic strength of both symptomatic and asymptomatic muscles.[336] Reinnervation often adequately compensates for the ongoing loss of spinal neurons particularly in patients whose condition has stabilized.[177,338] The new muscle weakness may also result from reduced force per unit of muscle area, reflecting impaired ability to activate the muscle fibers.[17]

Postpolio syndrome refers to a decline of muscle function usually occurring 30 to 40 years after partial or complete recovery from acute polio episode.[269] Autopsy findings of the spinal cord[287] or EMG studies[301] revealed no difference between the patients with stable postpoliomyelitis deficits and those with postpoliomyelitis progressive muscular atrophy. Those with a more severe illness, however, tend to develop postpolio weakness.[1] If poliomyelitis has already depleted motoneurons, minor additional damage to the surviving cells with age might result in exaggerated clinical signs. In addition, the diseased neurons may have a certain predisposition to senile degeneration, or some surviving motoneurons may have incorporated too many muscle fibers from the denervated units beyond their metabolic capability.[115,359] In addition, ALS can rarely develop in the postpolio population starting de nova rather than as evolution of postpolio syndrome.[313]

Routine electrophysiologic or morphologic techniques usually fail to differentiate weakening muscles in this syndrome from previously affected but stable muscles.[216] Monitoring muscle function with voluntary activation, however, helps assess the long-term effect of polio myelitis quantitatively.[3] A careful follow-up study of poliomyelitis patients with apparent late progression has shown only a modest decline in function.[333] Moderate-intensity strength training may improve voluntary motor drive.[51]

Even with adequate reinnervation, premature degeneration of diseased anterior horn cells may lead to the reappearance of spontaneous discharges. Individual muscle fibers may drop out if a motoneuron can no longer meet the increased metabolic demand of densely populated motor units after reinnervation. In survivors of poliomyelitis, SFEMG may show a significant increase in jitter and fiber density without neurogenic blocking. These findings of defective neuromuscular transmission probably represent disintegration of the reinnervated motor units with aging. In contrast, an increase in jitter with high-frequency stimulation implies ineffective conduction along immature nerve sprouts as the cause of the instability similar to ALS.[360]

A poliomyelitis-like disorder, Hopkins' syndrome, may develop in association with asthma.[165,224,389] The disease predominantly affects boys 10 years old or younger, although it may occasionally involve older children with acute onset of myelitis and asthma attacks after puberty.[166] Acute flaccid monoplegia of an

upper or lower limb accompanies no sensory deficits. Marked atrophy signals a poor prognosis for recovery. Cerebrospinal fluid examination reveals pleocytosis and slight protein elevation, but no rise in poliovirus antibody titers. The lesion may lie in the brachial plexus, but the absence of sensory abnormalities favors the motor roots or anterior horns[389] as the locus of the disease. Despite clinical and EMG similarities to poliomyelitis, the disease can affect previously vaccinated children. In one patient[389] C5 root synkinesis developed between biceps and inspiratory muscles from aberrant regeneration (see Fig. 14-21 in Chapter 14).

Patients with acute hemorrhagic conjunctivitis caused by enterovirus 70 may have polio-like paralysis of the limb and cranial muscles.[378] Early complaints include root pain and weakness. Affected and some clinically unaffected muscles show fibrillation potentials early and a large polyphasic MUP later. A motor or sensory NCS reveals no specific abnormalities. Patients with western equine encephalitis may also show a poliomyelitis-like syndrome associated with the EMG evidence of denervation.[5,319] The clinical spectrum ranges from acute flaccid paralysis, with or without fever, to disabling fatigue.[219,223] Elevated CSF biomarker levels suggest neuronal death and glial pathology.[286]

6. SYRINGOMYELIA

Signs and symptoms of syringomyelia result from cavitation and gliosis of unknown pathogenesis affecting the spinal cord and medulla. The disease may begin at any age, but it most often occurs sporadically or familially in the third or fourth decade, affecting both sexes equally. The patient frequently has other congenital defects such as spina bifida or Arnold-Chiari malformation. Other associated features include scoliosis, trophic changes, and intramedullary tumors found in conjunction with a syrinx. Secondary cavitation may develop after traumatic, vascular, or infectious lesions of the spinal cord. A slowly progressive course extends over a period of many years, although damage to medullary nuclei may lead to a rapid demise. The differential diagnoses include MND, multiple sclerosis, spinal cord tumor, posterior fossa lesions, and anomalies of the cervical spine.

The cavities vary in location and in longitudinal extent but most frequently affect the cervical cord, which may distend with the fluid or, conversely, flatten. Irregularly shaped gliosis and cavities, although ordinarily located near the central canal, may involve the entire white and gray matter, affecting motor and sensory cells and different fiber tracts in various combination. Damage to the anterior commissure of the spinal cord causes the characteristic dissociation of sensory abnormalities. Other common sites of involvement include the posterior and lateral funiculi, with damage to the corticospinal tract.

Clinical symptoms and signs depend on the location and extent of the pathologic changes. A syrinx in the cervical region causes atrophy and weakness of intrinsic hand muscles, sometimes mimicking a peripheral nerve lesion.[316] Patients often have dissociated loss of pain sensation with preservation of light touch in the lower cervical or upper thoracic dermatomes. A syrinx at the root entry zone causes a segmental loss in all modalities of cutaneous sensation, whereas lesions of the posterior column selectively diminish the vibratory sense. Other signs include spasticity, hyperreflexia, Babinski signs, ataxia of the lower limbs, a neurogenic bladder, and a wide spectrum of involuntary movements.[267] A syrinx may affect the lumbosacral region alone or in association with lesions at the cervical level. The clinical features, then, include muscular atrophy, dissociated sensory loss of the lower limbs, and paralysis of the bladder. The loss of stretch reflexes suggests lesions at the root entry zone or the anterior horn cells in the lumbar region.

Syringobulbia denotes a syrinx formed in the medulla that commonly involves the descending nucleus of the 5th nerve and nuclei of the lower medulla either unilaterally or bilaterally. Common features include atrophy of the tongue, loss of pain and temperature sensation in the face, abnormalities of extraocular muscles, and respiratory difficulties. A lesion of the spinal accessory nuclei causes atrophy of the trapezius and sternocleidomastoid muscles. Spastic paraparesis results from interruption of the upper motoneuron tracts.

Needle studies reveal fibrillation potentials and positive sharp waves in the atrophic muscle. Sparing of the lower limbs serves to distinguish syrinx from MND. Other abnormalities include continuous motor unit activity, synchronous discharges of MUP, respiratory synkinesis, and myokymic discharges.[268] A motor NCS shows normal velocities but reduced CMAP amplitudes in the affectedlimb. In some patients,[226,306] motor evoked potentials (MEPs) induced by TMS uncovered spinal cord dysfunction. The finding of a normal SNAP, despite clinical sensory loss, confirms a preganglionic involvement of the sensory pathway. In these instances, SEP studies may reveal central conduction abnormalities (see Fig. 19-14 in Chapter 19). One study showed absent or reduced N13 recorded by posterior-anterior cervical montage in 83% of median nerve SEP despite normal P14 and N20 recorded using a noncephalic reference.[304] Pain-related SEP elicited by CO_2 laser stimulation also shows clear abnormalities in most cases, thus providing a useful measure in the evaluation of dissociated sensory loss.[186] A lesion of the spinal tract or nucleus of the trigeminal nerve causes an afferent abnormality of the blink reflex with the absence of R2 bilaterally after stimulation of the supraorbital nerve on the affected side of the face (see Figs. 8-17 and 8-18 in Chapter 8).

7. MULTIPLE SCLEROSIS

In multiple sclerosis, a demyelinating lesion with relative preservation of axis cylinders primarily affects upper motoneurons.[383] Clinical presentations vary, although, the classical triad consists of nystagmus, scanning speech, and intention tremor. Patients also have symptomatic fatigue and muscle weakness. The lesion may also involve the autonomic nervous system causing incontinence as a characteristic feature of the disease. In one series, 3.9% of 282 newly diagnosed cases of multiple sclerosis developed acute radicular pain as a presenting symptom.[251] Demyelination in the ventral root exit zone probably accounts for lower motoneuron dysfunction and evidence of denervation.[323]

Depending on the site of demyelination, different neurophysiologic techniques can provide an accurate measure of impaired signal transmission. These include, in addition to visual and brainstem auditory potentials, blink reflex (see Chapter 8-6), SEP (see Chapter 19-6), MEP (see Chapter 20-8), and autonomic evaluation (see Chapter 10-1). Conventional and some specialized nerve conduction studies have revealed subclinical peripheral nerve involvement seen in about 10% of patients.[399] One study of motor nerve recovery cycle revealed reduced supernormality, increased refractoriness, and prolonged absolute and relative refractory periods.[30] In another study,[337] laser-evoked potential, which assesses spinothalamic tract, showed more abnormalities than SEP, which primarily evaluates the dorsal column. Administration of 4-aminopyridine[128] or intravenous methylprednisolone[171] may increase MEP amplitude in some patients.

8. OTHER MYELOPATHIES

Arteriovenous malformations of the spinal cord give rise to a characteristic pattern of clinical and physiologic changes. In one study of 24 patients, the lesion involved the thoracic cord in 7, conus and cauda equina in 10, and other levels in 6.[12] Electrodiagnostic studies revealed changes of tibial SEP in 7 of 8, nerve conduction abnormalities in 10 of 23, and evidence of denervation in 17 of 22. Isolated paraplegia may develop from a remote stab wound probably as the result of radicular artery interruption in combination with systemic hypotension.[190] Spontaneous abdominal compartment syndrome may cause painful paraplegia.[160] Infarction of the conus medullaris may abolish lower-limb F waves as an early electrophysiologic finding.[61] The anterior spinal artery syndrome results from ischemic cord infarction, which, during acute stage, may also abolish the F wave on the affected side below the level of involved segment.[6] A high cervical cord infarction may reduce or abolish R2 of the blink reflex, indicating dysfunction of the spinal tract of the trigeminal nerve.[272]

Some patients with human T-lymphotropic virus I (HTLV-I) infection develop chronic progressive myelopathy[48,225] called HTLV-I associated myelopathy (HAM) in Japan and tropical spastic paraparesis (TSP) in South America.[307,365] Autopsies disclose a mononuclear inflammatory

reaction with myelin and axonal destruction involving mostly the white matter of the thoracic spinal cord. A predominantly proximal muscle weakness may result from a concomitant myopathy (see Chapter 27-7).[130] Electrophysiologic abnormalities in HAM include segmental denervation of paraspinal muscles,[11] SEP changes reported in 86% of patients,[47] and peripheral nerve dysfunction seen in 43%.[25] Pain-related SEP following CO_2 laser stimulation also shows subclinical abnormalities of the spinothalamic tract in most patients.[185]

In traumatic quadriplegia, spontaneous activity detected in muscles well below the level of spinal cord injury indicates the loss of motor axons in the region several segments caudal to the level of injury.[22] These findings provide supportive evidence for transsynaptic neuronal degeneration as the result of a rostral lesion, which effectively blocks descending impulses. Upper-limb effort does not increase maximal voluntary muscle activation in individuals with incomplete spinal cord injury.[168] Multichannel EMG can establish recovery of voluntary movement after acute spinal cord injury.[43] Selective calf weakness usually suggests intraspinal pathology rather than peripheral neuropathy, which characteristically involve muscles innervated by the peroneal nerve.[33] Muscles from individuals with chronic spinal cord injury show less resistance to fatigue.[26]

Intervertebral recording of spinal SEP (see Chapter 19-6) help elucidates clinically relevant structural changes in cervical spondylotic myelopathy,[351] directing surgical intervention to the appropriate level of concern. Ascending axonal volleys analyzed at multiple sites after epidural stimulation reveal a high incidence of focal conduction block at C3, 4 or C4, 5 in the older group aged over 70, and at C5, 6 and C6, 7 in the younger group.[350] Compressive lumbar myelopathy may mimic a segmental presentation of MND.[196] Patients with acute cervical spinal cord injury[68] or transverse myelitis[346] may show a complete loss of lower-limb F waves during spinal shock followed by gradual recovery.

Subacute combined degeneration results either from a low serum vitamin B12 level or abnormalities of the binding protein.[305] A prolonged central conduction time detected by SEP studies[96] may improve after cyanocobalamin therapy without a concomitant recovery of peripheral nerve function.[356] These findings suggest demyelination in the posterior column and axonal degeneration in the peripheral nerve.

Myelopathy may follow influenza vaccination in patients treated with chronic immunosuppression.[217] Other infectious agents associated with myelitis include Lyme borreliosis [200] and toxoplasmosis, especially in patients with AIDS,[161] who may also develop AIDS-associated myelopathy.[340,347]

An epidemic of spastic paraparesis called konzo developed in a drought-affected rural area of Northern Tanzania. Konzo constitutes a distinct upper motoneuron disease probably caused by a toxic effect from insufficiently processed cassava ingested under adverse dietary circumstances.[167] In this entity, TMS may fail to elicit an MEP, but other neurophysiologic studies remain largely normal.[364]

Irradiation of the lumbosacral spinal cord for malignancy may cause monomelic amyotrophy as the result of selective injury to the lower motoneuron.[214] Other rare causes of transverse myelitis include intravascular lymphomatosis, which may present as an ascending cauda equina, conus medullaris syndrome,[264] electrical injury associated with delayed conduction of central motor and sensory pathways as tested by SEP and MEP,[357] and odontoid fractures, which may account for delayed progressive myelopathy years after a forgotten injury.[67]

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Radiculopathies and Plexopathies

Abbreviations: CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, CTS—carpal tunnel syndrome, EMG—electromyography, HNPP—hereditary neuropathy with predirection to pressure palsy, MEP—motor evoked potential, MMN—multifocal motor neuropathy, MRI—magnetic resonance image, MUNE—motor unit number estimation, MUP—motor unit potential, NCS—nerve conduction studies, SEP—somatosensory evoked potential, SNAP—sensory nerve action potential, TOS—thoracic outlet syndrome

1. INTRODUCTION

Proximal lesions at the level of the root or plexus affect either the motor or sensory fibers or both. The features of motor involvement include weakness and atrophy of the muscle, hyporeflexia, fatigue, cramps, and fasciculations. Sensory abnormalities, which usually accompany motor deficits, sometimes dominate the picture. Such symptoms range from mild distal paresthesias to complete loss of sensation, dysesthesias, and severe pain. As seen in the carpal tunnel syndrome (CTS), peripheral lesions can mimic proximal abnormalities. Selective damage to the root or plexus usually results from trauma, mechanical compression, and, less frequently, neoplastic and inflammatory processes such as polyradiculopathy associated with Sjogren's syndrome.[154] Other possibilities include methotrexate-induced Epstein-Barr-virus-related lymphoproliferative disorder[101] or diffuse infiltrative lymphocytosis in HIV patients.[34] Thus, a relatively short list

makes up the differential diagnoses of proximal lesions compared with the much wider range of possibilities for distally prominent involvement seen in neuropathies (see Chapter 24-1).

In the evaluation of radicular or plexus injuries, electrophysiologic studies help delineate the distribution of the affected muscles to localize the lesion and elucidate its extent and chronicity.[220] A combination of clinical, laboratory, and electrodiagnostic features determine the level of a radicular involvement. Some studies report a high correlation among evidence of denervation in electromyography (EMG), myelographic abnormalities, and surgical findings.[113] In one series[129] comparing EMG and magnetic resonance imaging (MRI), 60% of patients had abnormalities in both, whereas the remaining 40%, in only one of them. Broad and frequently anomalous segmental innervations challenge the clinician in attributing any pattern of clinical or EMG findings to a specific spinal level.

In the affected muscle, needle examination initially reveals poor recruitment of motor units indicating structural or functional loss of axons. Subsequent appearance of fibrillation potentials and positive sharp waves in 2–3 weeks suggests axonal degeneration. A low-amplitude, polyphasic motor unit potential (MUP) has temporal instability during active regeneration of motor axons. In contrast, a high-amplitude, long-duration MUP with stable configuration appears later after completion of reinnervation. Nerve conduction studies (NCSs) may reveal a reduction in amplitude of muscle or sensory response in appropriate distribution, elucidating the site of involvement. Some authors advocate the use of F waves,[64] H reflex, and somatosensory evoked potentials (SEPs) for assessing radiculopathies, but without general agreement.

2. CERVICAL AND THORACIC ROOTS

Cervical radiculopathy causes pain in the neck and arm with a combination of sensory loss, weakness, and reflex changes in the affected nerve root distribution.[21,30] Anatomic peculiarity stems from a mismatch in number for the 8 cervical roots and versus 7 cervical vertebrae. Whereas C1 through C7 emerge above their respective vertebrae, C8 exits between the C7 and T1 vertebrae. In a compressive lesion of C5, pain in the interscapular region radiates along the lateral aspect of the arm to the elbow. With involvement of C6, pain extends over the shoulder to the lateral aspect of the arm and forearm, and thumb. Pain induced by irritation of C7 typically involves the entire arm and forearm with radiation into the long finger, and to a lesser extent, index and ring fingers. Less commonly encountered C8 pain radiates to the ring and little fingers, and T1 root pain, deep in the shoulder, axilla, and medial aspect of the arm. Although sensory symptoms help evaluate radiculopathy, they often fail to elucidate the exact level of the lesion because the dermatomes overlap with considerable variability.

The distribution of motor deficits and changes in the stretch reflexes provide more reliable localization. Clinical assessment of radiculopathy depends on testing movements of the arm, which rely on the almost exclusive control by single roots. Recommended maneuvers include 180 degree shoulder abduction (C5), elbow flexion in full and half supination (C6), and adduction of the shoulder, extension of the elbow, and flexion of the wrist (C7).[138] A C8 lesion affects the long extensors and flexors of the fingers and, to a lesser degree, the intrinsic hand muscles, which receive substantial supply from T1. An ulnar nerve lesion spares the median-innervated thenar muscles, whereas a T1 lesion affects all the small hand muscles, and particularly abductor pollicis brevis, according to some reports.[111] Lower cervical root lesion may cause selective finger drop, mimicking the "claw hand" associated most commonly with ulnar nerve and, to a lesser degree, with radial nerve involvement.[28] The abnormalities of certain muscle stretch reflexes assist in determining the level of root lesions, for example, biceps brachii (C5 or C6), brachioradialis and supinator (C6), triceps (C7), and finger flexors (C8).

In addition to traumatic avulsion, common causes of cervical radiculopathy comprise spondylosis and herniated disc.[100] The differential diagnoses include lymphomatous meningitis,[69] a rare anomalous ectatic vertebral artery,[175] Pancoast tumor with apical lung tumor eroding through the C7 and T1 pedicles,[204] and rare manifestation of intracranial hypertension,[131] or meningeal melanocytoma.[189] Misdiagnosis leads to progression

of neurologic signs and symptoms, and improper mode of therapy. Spinal manipulation performed in the presence of an organic lesion carries the risk of spinal cord injuries.[148] A motor vehicle accident appears to cause a small but significant increase in the frequency of cervical radiculopathy and plexopathy.[24] A disc injury plays no role in a majority of patients with whiplash-associated disorders.[140,155]

Full knowledge of innervation pattern (see Appendix Tables 1-1, 1-2, and 1-3) facilitates EMG studies, which provide an objective means to corroborate the clinical diagnosis of radicular lesions. Clinical findings should dictate which muscles to examine for the optimal identification of the involved root.[105] Abnormalities of the paraspinal muscles help document the involvement of the posterior rami, thus confirming a radicular as opposed to plexus lesion. The length-dependent delay of nerve degeneration would predict the appearance of denervation potentials first in the paraspinal muscle. In practice, however, this time relationship may not necessarily hold. In fact, multivariate estimates in one study[143] showed no correlation between paraspinal muscle abnormalities and symptom duration.

Affected muscles show a reduced recruitment and incomplete interference pattern at the beginning, followed by fibrillation potentials and positive sharp waves, and a high-amplitude, long-duration MUP later in the course of the disease. Preganglionic involvement spares the sensory nerve action potentials (SNAPs) despite the degeneration of motor axons, muscle atrophy, and reduction in amplitude of compound muscle action potential (CMAP). Affected muscles may show a decremental response to repetitive nerve stimulation.[69] A usually very focal abnormality seen in radiculopathy generally escapes detection by long-latency responses such as cervical root stimulation, late responses, or SEP. Short incremental stimulation would help, if technically feasible (see Chapter 11-7). Thermography, although abnormal in some patients, has proven ineffective as a diagnostic tool for radicular lesions.[178]

Cervical Spondylosis

Cervical spondylosis results from bony overgrowth of the vertebrae following degeneration of the intervertebral disc. A spondylotic bar may protrude posteriorly, impinging most commonly on C5 and C6, less frequently, on C7, and rarely, on other cervical and thoracic roots. In most typical cases, neck movement triggers pain in the appropriate dermatome. Some patients have asymptomatic bars and others suffer from constant pain not alleviated by postural maneuvers. A C5 or C6 lesion suppresses the biceps and supinator stretch reflexes, whereas a C7 radiculopathy diminishes the triceps reflex. Compressive cervical myelopathy just rostral to the origin of C7 may enhance the triceps response and suppress the biceps and supinator reflexes. Considerable individual and age-related variability of deltoid CMAP notwithstanding, the side-to-side amplitude ratios yield a useful, reproducible value to assess C5 lesions. The initial CMAP measures correlated significantly with the eventual recovery of deltoid strength but, interestingly, not with the initial degree of weakness.[188]

Herniated Cervical Disc

Cervical disc lesions, less common than the lumbar counterpart, usually affect patients having a history of neck trauma unilaterally at a single level. Injury to a spine with preexisting cervical spondylosis may cause bilateral symptoms, multiple root involvement, or myelopathy secondary to compression of the spinal cord. The most common herniation between C5 and C6 vertebrae compresses C6 and those between C6 and C7 vertebrae, C7. Movement of the neck or the arm, irritating the dorsal root, aggravates the initial symptom of pain over typical root distribution, whereas compression of the ventral root causes weakness in the appropriate myotome (see Appendix Table 1-2).

Root Avulsion

The Erb-Duchenne palsy results from avulsion of C5 and C6, usually caused by downward traction on the plexus as seen during a forceps delivery with the shoulder fixed in position. This type of stretch increases the angle between the head and shoulder, which stretches the roots but not the proximal nerve branches like the long thoracic or

dorsal scapular nerves. The palsy produces a characteristic posture, sometimes called the "waiters' tipping hand," with adduction and internal rotation of the arm, and extension and pronation of the forearm. Despite the preservation of the intrinsic hand muscles, the patient cannot abduct the arm or supinate the forearm to bring the hand into a useful position. Motor examination reveals weakness and atrophy of the muscles innervated by C5 and C6, but sensory evaluation, although often limited in infants, usually elucidates only mild changes, if at all.

The Klumpke palsy, or avulsion of C8 and T1, occurs from forced upward traction on the plexus, for example with an attempt to grasp an overhead support to prevent a fall or to block by hand with the arm extended to cushion landing. This type of maneuver increases the angle between the arm and thorax beyond the ordinary limit. This type of injury involves the ulnar nerve, the inner head of the median nerve, and a portion of the radial nerve. Atrophy of the intrinsic hand muscles and long finger flexors and extensors produces a partial clawhand. The patient also develops numbness along the inner aspect of the hand, forearm, and arm, although nerve stimulation elicits a normal SNAP if the injury strictly involves the preganglionic segment. Horner's syndrome indicates damage to the cervical sympathetic fibers.

Traumatic injury may cause preganglionic avulsion of cervical roots from the spinal cord, postganglionic damage to the plexus, or both. This distinction has practical implications as nerve grafting onto the avulsed root results in no return of function in humans, although experimental studies show some functional recovery in primates.[31] Structural abnormalities delineated by myelography do not necessarily coincide with functional deficits uncovered by electrophysiologic studies.[194] Pseudomeningoceles may accompany intact roots, whereas root avulsion may fail to produce detectable meningoceles. For definitive exclusion of root injury, direct stimulation of the surgically exposed individual nerve root must elicit a reproducible SEP.[80] Preganglionic separation of the cell body with lesions at the root level preserves anatomic and physiologic integrity of the peripheral axon. Thus, intradermal histamine injection induces a physiologic skin reaction, and nerve stimulation elicits a normal SNAP despite the clinical sensory loss. In contrast, patients with plexus lesions show the loss of chemical or electrical reactivity along the distal nerve segments.

The deep cervical muscles receive innervation from the posterior as opposed to the anterior rami of the spinal nerves (see Chapter 1-3). Evidence of denervation here, therefore, indicates an intraforaminal lesion affecting the root or spinal nerve before the division into the two rami. Other muscles innervated proximally to the brachial plexus include the rhomboids supplied by the dorsal scapular nerve and the serratus anterior subserved by the long thoracic nerves. Spontaneous activity in these very proximal muscles also serves to distinguish between root and plexus lesions.

Thoracic Radiculopathy

Radiculopathies from herniated thoracic discs account for only 0.1% to 4% of symptomatic disc herniations.[132] Isolated involvement of lower thoracic or upper lumbar roots, although rare, may result from collapsed vertebral bodies. With lesions at this level, proximal weakness of the legs may lead to an erroneous diagnosis of myopathy. Needle studies show spontaneous discharges localized to the affected myotomes in the limb and paraspinal muscles. This should provide an important criterion, especially because myelography often fails to differentiate symptomatic and asymptomatic thoracic herniated discs.[9] Patients may have axillary pain as a heralding sign of neoplasm involving the upper thoracic root.[158]

3. BRACHIAL PLEXUS

The high incidence of lesions affecting the brachial plexus reflects its vulnerability to trauma and its tendency to have secondary effect from disorders involving adjacent structures.[62] Idiopathic plexopathy ranks the first in incidence among nontraumatic conditions of the brachial plexus.[13] The differential diagnoses include symptomatic plexus involvement related to Hodgkin's disease,[142] desensitizing injections,[222] Ehlers-Danlos syndrome,[94] systemic lupus erythematosus,[19] an uncommon side effect of interferon therapy,[16] localized

chronic inflammation with fusiform segmental enlargement,[41] subclavian-axillary artery aneurysm,[108,206] hereditary neuropathy with predirection to pressure palsy (HNPP),[22] acute Epstein-Barr virus infection,[212] complication of fever,[168] and rare presenting manifestation of scorpion envenomation.[159]

Chronic compressive lesions of the brachial plexus range from primary nerve tumors[7] to painful metastatic breast cancer and lymphoma, which tend to cause Horner's syndrome.[107] Intermittent compression seen in some cases of the thoracic outlet syndrome produces less well-defined neurologic syndromes with little or no objective abnormalities. Radiation therapy of the axillary region also causes plexopathy, raising concerns of tumor recurrence. Cervical cord compression may mimick the neuralgia.[163] Asymptomatic professional baseball pitchers may have a reduced SNAP, probably as an example of a repetitive use syndrome affecting the brachial plexus.[119]

Traumatic or Compressive Lesions

During times of peace, brachial plexus lesions usually result from vehicle accidents or civilian gunshot wounds. Penetrating injuries from bullet wounds often injure the upper or lower trunk, or posterior cord. In one study,[35] abnormalities of phrenic nerve conduction study showed a high correlation with a C5 preganglionic root lesion in patients with traumatic brachial plexopathy. A difficult birth or sudden traction applied to the arm or neck can also damage the plexus as a common problem in pediatric neurology with an incidence of 0.6 to 2.5 per 100 live births.[130] Full recovery occurs in most patients with rapid and complete resolution of weakness by 3 to 4 months of age,[10] although some severely affected infants, showing no recovery, remain profoundly weak.[54] Some infants may suffer from developmental apraxia arising from neonatal brachial plexus palsy.[26,203]

In a series of 33 babies[78] with obstetrical brachial plexopathies serially followed until 6 months of age, a CMAP amplitude reduction of more than 90%, compared to the unaffected side, predicted severe weakness of the corresponding root level. Early surgical reconstruction may benefit those having no improvement by the age of 4 months.[106,179] In one series,[115] patients showed a notable gain of motor and sensory function after a contralateral C7 transfer to the musculocutaneous and median nerves on the affected side. Variable selection criteria and methodology make outcome evaluations difficult to interpret.

In addition to direct injuries, indirect trauma results from fractures of the humerus or dislocations of the shoulder.[139] Plexopathy may develop after a prolonged anesthesia with the patient in an unusual posture. Hemiplegics may sustain an injury from repeated pressure under the arms caused by lifting. Other possible traumatic causes include complications during brachial artery-antecubital vein shunts,[56] axillary arteriography,[198] median sternotomy,[114] thoracic outlet syndrome (TOS) surgery,[218] liver transplantation,[91] jugular vein cannulation for coronary artery bypass graft,[75,187] axillary regional block,[199] and constraints from a tight vest.[167] Appropriate radiologic and electrophysiologic studies help determine the indications for surgical intervention, which benefits only well-selected patients.[50,89]

The clinical features depend on the area of the primary pathology. The upper trunk bears the brunt of damage from injury by firearm recoil, which forcefully retracts the clavicle against the underlying scalene muscles,[214] a heavy backpack,[45] or the common football injury called a "stinger."[46] The damage here causes the distribution of weakness similar to that seen in Erb-Duchenne palsy, with involvement of the shoulder and upper arm and sparing of the hand function. The patient cannot abduct the arm, rotate the shoulder internally or externally, flex the elbow, or extend the wrist radially, but the patient has full strength of the rhomboid and serratus anterior innervated by more proximal branches. Other clinical features include sensory changes over the lateral aspect of the arm, forearm, and hand, and reduced or absent biceps and supinator stretch reflexes. Rare isolated injury to the middle trunk produces weakness in the general distribution of the radial nerve, involving the triceps only partially and sparing the brachioradialis entirely.

Metastasis can occur to any portion of the plexus but predominantly to the lower trunk as expected from the location of lymph nodes. Selective damage to the lower trunk also results

from local trauma or direct invasion from a Pancoast tumor in the apex of the lung, impairing hand function and causing Horner's syndrome. The clinical features resemble Klumpke's palsy, with the weakness of the intrinsic hand muscles and finger flexors and extensors. Sensory changes involve the medial aspect of the arm, forearm, and hand, and the ring and little fingers.

Compressive lesions in the thoracic outlet tend to affect the medial cord. Motor and sensory deficits develop in the median- and ulnar nerve-innervated regions that receive supplies from C8 and T1. The presence of Horner's syndrome implies avulsions of C8 and T1 ventral roots in adults. In infants, however, it may relate in part to injury of C7, which innervates the superior cervical ganglion with sympathetic preganglionic neurons originating from T1.[82] Though rare, local trauma can selectively damage the lateral cord, causing weakness in musculocutaneous and median nerve-innervated muscles that receive axons from C6 and C7 as well as sensory changes over the lateral side on the volar aspect of the forearm. Injury to the posterior cord seen in shoulder dislocation gives rise to the clinical picture of combined axillary and radial nerve palsies. The patient cannot extend the elbow, wrist, or fingers. The weak deltoid causes limited arm abduction after the first 30 degrees, the range subserved by the supraspinatus. Sensory changes involve the lateral aspect of the shoulder and arm, the posterior portion of the forearm, and dorsal aspects of the lateral half of the hand, and the index finger and thumb.

The pattern of SNAP abnormality from each digit assists in localizing axonal injury.[157,209] In one series,[63] upper-trunk lesions showed a consistent sensory change of lateral antebrachial cutaneous nerve and the median nerve recorded from thumb rather than index finger. In contrast, lower-trunk lesions regularly showed a diminished SNAP of the medial antebrachial cutaneous nerve, the ulnar nerve recorded from little finger, and the dorsal ulnar cutaneous nerve. These findings suggest the importance of studying these uncommonly tested sensory potentials for effective evaluation of brachial plexus lesions.[170,174]

In traumatic plexopathies, EMG renders more information than nerve conduction studies in delineating the degree, distribution, and time course of the disease. Synkinetic movements may involve different, sometimes antagonistic, muscles in patients with brachial plexus injury at birth.[67] Aberrant regeneration of phrenic motoneurons may induce arm-diaphragm synkinesis after injury to the proximal portion of the brachial plexus or cervical nerve roots.[185] Simultaneous needle studies from multiple muscles help document such misdirected reinnervation (see Fig. 14-21 in Chapter 14).

Idiopathic Brachial Plexopathy

Idiopathic brachial neuritis, also known as neuralgic amyotrophy[137] or brachial neuralgia, probably originates distal to the roots. It often shows the pattern of mononeuropathy multiplex, although the exact site of lesion remains unknown.[40,182] Rare infantile plexopathies result from intrauterine causes. Otherwise, most cases occur sporadically after the third decade, affecting men more than twice as frequently as women. The symptoms may develop during pregnancy, sometimes recurrently.[150] The disease may follow a surgical procedure as recognized in Parsonage and Turner's original description[124] or various vaccinations, especially with injection into the deltoid. Other conditions known to precede acute onset of pain and other symptoms of neuralgia include trauma, infection, serum sickness, rhabdomyolysis,[122] Hashimoto encephalopathy,[90] and diabetic ketoacidosis.[162] Complement-dependent, antibody-mediated process may also precipitate peripheral nerve damage,[210] suggesting inflammatory-immune pathogenesis.[181]

Most patients have unilateral symptoms, but the condition may occasionally occur bilaterally and in rare incidences, recurrently. The disease usually takes a monophasic course with gradual improvement over months, generally showing a good prognosis. It may, however, take a few years before achieving the maximal recovery if patients show no improvement during the first few months after onset. Chronic relapsing brachial plexus neuropathy with persistent conduction block probably falls within the spectrum of multifocal motor neuropathy (MMN) (see Chapter 24-3).[3]

The disease typically begins with pain localized in the distribution of C5 and C6 dermatomes.[137]

The clinical picture varies considerably with some patients showing a chronic and painless form[166] and others evidencing progressive monomelic sensory neuropathy.[229] An intense aching sensation may radiate along the arm. Two-thirds of the patients experience relatively mild sensory impairment. Within a few days, the shoulder girdle musculature becomes weak and atrophic. The disease most severely affects the C5 and C6 myotomes and, to a lesser extent, the muscles innervated by C7, as well as the trapezius via the spinal accessory nerve. Pain usually subsides with the onset of weakness but may last much longer. The characteristic posture with the arm flexed at the elbow and adducted at the shoulder often leads to a frozen shoulder syndrome. Some patients develop multiple cranial nerve lesions associated with otherwise typical neuralgic amyotrophy.[146] Conversely, structural pathology of the skull base may cause spinal accessory mononeuropathy with ipsilateral cranial nerve involvement, mimicking brachial neuropathy.[104]

The disease may cause selective paralysis in the distribution of a single root, trunk, cord, peripheral nerve, or individual nerve fascicles.[55,171,216] Such mononeuropathies tend to involve the radial, long thoracic, phrenic, and suprascapular and accessory nerve.[18,103,197] Occasionally, the initial presenting symptoms mimick an anterior interosseous nerve palsy.[225] Isolated involvement of the forearm muscles in neuralgic amyotrophy suggests two possibilities[152] (1) spatial scatter of the underlying pathology to the forearm or (2) selective damage of the brachial plexus nerve bundle with topographic grouping at the level of the cord.[183]

The nerve conduction abnormalities commonly seen in demyelinative plexus lesions include (1) severe amplitude attenuation of CMAP and antidromic SNAP elicited by proximal as compared with distal site of nerve stiulation; and (2) slowing of conduction across the site of injury. These findings suggest a local conduction block with or without axonal loss. Mild injury leading to pure demyelination improves rapidly without loss of axons.[152] A selective latency increase from Erb's point to individual muscles of the shoulder girdle suggests multiple mononeuropathies. Patients may have slow conduction velocity in the segment above the axilla as calculated by F wave, but not consistently.[96] Magnetic or low-cut impedance electric stimulation of nerve roots may help document proximal segmental demyelination.[133,215] Needle stimulation of cervical roots may also reveal focal conduction block, suggesting proximal demyelination.[118]

In the absence of demyelination, conduction studies reveal slightly increased latencies from Erb's point to severely affected muscles. The loss of fast-conducting fibers accounts for this change accompanied by reduced CMAP amplitude. Conduction abnormalities may become more conspicuous after reinnervation has begun. The nerves in clinically unaffected limbs sometimes show widespread changes. An absent or diminished SNAP localizes the lesion distal to the dorsal root ganglion. Motor unit number estimation (MUNE) (see Chapter 10-2) may elucidate pattern of reinnervation in serial studies of congenital brachial plexus palsy.[164]

Needle EMG, which usually shows the evidence of denervation on the affected side, may also reveal subtle changes on the clinically asymptomatic side. Typical findings seen in the involved muscles include fibrillation potential, positive sharp wave, high-amplitude polyphasic MUP, and reduced interference pattern. This, together with the time course of clinical recovery, suggests axonal interruption and wallerian degeneration. Normal paraspinal examination favors plexopathy but does not rule out radiculopathy. The diagnosis often depends on the combination of sensory amplitude abnormalities of median, ulnar, and antebrachial cutaneous nerves; slowed motor conduction of musculocutaneous nerve; and lack of paraspinal fibrillation potentials on needle examination. Magnetic resonance neurography may also help evaluate the lesion.[230]

Familial Brachial Plexopathy

Nontraumatic brachial plexus neuropathy may develop on a familial basis in association with lesions outside the plexus.[97] Acute episodes have features indistinguishable from sporadic idiopathic neuralgic amyotrophy, but the familial variety shows less pain. Hereditary neuralgic amyotrophy linked to chromosome 17q24,25

has an autosomal dominant trait with genetic heterogeneity.[180,217] The disease tends to affect a younger age group with no preference for either sex, although pregnancy may herald its onset. The symptoms recur more frequently in the familial, than in the sporadic, variety. The lesions outside the plexus cause additional signs such as Horner's syndrome, dysphonia, and craniofacial and cutaneous abnormalities.[86] The disease can also involve the lumbosacral plexus, cranial nerves, autonomic nervous system,[6] and individual peripheral nerves such as long thoracic nerve.[144] Electrophysiologic abnormalities include reduced amplitude of the recorded response in NCS and fibrillation potentials, positive sharp waves, and reduced MUP recruitment in EMG, suggesting axonal damage.

Some patients with HNPP with chromosome 17p11,2-12 deletions may also develop acute attacks of brachial plexopathy (see Chapter 24-5). This condition affects the peripheral nerves diffusely, showing a predilection for the common sites of compression. Sural nerve biopsies reveal nerve fibers with bizarre focal swelling, mild reduction in the total myelinated fiber count, and an abnormal fiber diameter spectrum with loss of a bimodal distribution seen normally. The term *tomaculous neuropathy* implies the sausage-shaped thickenings of the myelin sheaths, which characterize this pathologic condition. Focal chronic inflammatory demyelinating polyneuropathy (CIDP) may also present as painless brachial plexus neuropathy.[202]

Neoplastic versus Radiation-Induced Plexopathy

In one series of 79 breast cancer patients, 35% had radiation-induced plexopathy, most developing symptoms during or immediately after the exposure.[127] Plexopathy, however, may develop months to years after radiation treatment and take a progressive course.[60] Electrophysiologic studies[107] often reveal a reduction in amplitude of SNAP and CMAP associated with proportionately increased latencies. Needle studies also show fibrillation potentials, positive sharp waves, and myokymic discharges, which favor the diagnosis of radiation plexopathies.[1,77]

In brachial plexopathy patients with a history of cancer, recurrence of symptoms may indicate radiation injury or tumor infiltration. Based on a study of 100 cases, painless upper-trunk lesions with lymphedema suggest radiation injury, whereas painful lower-trunk lesions with Horner's syndrome imply tumor infiltration.[98] Neoplastic lesions may cause considerable slowing of conduction across the plexus, but not in all cases. In another study,[77] characteristic features in favor of radiation plexopathy included absence of pain as the presenting symptom, no sign of discrete mass on computed tomography, detection of myokymic discharges in EMG, and temporal relationship to therapy.

Cervical Rib and Thoracic Outlet Syndrome

Although the once widely publicized compression by the scalenus anticus muscle fell into disrepute,[92] a variety of anomalous structures in the neck may affect the roots or trunks of the brachial plexus, causing a vascular or neurogenic syndrome.[117] The cervical rib, though rare, may compress the neurovascular structures, especially in women with low-set "droopy" shoulders and a long swan neck[186] or after spinal accessory nerve injury causing trapezius weakness.[2] A compression syndrome may also result from the first thoracic rib pressed upward by distortion of the thorax. In one study,[135] magnetic resonance images (MRI) showed a band-like structure extending from the C7 transverse process in 25 of 33 sides in patients with vascular symptoms and in 3 of 18 sides in control subjects.

The patients usually complain of unilateral symptoms, even in the presence of bilateral cervical ribs, although the condition may occasionally develop bilaterally.[192] A rudimentary cervical rib with a fibrous band causes symptoms more often than a fully formed cervical rib. Some patients develop pain, numbness, and weakness principally over an ulnar distribution immediately after median sternotomy for coronary artery bypass graft. Despite superficial resemblance, sternotomy-related brachial plexopathy shows predominant damage in the C8 distribution at the level of the anterior primary rami of the cervical

roots rather than the lower trunk implicated in thoracic outlet syndrome.[114]

Vascular features result from upward displacement of the axillary or subclavian artery by the cervical rib. Stenosis of the compressed artery may cause intermittent embolic phenomena of the brachial artery with ischemic changes in the fingers. The hand turns cold and blue with diminished or absent pulsations in the radial and ulnar arteries. Erroneous diagnosis may lead to inappropriate scalenotomies or removal of the first rib.[66,114] The procedure has limited indication for the majority of patients with vascular symptoms.[70] If such intervention offers a beneficial effect in the management of arm pain, the initially normal electrophysiologic studies usually fail to substantiate the subjective change. Careful electrophysiology studies may help resolve the question of underdiagnosing[156] or overdiagnosing the entity.[219]

Unlike the poorly defined condition described earlier, the classical thoracic outlet syndrome denotes a rare but more clearly recognizable neurologic entity, usually affecting women with a rudimentary cervical rib.[71] The neural symptoms include local and referred pain secondary to pressure, paresthesias in the hand and forearm along the medial aspect, and weakness of the intrinsic hand muscles. Rare complications include focal hand dystonia on the compression site.[149] Prominent atrophy of the abductor pollicis brevis may superficially suggest a diagnosis of carpal tunnel syndrome.[172,173] The thoracic outlet syndrome, however, gives rise to pain and sensory changes in the ulnar-innervated fingers. Focal atrophy and weakness from a cerebral lesion can also simulate a thoracic outlet syndrome, although electrophysiological studies demonstrate no abnormalities.[177,227]

In contrast to those with CTS,[172,173] patients with neurogenic thoracic outlet syndrome have reduced or absent SNAP of the ulnar and medial antebrachial cutaneous nerves.[99,114] Other findings include normal median nerve SNAP, reduced ulnar and median nerve CMAP,[109] and increased ulnar nerve F-wave latencies on the affected side as compared with the normal side.[223] A reduced SNAP amplitude confirms a postganglionic involvement, whereas normal conduction velocities help exclude the possibility of more distal entrapment. Needle studies show evidence of denervation in the intrinsic hand muscles, especially the abductor pollicis brevis. Patients free of neurologic deficits have none of these abnormalities even when vascular symptoms appear with postural maneuvers. Some investigators advocate the use of dermatomal or median or ulnar nerve SEP studies, but without further confirmation.[27]

4. LUMBOSACRAL ROOTS

Injuries at the lumbosacral level most commonly involve the spinal nerve at the point where it exits through the foramen. Preganglionic radicular damage can also occur anywhere along the long subarachnoid pathway of the cauda equina within the spinal canal, showing frequent anomalies such as conjoined lumbosacral dorsal nerve roots.[145] This anatomic peculiarity makes clinical and electrophysiologic localization of radicular lesions more difficult in the lower than upper limbs. Unlike the cervical roots, the lumbar roots emerge from the intervertebral spaces below their respective vertebrae. In the upper limbs, motor deficits serve as a more reliable localizing sign than sensory impairments. The reverse seems to hold in the lower limbs. A stepwise multivariate analysis of lumbosacral nerve root showed that the history items reveal most of the diagnostic information detectable by physical examination.[211]

Radiculopathies rarely involve the first three lumbar roots that supply the skin of the anterior thigh. With compression of L4, pain radiates from the knee to the medial malleolus along the medial aspect. With L5 irritation, pain originates in the buttock and radiates along the posterior lateral aspect of the thigh, lateral aspect of the leg, dorsum of the foot, and first four toes. A lesion of S1 causes pain to radiate down the back of the thigh, leg, and lateral aspect of the foot. Irritation of S2 through S5 results in pain along the posteromedial aspect of the thigh, over the perianal area of the buttock, and in the genital region.

In the lower limbs, involvement of a single root does not necessarily cause prominent weakness or wasting, reflecting multiplicity of root supply (see Table A5-3). In most leg muscles, however, a single root primarily controls certain

movements. These include hip flexion by L2, knee extension and thigh adduction by L3, inversion of the foot by L4, toe extension by L5, and eversion of the foot by S1.[138] Lesions of a single root affect dorsiflexion of the foot to a lesser extent because of the dual control by L4 and L5. Similarly, both S1 and S2 subserve plantar flexion. A lesion of the L4 root depresses the knee stretch reflex, whereas an S1 root lesion affects the ankle jerk and its electrical counterpart, the H reflex. In one series, studies of extensor digitorum brevis reflex for localization of L5 lesions yielded disappointing results.[125]

Electrodiagnosis plays a particularly important role in justifying surgical exploration when radiologic and clinical findings render conflicting views.[37,200] For example, extraforaminal compression of L5 by lumbosacral ligaments may cause denervation despite a normal myelogram and other imaging studies.[134] Conversely, asymptomatic subjects may have abnormal MRI scans of the lumbar spine, making it imperative to seek a clinical and physiologic correlation.[20] In some cases, T2-weighted and short time inversion recovery MRI sequences may supplement the electrophysiologic evidence of functional deficits, elucidating denervated skeletal muscle, which shows increased signal intensity. In one study,[32] this abnormality corresponded closely with spontaneous activities seen in EMG.

Conus Lesion

Tumors known to involve the conus medullaris, which comprises the S2 to S5 segments, include ependymoma,[128] dermoid cyst, lipoma, arteriovenous malformation,[112] and, less frequently, metastasis.[25] They typically invade the sacral roots from below, beginning with S5. Thus, the usual presenting features consist of a dull backache and sensory disturbances in the genital and perianal regions, which even a careful examiner may fail to detect. Impotence and impaired sphincter control soon develop. Bilateral diminution of the ankle jerk indicates upward extension of the tumor to the origin of S1. The lesion typically spares the knee reflex. Initial unilateral weakness soon spreads to the other limb, leading to relatively symmetric involvement. Bilateral foot drop seen secondary to a conus medullaris tumor implies further upward extension to involve L5.[123]

Despite asymmetric clinical signs, EMG abnormalities often indicate a bilateral involvement of multiple roots. The anal sphincter also shows the evidence of denervation and loss of tonus. As predicted from the preganglionic site of involvement, NCS reveals a normal SNAP despite a reduced CMAP. Some ascending spinal fibers undergo degeneration as evidenced by abnormal scalp SEP after intrathecal stimulation of the lumbosacral cord.[57]

Cauda Equina Lesion

The lesions responsible for the lateral cauda equina syndrome include herniated disc, meningioma, neurofibroma,[14] and rarely, aneurysm in the sacral canal.[165] Such a mass lesion in the spinal canal below the T12 vertebrae affects any one of the lumbar or sacral roots singly or in combination. Some of these tumors may escape detection by casual imaging studies because of their mobility.[84] With a laterally located lesion at the level of L1, L2, or L3, pain typically radiates over the anterior thigh. Involvement of L4 results in atrophy and weakness of the quadriceps muscle and foot inverters with a diminished knee reflex. A high, laterally located lesion may simultaneously compress the cord, giving rise to a hyperactive ankle reflex and other upper motoneuron signs. This rare, confusing presentation may lead to an erroneous diagnosis of amyotrophic lateral sclerosis.

A lipoma may involve a few cauda fibers, producing distension in the region of the conus medullaris with only sexual and voiding dysfunction.[68] Midline or diffuse involvement of the cauda equina suggests metastasis from prostate cancer, direct spread of tumors in the pelvic floor, or chondromas of the sacral bone. Similar clinical features may result from leukemic or lymphomatous infiltration or seeding with medulloblastoma, pinealoma, or other malignant tumors of the nervous system. Lower motoneuron syndromes may also follow radiation therapy,[81] redundant nerve root syndrome,[151,184] spinal arachnoiditis,[136] ankylosing spondylitis,[12] and brucellosis involving the anterior lumbosacral nerve roots.[201]

Lumbosacral radiculopathy may also follow radiofrequency ablation therapy used in the treatment of solid malignancies and vascular malformation.[38] Ventral polyradiculopathy may develop after intrathecal chemotherapy administered for treatment of leukemic meningitis.[4]

Except for asymmetric distribution and severe pain, signs and symptoms of a cauda equina lesion resemble those of a conus medullaris lesion.[147] It often causes bilateral involvement of the dermatomes ordinarily unaffected by a herniated lumbar disc. Unlike the compression at the intervertebral space, changing positions of the lower limbs fails to alleviate the discomfort. Reduced muscle stretch reflexes at both the knee and ankle also tend to localize the lesion at the cauda equina rather than the conus medullaris. EMG studies show fibrillation potentials and a large MUP in the distribution of several lumbosacral roots, including paraspinal muscles[12] and urethral sphincter.[65] Again, the findings mimic those of an intrinsic cord involvement except for an asymmetric distribution of the abnormalities with spread above the sacral myotomes. Thus, a substantial side-to-side difference in amplitude of the CMAP favors the diagnosis of cauda equina rather than conus medullaris lesions. In lumbosacral radiculopathy, unlike in axonal polyneuropathy, motor conduction studies tend to show normal amplitude and distal latency.[15]

Herniated Lumbar Disc

Although degenerative disease usually affects the middle and old age group, patients with familial predisposition may develop lumbar disc herniation at a young age.[205] Lumbar radiculopathy may also develop following spinal fusion for scoliosis.[76] Disc protrusion involves the L4 to L5 and L5 to Sl interspaces in a most of cases and in the L3 to L4 space much less frequently. Lesions at the remaining higher or lower levels should suggest diagnostic possibilities other than uncomplicated herniation. Conversely, rare L1 or L2 radiculopathy may mimic meralgia paresthetica.[23,224] The protruding disc tends to compress the lumbosacral roots slightly above the level of their respective foramina before their lateral deviation toward the exit. A herniated disc at the L4 to L5 intervertebral space, therefore, compresses L5, which emerges under the L5 vertebrae. Similarly, a disc protrusion between the L5 and S1 vertebrae damages S1 exiting the interspace below. As mentioned earlier, cervical disc herniation at the C6 to C7 space compresses C7, which exits above the C7 vertebra. Thus, in both the cervical and lumbar regions, the root most frequently subjected to damage carries the same number as the vertebra below the herniated disc albeit with a differing relationship of the roots to the interspace.

Clinical symptoms consist of weakness in the affected myotomes and pain in the appropriate dermatomes, aggravated by leg raising or other maneuvers that stretch the root. Patients may have pure sensory or pure motor symptoms. In rare instances, fiber hypertrophy exceeds atrophy, resulting in unilateral enlargement of the calf muscles with a chronic S1 radiculopathy[39,153] and of the anterior tibial muscle with an L4 radicular lesion.[126] Neurogenic muscle hypertrophy may also result from a passive stretch mechanism, a tethered spinal cord,[17] and excessive spontaneous muscle activities.[126] Because of anatomic peculiarities, lesions located much higher than the ordinary disc protrusion may compress L5 or S1 within the cauda equina. For example, a tumor of a high lumbar root may produce this type of confusing clinical and myelographic abnormalities.

Needle studies help confirm the diagnosis and identify the damaged root (see Fig. 14-10A in Chapter 14).[47] In one study of 45 patients with single-level radiculopathy,[196] preoperative EMG abnormalities of tibialis anterior correlated predominantly with L5 lesions confirmed radiologically and surgically. In contrast, S1 lesions predominantly affected short and long heads of biceps femoris and medial and lateral heads of gastrocnemius. In addition to the diagnostic use, serial examination can guide the management by substantiating clinical progression or improvement.[88] Electrophysiologic abnormalities demonstrate the course of radiculopathy better than the computed tomography.[95] Denervation of the paraspinal muscles (see Fig. 14-8C in Chapter 14) implies a lesion located proximal to the origin of the posterior ramus. Thus, paraspinal studies help differentiate radiculopathy from diseases of the plexus or peripheral nerve. The absence of

denervation here, however, does not necessarily exclude the possibility of root compression. The multifidus muscles, innervated by a single root, serve better for segmental localization of the lesion compared to the rest of the polysegmentally innervated paraspinal muscle mass.[29] Nonetheless, paraspinal abnormalities usually fall short of establishing the level of involvement on this basis alone.[74] Precise localization of lesion, therefore, depends on careful exploration of the lower-limb muscles.

The assessment of radiculopathy should include an NCS to exclude a neuropathy. Despite the commonly held belief that root lesions spare sensory amplitude, L5 radiculopathy often causes reduction in superficial peroneal SNAP.[110] In such cases, the herniated disk may compress the dorsal root ganglion located at the intraspinal canal, thus causing postganglionic rather than preganglionic damage. Under this circumstance, amplitude asymmetry of SNAP, in addition to CMAP, assists in assessing the degree of nerve damage.

Studies of the H reflex may reveal abnormalities of S1 radiculopathy, especially if elicited by electrical stimulation of the spinal nerve [44,121,141] or magnetic activation of the root[120,195,231] to isolate the short radicular segment (see Chapter 9-2 and Chapter 20-4). These studies help differentiate S1 from L5 involvement. Although some investigators advocate the use of dermatomal SEP as a screen for radiculopathy,[213] conduction studies over long distances generally provide an insensitive measure in evaluating focal nerve lesions (see Chapter 11-7).[96] For the same reason, the latency measures of F-wave and motor evoked potentials (MEPs) may not delay the conduction enough to detect an early or mild radiculopathy.[51,96,116]

A relatively normal EMG finding provides a good outcome, whereas neurogenic abnormalities generally imply a poor prognosis.[59] Following laminectomy, spontaneous activity may persist indefinitely, although it usually diminishes substantially by 3–6 months.[49] In one study, postoperative focal abnormalities found in the paraspinal muscles at least 3 cm lateral to the incision and 4 to 5 cm deep suggested a new lesion.[87] Other findings supportive of an active radiculopathy in post laminectomy patients include the following: (1) fibrillation potentials and positive sharp waves at a specific level on the symptomatic side only; (2) a mixture of large and small fibrillations and positive sharp waves segmentally on the symptomatic side, but only small sparse spontaneous discharges on the asymptomatic side; and (3) the appearance in serial studies of new spontaneous activities at the suspected level on the symptomatic side.

Spinal Stenosis

Neurogenic claudication usually results from multilevel central narrowing of the spinal canal with or without associated constriction in the nerve root canals.[147] Nerve root hypertrophy may also cause lumbar stenosis in CIDP.[73] In a review of 37 patients, stenosis most commonly affected the L4 or L5 level or both.[169] Lumbosacral polyradiculopathy may mimick distal polyneuropathy.[160] Electrophysioogic studies have revealed various, sometimes conflicting results. In 36 patients, EMG revealed fibrillation potentials and a poorly recruiting, polyphasic, long-duration MUP in several leg muscles and, to a lesser extent, in the paraspinal muscles bilaterally. Of 32 symptomatic older adults evaluated for spinal stenosis, 18 had a false-positive MRI whereas 13 had misleading EMG abnormalities erroneously suggesting the diagnosis.[36] In 244 patients with spinal stenosis, retrospective analyses of lumbar laminectomy showed a high, medium- to long-term success and rare postoperative lumbar instability, requiring lumbar fusion only infrequently.[176]

Root Avulsion

Intradural avulsion involves the lumbosacral roots less often than the cervical roots, although this condition may escape detection in patients with pelvic fractures or sacroiliac dislocation. In these instances, tension in the lumbar and sacral plexuses stretches the root intradurally. Needle studies reveal denervation in the appropriate myotomes, including the paraspinal muscles. Myelography delineates the level of involvement.

5. LUMBOSACRAL PLEXUS

The lumbosacral plexus, often considered a single anatomic entity, consists of lumbar and sacral

portions with a connection between them. The division helps differentiate clinical problems that tend to affect each portion independently.[48] A lesion involving the lumbar plexus diminishes the knee reflex and causes sensory loss over the L2, L3, and L4 dermatomes. It also weakens not only the hip flexors and knee extensors but also leg adductors. In contrast, isolated femoral neuropathy spares the obturator-innervated muscles. A lesion of the sacral plexus produces a clinical picture similar to that seen with a sciatic nerve lesion, but with additional involvement of the gluteal muscles and, at times, the anal sphincter.

Idiopathic Lumbosacral Plexopathy

Immune or vascular etiologies probably play an important role in idiopathic type, similar to the better described and more frequently identified brachial plexopathies.[181] Acute pain in one or both legs usually precedes the onset of weakness and areflexia, followed by atrophy of affected muscles.[161] In 10 cases of idiopathic lumbosacral plexopathy studied sequentially for an average of 6 years, the patients recovered slowly and often incompletely.[58] Some patients relapse[8] and others suffer from persistent pain, the most prominent and debilitating symptom,[79] and still others respond to corticosteroids or intravenous immunoglobulin.[193,207,226]

Patients with diabetes mellitus or amyloid polyneuropathy[5] may also develop lumbar plexopathy, femoral neuropathy, or radiculopathy. Both diabetic and nondiabetic cases show similar clinical features characterized by subacute, asymmetric lower-limb weakness associated with pain and weight loss.[52] Intravascular lymphomatosis may present as lumbosacral polyradiculopathy.[208] Exercise-induced ischemia of the lumbosacral plexus may induce intermittent claudication.[221]

Traumatic Lesions

In one series of 22 consecutive patients with lumbosacral plexopathy associated with pelvic trauma, 68% had sacral fractures or sacroiliac joint separation; 14%, acetabular fracture; and 9%, femoral fracture.[102] Patients with acetabular or femoral fracture suffered injury to multiple proximal nerves rather than the plexus per se. Traumatic injuries may also result from inappropriate traction during orthopedic or other operative manipulations including hip arthroplasty.[72]

The risk of delivery-related lumbosacral plexus injury increases in pregnant women with small maternal size, a large fetus, midforceps rotation, or fetal malposition. Electrophysiologic studies often localize the site of this obstetrical paralysis to the L4 to L5 lumbosacral trunk or S1 root, where they join and pass over the pelvic rim.[61] In one series,[93] 6 had short stature and 1 had a large newborn. All had foot drop with selective denervation in L5 innervated muscles and sensory loss over L5 dermatome. Measurements used to assess postpartum lumbosacral plexopathy include bulbocavernosus reflex latencies and pudendal nerve SEP and terminal motor latencies.[83]

Perioperative nerve injuries include stretch compression, ischemia, and direct trauma.[11] Regional nerve injury may also develop after internal or external iliac artery catheterization for intraarterial chemotherapy for a localized pelvic or lower-limb tumor. In one series of 11 such patients, 9 had a lumbosacral plexopathy and 2, a mononeuropathy within 48 hours of an intraarterial infusion.[33]

Neoplastic versus Radiation-Induced Lesions

Neoplasms extending from the rectum, prostate, or cervix often invade the lumbosacral plexus. Metastatic, leukemic, or lymphomatous infiltration gives rise to painful and slowly progressive paralysis, sometimes associated with sympathetic signs such as a hot and dry foot.[42] In one series of 85 cases of documented pelvic tumors,[85] plexopathy involved the upper portion (L1 to L4) in 31%, the lower portion (L4 to S3) in 51%, and both in 18%. Clinical features comprised quintet of leg pain, weakness, edema, rectal mass, and hydronephrosis. Electrophysiologic studies revealed denervation and reinnervation together with conduction abnormalities of the motor fibers, on average, 4 months after onset. In another series of 50 patients,[191] radiation plexopathy caused indolent painless leg weakness early, often bilaterally, whereas tumors typically give rise to painful

unilateral weakness. Needle studies revealed partial denervation and chronic reinnervation in both entities, and myokymic discharges in more than half the cases of radiation plexopathy but rarely, if at all, in patients with tumors.

Vascular Lesions

Compression plexopathy may result from a hematoma in patients with hemophilia or other coagulopathies or in those receiving anticoagulation therapy occurring as one of two anatomically distinct syndromes: (1) involvement of the lumbar plexus by a hematoma within the psoas muscle,[53] and (2) selective compression of the femoral nerve.[228] With plexus lesion, weakness involves the thigh adductors, hip flexors, and quadriceps. Sensory loss affects the entire anterior thigh, including the area supplied by the lateral femoral cutaneous nerve. In contrast, femoral neuropathy selectively weakens the quadriceps and hip flexors and causes sensory deficits limited to the distribution of the anterior femoral cutaneous and saphenous nerves.[53] Other etiologies include aortoiliac vascular disease, which may cause neurologic deficit involving the lumbosacral plexus, or sciatic or femoral nerve, with a good correlation between the level of the vascular lesion and the type of peripheral nerve abnormality.[43]

Electrophysiologic Studies

In distinguishing a plexopathy from radiculopathy, EMG plays a major role by examining the proximal muscles innervated rostral to the plexus. These include, in addition to the paraspinal muscles, iliopsoas and gluteus maximus, medius and minimus. Typical findings of plexopathy include fibrillation potentials at rest and poor recruitment of MUP in the myotomes supplied by the anterior rami of multiple spinal nerves. Distal nerve stimulation elicits a low-amplitude CMAP and SNAP on the affected side as compared to the normal side. Root stimulation may reveal an increased latency across the plexus in the appropriate distribution.[121] F waves may or may not have a prolonged latency (see Fig. 7-12 in Chapter 7). Involvement of S1 causes a decrease in amplitude and an increase in latency of the H reflex (see Chapter 9-2). Electrodiagnostic studies help assess sacral plexopathy, although multiple complicating factors sometimes preclude definite localization of the lesion. In one series of 171 clinically suspected sacral plexopathies,[190] electrophysiologic studies confirmed the diagnosis in 60 cases based on reduced or absent SNAP of the sural or superficial peroneal nerve, denervation of plexus-innervated muscles, and the absence of paraspinal abnormalities. The remaining 111 cases with less precise localization comprised 52 with lesions in either the plexus or roots; 32, in either plexus or sciatic nerve; and 27, in the plexus, sciatic nerve, or roots.

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24

Polyneuropathies and Mononeuropathies Multiplex

Abbreviations: AChR—acetylcholine receptor, AIDP—acute inflammatory demyelinating polyneuropathy, AIDS—acquired immunodeficiency syndrome, ALS—amyotrophic lateral sclerosis, AMAN—acute motor axonal neuropathy, AMCBN—acute motor conduction block neuropathy, AMSAN—acute motor sensory axonal neuropathy, ASAN—acute sensory ataxic neuropathy, BAEP—brainstem auditory evoked potential, CCT—central conduction time, CIDP—chronic inflammatory demyelinating polyneuropathy, CMAN—chronic motor axonal neuropathy, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CMTX—X-linked dominant CMT, CNS—central nervous system, CRD—complex repetitive discharge, CSF—cerebral spinal fluid, CTS—carpal tunnel syndrome, DADS—distal acquired demyelinating symmetric polyneuropathy, EMG—electromyography, FHSD—fascioscapulohumeral dystrophy, GALS—galatocerebrosidase, GAN—giant axonal neuropathy, GBS—Guillain-Barré syndrome, GDAP—ganglio side-induced differentiation–associated protein 1 gene, HIV—human immunodeficient virus, GJB1—gap-junction beta-1 protein, HNA—hereditary neuralgic amyotrophy, HNPP—hereditary neuropathy with liabilities to pressure palsies, HSAN—hereditary sensory autonomic neuropathy, HSMN—hereditary sensory and motor neuropathy, IgA—immunoglobulin A, IgG—immunoglobulin G, IgM—immunoglobulin M, IVIG—intravenous immunoglobin, LLN—lower limit of normal, MADSAM—multifocal acquired demyelinating sensory and motor neuropathy, MAG—myelin-associated glycoprotein, MFS—Miller Fisher syndrome, MG—myasthenia gravis, MFN 2—mitofusion 2, MJD—Machado-Joseph disease, MGUS—monoclonal gammopathy of unknown significance, MMN—multifocal motor neuropathy with persistent conduction block, MND—motor neuron disease, M-protein—monoclonal protein, MPZ—myelin protein zero, MRI—magnetic resonance imaging, MUNE—motor unit number estimates, MUP—motor unit potential, NCS—nerve conduction studies, PMP-22—peripheral myelin protein-22, POEMS—polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, QOL—quality of life, SCA—spinocerebellar ataxia, SEP—somatosensory evoked potential, SGPG—sulfonated glucuronyl paragloboside, SMA—spinal muscular atrophy, SNAP—sensory nerve action potential, SSR—sympathetic skin response, TLI—terminal latency index, TMS—transcranial magnetic stimulation, TTR—transthyretin, ULN—upper limit of normal, VEP—visual evoked potential

1. INTRODUCTION

Clinical features of polyneuropathy consist of the triad of sensory changes in a glove-and-stocking distribution, distal weakness, and hyporeflexia (see Fig. 1-1 in Chapter 1). Exceptions abound, however, as certain types of neuropathy may show widespread sensory symptoms, more prominent proximal weakness, or normal muscle stretch reflexes. Also, most patients initially complain of positive sensory symptoms, which result from ectopic impulse generation and autoexcitation of myelinated afferent fibers. In addition to sensorimotor symptoms, mild autonomic dysfunctions accompany most peripheral neuropathies, but clinically detectable abnormalities appear only in a few conditions, such as diabetes mellitis, amyloidosis,

Guillain-Barré syndrome (GBS), porphyria, and familial dysautonomia.

A detailed history often reveals general medical conditions like diabetes mellitis, alcoholism, renal disease, malignancies, sarcoidosis, periarteritis nodosa, amyloidosis, and infectious processes such as diphtheria and leprosy. Connective tissue diseases, such as rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, systemic sclerosis, and vasculitis may also cause various disorders of the peripheral nervous system.[931] Inflammatory neuropathies include GBS, chronic inflammatory demyelinative polyneuropathy (CIDP), and multifocal motor neuropathy with persistent conduction block (MMN). Metabolic neuropathies result from nutritional deficiencies or toxic effects of drugs or chemicals.

Patients with signs and symptoms of polyneuropathy not confirmed by electrophysiologic studies may have small-fiber sensory neuropathy.[14,932] Quantitative sensory threshold and autonomic tests may help document this type of neuropathy.[238] Of these, pandysautonomic neuropathy characteristically shows severe postganglionic sympathetic and parasympathetic dysfunction, with relative or complete sparing of motor and sensory dysfunction. Autonomic symptoms in painful neuropathy predominantly involve cholinergic neurons forming a unique constellation of features.[45] Such autonomic disturbances usually result from damage to unmyelinated and small myelinated fibers. Noninvasive autonomic testing (see Chapter 10-1) complements clinical and electrophysiologic characterization of the autonomic neuropathies).[301,667]

A careful review of the family history helps establish the type of inherited conditions associated with polyneuropathy. A patient's own account may not provide sufficient information, sometimes necessitating independent examination of individual family members. The absence of family history does not preclude sporadic mutations. Some of these patients with hereditary predisposition may seek medical attention in adulthood for neuropathic symptoms of unknown etiology. These patients often report having had operation on their feet or frequently sprained ankles while participating in sports. Slowly progressive polyneuropathies with features of central nervous system degeneration may also have genetic bases. Thus, in patients with neuropathy who also have brisk stretch reflexes, direct examination of the patient's relatives sometimes reveals a hereditary condition. In some of these patients, sural nerve biopsy shows a typical hypertrophic polyneuropathy and in others only loss of nerve fibers.[930]

For some patients with an unequivocal diagnosis of polyneuropathy, extensive studies may fail to uncover the exact etiology.[650] In this type of neuropathy, more common in elderly patients,[1147] serial neurophysiologic studies often suggest stable or only slowly progressive, possibly age-related axonal degeneration.[471] Hereditary and immune-mediated polyneuropathy accounts for some of the remaining cases. In one study, intensive evaluation permitted classification of 76% of 205 patients with initially undiagnosed neuropathy; final diagnoses included inherited disorders (42%), CIDP (21%), and neuropathies associated with systemic disorders (13%).[285]

We usually classify peripheral neuropathies into acute (weeks), subacute (months), early chronic (a few years), and late chronic categories (many years) based on the clinical course of the disease progression before reaching its peak. In contrast to an acute, very rapidly developing polyneuropathy, subacute cases have prominent sensory features, usually showing axonal degeneration. Asymmetrical axonal polyneuropathies in this category include diabetes mellitis, polyarteritis nodosa, cryoglobinemia, and Sjögren syndrome. To complicate the issue, some entities, which usually present as asymmetrical and multifocal polyneuropathies, may sometimes develop subacute involvement of multiple individual nerves almost simultaneously. This gives rise to the clinical picture that resembles syndrome of subacute symmetric axonal sensorimotor neuropathy. In addition, many cases in the same category evolve over shorter or longer periods, making dividing lines difficult to draw.

One must also distinguish the main topographic distribution of symptoms (symmetric or asymmetric; legs or arms; distal or proximal) and determine the predominantly affected nerve fibers (motor, sensory, or autonomic). The histological classification based on the nerve elements primarily involved (neuronopathy, axonopathy, or myelinopathy)[289] also facilitates differential

diagnosis. Anatomic diagnosis depends on clinical and electrodiagnostic evaluation, but few specific patterns of peripheral nerve involvement characterize a given disorder. Nerve conduction studies (NCSs) and electromyography (EMG) delineate the extent and distribution of the lesions and differentiate two major pathologic changes in the nerve (see Chapter 4-6): axonal degeneration and demyelination. Electrical studies alone rarely distinguish clinical types of neuropathies or establish the exact etiology in a given case, underscoring the need that a specialist performs the electrodiagnosis as an extension of clinical examination.[1018]

Among neuronopathies, sensory ganglionopathies have a frequent association with neoplastic, disimmune, and drug-induced neuropathies, as well as some inherited disorders with degeneration of dorsal root ganglion cells.[576] A widespread decrease in sensory nerve action potentials (SNAP) and undetectable somatosensory evoked potentials (SEP) constitute the electrophysiologic hallmark.[615] A non-length-dependent pattern of peripheral axon degeneration stands in contrast to the length dependent loss of large sensory fibers, which reduces sural more than radial, sensory potentials, altering the amplitude ratio.[895] The evidence of central sensory pathway hyperintensity by cervical magnetic resonance imaging (MRI) also allows the localization of pathology to the dorsal ganglion neurons.

Another classification employs the anatomic principles of localization and distribution of lesions as shown in Figure 24-1 with divisions into three major categories.[299] Of these, mononeuropathies (see Chapter 25) comprise any entities with involvement of only one nerve, most commonly at the common sites of compression or entrapment as evidenced by changes of SNAP and compound muscle action potential (CMAP). Polyneuropathies usually denote a diffuse process affecting all nerves more or less symmetrically, showing length-dependent signs and symptoms.[303] In mononeuropathy multiplex, the disease process affects one nerve at a time but eventually many of them, usually with considerable asymmetry. Hence, this entity may begin as a mononeuropathy and may superficially resemble polyneuropathy in advanced stages. Historical accounts of disease process can establish the stepwise progression of involvement. Electrodiagnostic studies can distinguish two subdivisions, axonal degeneration as seen in polyarteritis nodosa and other vasculitis, and demyelination, which characterizes multifocal motor neuropathy.

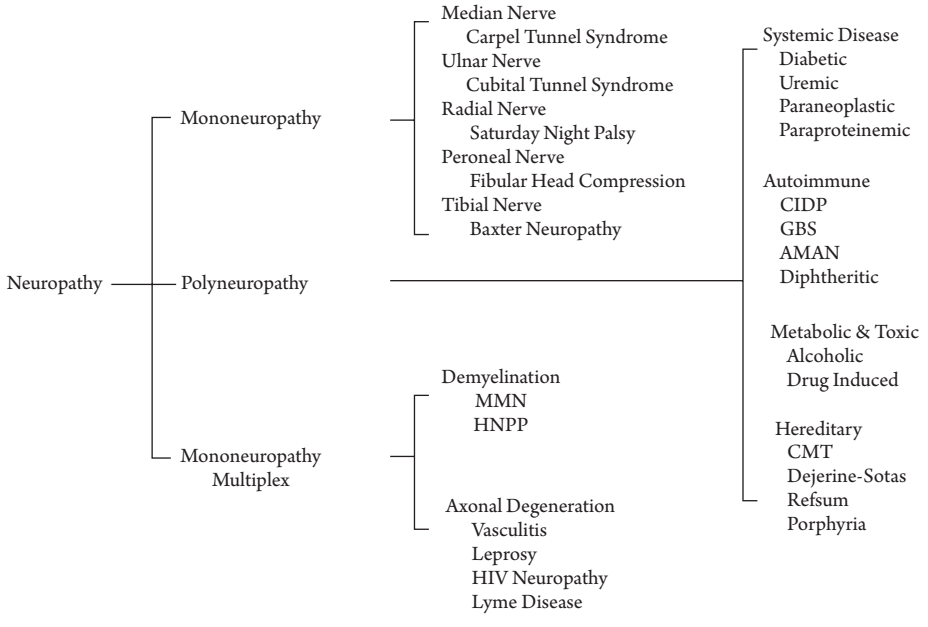

FIGURE 24-1 Differential Diagnosis of Neuropathy.

Screening laboratory tests with the highest yield include blood glucose, serum B12 with metabolites, and serum protein immunofixation electrophoresis.[303] Arriving at a specific diagnosis and establishing a course of therapy sometimes depends on skin biopsy and histologic assessments.[239,303,361,420,1024] The use of the overall neuropathy limitation scale[377] standardizes clinical scoring of patient disability, which may affect daily activities such as driving.[186] This chapter reviews the essential characteristics of peripheral neuropathies as they relate to electrophysiologic abnormalities.[289,299,529,1043]

2. NEUROPATHIES ASSOCIATED WITH GENERAL MEDICAL CONDITIONS

The most commonly encountered polyneuropathy in this category includes distal symmetric polyneuropathies.[303] Despite their clear association with a general medical condition, the exact cause of neuropathies often remains uncertain.

Diabetic Neuropathy

Overall, two-thirds of diabetic patients have objective evidence for some variety of neuropathy, but only about 20% have symptoms.[278] The most commonly used clinical classification of a wide spectrum of neuropathic process[44,1235] consists of (1) distal symmetric primarily sensory neuropathy; (2) autonomic neuropathy; (3) proximal asymmetric painful motor neuropathy; and (4) cranial mononeuropathies. The spectrum of neuropathy includes those associated with impaired glucose tolerance, which causes the earliest detectable sign of glucose dysmetabolism.[1058]

A symmetric polyneuropathy likely has a metabolic basis.[288] One theory postulates an increased amount of sorbitol in diabetic neural tissue. In hyperglycemia, glucose, shunted through the sorbitol pathway, causes the accumulation of sorbitol in Schwann cells, which undergo osmotic damage leading to segmental demyelination. Other factors considered important in the pathogenesis include insulin deficiency and altered myoinositol metabolism. Diabetic patients may also have additional causes for distal sensory polyneuropathy unrelated to diabetes.[372] One survey of physicians' clinical diagnosis[286] elucidated excessive variability and frequent inaccuracy, often overestimating diabetic sensorimotor polyneuropathy.

In contrast, asymmetric types of diabetic neuropathy and diabetic cranial mononeuropathies probably result from small-vessel disease that leads to infarcts within the nerve.[893] In some affected patients, an inflammatory vasculopathy[951] or microvasculitis with infiltrative T cells[1223] may contribute to the pathogenesis. The spatial distribution of fiber loss also suggests ischemia and hypoxia similar to those found in experimental embolization of nerve capillaries.[273] To support the vascular theory, predominantly sensory neuropathies may also develop in healthy subjects associated with chronic and critical limb ischemia.[1182] In animal studies, reduced endoneurial blood flow, insufficient to cause infarction, may result in measurable functional and morphologic abnormalities in peripheral nerves.[1010] Ischemic changes in the nerve presumably result from proliferation of the endothelium in blood vessels and abnormalities of the capillaries.[687]

Pathologic classification separates diabetic neuropathies into two groups. In the larger fiber type, segmental demyelination develops as a secondary change to diffuse or multifocal axonal loss,[280] the process that distorts the normally linear relationship between internodal length and fiber diameter. Histologic studies show degeneration of both myelinated and unmyelinated axons.[150] Spontaneous axonal regeneration abounds even in advanced cases.[952] In the small-fiber type, the primary impact of the disease also falls on the axons with secondary demyelination. In some patients, abnormalities in the autonomic nervous system closely parallel those in the peripheral nervous system. In these cases, prominent histologic changes include active axonal degeneration, affecting mainly unmyelinated and small myelinated fibers.[601]

The clinical presentation depends on varying combinations of the two basic types. On the whole, patients with adult-onset diabetes have the large-fiber type, with symptoms consisting of distal paresthesias and peripheral weakness. The patients have dissociated loss of vibratory,

position, and two-point discrimination sense with relative sparing of pain and temperature sense. The vulnerability at the common sites of compression may cause multiple pressure palsies. The small-fiber type of neuropathy characteristically affects those with insulin-dependent juvenile diabetes. Dysautonomia and pain predominate, often awakening the patients at night with painful dysesthesias, thus the designation *autonomic or painful diabetic neuropathy*. Charcot's joints, perforating ulcers, and other trophic changes of the feet may develop after severe loss of pain. Impotence and postural hypotension result from involvement of the autonomic nerves. Parasympathetic pupillary dysfunction precedes sympathetic pupillary denervation.[610] Quantitative measures of impaired sudomotor function correlate well with the severity of polyneuropathy.[512,517]

In contrast to distally prominent diffuse polyneuropathy, mononeuropathies most often involve the femoral nerve and lumbosacral plexus, and, to a lesser extent the sciatic, common peroneal, median, ulnar, and cranial nerves. Unilateral femoral neuropathy commonly develops as a complication in elderly men with poorly controlled diabetes. Thigh pain precedes wasting of the quadriceps and other proximal muscles of the anterior thigh. Diabetic mononeuropathy multiplex, part of the same spectrum, involves more than one nerve, most commonly ulnar and peroneal nerves, simultaneously or serially. This type of mononeuropathy, often vasculitic in nature, evolves more rapidly than the usual compression neuropathy, and show pain and sensory loss as primary symptoms. These patients do not respond to decompressive surgery, showing a poor prognosis as expected from axonal degeneration.

The sudden onset of pain associated with weight loss and Type II diabetes may herald involvement of a major proximal nerve trunk. This condition, although usually distinguished as diabetic amyotrophy, probably represents a form of diabetic mononeuropathy rather than a separate entity.[40,189] Acute painful neuropathy may also follow precipitous weight loss, but severe symptoms subside within 10 months. Unlike the distal symptoms of diffuse polyneuropathy, the proximal weakness tends to improve with adequate control of the diabetes. Diabetic and nondiabetic lumbosacral radiculopathies share many common clinical features with immune-mediated neuropathies.[290] The clinical spectrum of diabetic amyotrophy includes progression to severe quadriparesis.[1075] Some authors advocate pulsed methylprednisolone as a safe and effective therapy.[519]

Diabetic thoracic radiculopathy produces a distinct syndrome characterized by radicular involvement, abdominal or chest pain, and weight loss. Itmimics a myelopathy, but it has a relatively good prognosis. Polyradiculoneuropathy and truncal mononeuropathy may accompany advanced distal polyneuropathy. The episodes of diabetic truncal neuropathy may selectively involve the ventral or dorsal rami or branches thereof.[1042] Focal, unilateral protrusion of the abdominal wall on this basis may mimic abdominal hernia.[855] In one study of 60 patients with diabetic lumbosacral radiculoplexpathies, 9 also developed cervicobrachial involvement simultaneously or concurrently.[501] Two overlapping subgroups comprise (1) rapidly evolving form, considered immune-mediated vasculopathy in nature,[505] and (2) more slowly progressive condition, regarded as metabolic in origin.[57]

Electrophysiologic studies have revealed a number of different abnormalities in diabetic neuropathies, showing a close correlation between clinical findings and the degree of conduction changes.[275,838,864] A decline of motor nerve conduction velocity, however, does not underlie muscle weakness in Type II diabetic neuropathy.[447] Patients with signs of neuropathy have slower nerve conduction velocities and smaller amplitudes than those without symptoms.[315] In juvenile patients, those with the longest duration of disease have the highest incidence of abnormalities. Sural sensory potentials serve as a good predictor of diabetic neuropathy.[909] Interdigital nerve conduction study (NCS) of the foot using near-nerve needle technique may identify diabetic sensory polyneuropathy in the early stage.[850] Detection of small-fiber sensory neuropathy also improves by studying most distal sensory fibers such as medial plantar and dorsal sural nerves.[788,1115]

In the most common length-dependent polyneuropathy, conduction abnormalities develop symmetrically along the entire length of the nerve, but more in the distal than proximal segments

(see Fig. 7-11 in Chapter 7).[205,532,865,934] Studies reveal length-dependent changes involving the tibial and peroneal nerves more than the median and ulnar nerves with preferential involvement of the fastest conducting large myelinated fibers.[532] Despite reduction in number of motor units, however, this alone cannot explain the degree of conduction velocity slowing.[1196] Thus, in addition to amplitude-dependent distal slowing indicating a loss of large myelinated fibers, amplitude-independent slowing in intermediate segment suggests an additional demyelinative component.[419]

The conduction abnormalities in diffuse diabetic neuropathy can affect any part of the body, including the femoral[581] and phrenic nerve.[1204] Abnormalities, however, predominate at the common sites of compression, for example, across the carpal tunnel for the median nerve,[19,477] showing a delay with no major conduction block.[3] Minimal F-wave latencies serve as the most sensitive[29,205,532] and reproducible[551] measure of motor conduction abnormalities in diabetic polyneuropathy. Consistent with a length-dependent involvement, EMG detects fibrillation potentials and positive sharp waves in distal muscles, most prominent in the intrinsic foot muscles, indicating axonal degeneration.

Improved clinical management may relieve pain caused by diabetic neuropathy and promote the recovery of nerve conduction abnormalities.[112] Attempts for better glycemic control, in general, show encouraging results in reversing slowed conduction velocity and shortening F-wave latencies[444,518] and in preventing neuropathy.[248] In diabetic nerves, aldose reductase pathway inhibition could rapidly increase nodal sodium currents. This may restore the membranous sodium gradient reduced by activation of polyol pathway, thereby improving the slowed nerve conduction.[734]

Most patients with sensorimotor peripheral neuropathy also show absence of sympathetic skin response (SSR) and other abnormalities of sudomotor function,[1045] despite current limitations inherent in this technique.[113,1103] Other useful measures for detecting a subclinical neuropathy include quantitative autonomic examination of heart beat during deep breathing or the Valsalva maneuver (see Chapter 10-1).[195,202] Combined cardiorespiratory and nerve conduction scores may predict survival better than separate scores.[766] In one study,[563] cutaneous silent period study yielded more abnormalities than autonomic tests in the diagnosis of small-fiber diabetic neuropathy.

Patients with diabetes have abnormal persistence of sensory evoked potentials during induced ischemia. Other abnormalities reported include shortened refractory periods, indicating lower inactivation of sodium channels as the result of reduced sodium currents.[585,682] Studies of SEP suggest impairment of peripheral as well as central afferent transmission.[213,1061] Increased interpeak latencies of the brainstem auditory evoked responses (BAEPs) also suggest the presence of a central neuropathy in some cases,[257] but not in others.[1148]

Some studies emphasize other measures to characterize and quantitate the severity of neuropathy.[250,279,1092] Laser evoked potentials help assess dysfunction of small myelinated afferents.[7,8] Thermal thresholds testing confirm length-dependent abnormalities of the small myelinated and unmyelinated nerve fibers, showing a good correlation with the severity of polyneuropathy.[395,765] Study of vibration perception threshold, in contrast, provides a useful measure in the assessment of the large-diameter fibers.[542] Quantitative sensory testing complements NCS despite a low correlation between the two.[533]

Uremic Neuropathy

A variety of neuropathies result from complex effect of renal failure on peripheral neurons, myelin, and Schwann cells. Polyneuropathy usually develops in patients with severe chronic renal failure or in patients undergoing chronic hemodialysis. Clinical symptoms of neuropathy often begin rather abruptly with a sudden rise in vibratory threshold as one of the early signs. The lower limbs tend to show earlier and more prominent disturbances than the upper limbs. Some patients have restless legs as a presenting symptom. Thermal threshold testing reveals only infrequent abnormalities in

end-stage renal failure, showing little correlation with clinical and electrophysiologic evidence of polyneuropathy. These findings indicate relative sparing of small-diameter axons.[33] Histologic findings comprise axonal degeneration, secondary segmental demyelination, and, less frequently, segmental remyelination.[41,928] After successful treatment, vibratory perception generally returns to normal, followed by improvement in other clinical signs. The use of neurotoxic drugs such as nitrofurantoin can contribute to the nerve damage. Proximal muscle weakness may also appear in uremic patients receiving hemodialysis.[620] A distal ischemic mononeuropathy has developed following the placement of bovine arteriovenous shunts for chronic therapy.[89]

Mild electrical abnormalities sometimes herald clinical manifestations.[1224] Studies of late responses and sural nerve conduction also reveal a high degree of abnormality.[4,600] Conduction velocities decrease with the deterioration of signs and symptoms and increase with improvement after dialysis or kidney transplantation,[227,1159] but the question still remains whether NCS can monitor the adequacy of renal dialysis.[873] In acute renal failure, the muscle response may show a marked transient reduction in amplitude, presumably as the result of conduction block.[121] The partly reversible acute uremic neuropathy may show some demyelinating features simulating the GBS.[928] In contrast, a diminution in size of the CMAP seen in chronic renal failure signals axonal degeneration usually associated with fibrillation potentials.[91] Most uremic patients have an abnormal VEP and SEP.[933]

Neuropathies in Malignant Conditions

Malignant processes affect the peripheral nerve directly or indirectly.[214,885,942,1054] Lymphomas and leukemias may invade or infiltrate nerves through hematogenous spread, causing axonal damage,[510,840] whereas nonlymphomatous solid tumors may cause external compression. Cutaneous malignancies may spread to underlying nerves, a process known as perineural invasion, which may develop at a site distant from the original lesion after a long asymptomatic period.[1059] Subacute sensory neuropathy of oat cell carcinoma may result in severe sensory loss secondary to dorsal root ganglionitis. Remote malignancies may also affect the dorsal root ganglia and occasionally the anterior horn cells. Neuralgic amyotrophy may develop in association with radiation therapy for Hodgkin's disease.[688]

Approximately one-third of patients with malignancies develop clinically latent neuropathies.[858] Patients with lymphoma have heterogenous involvement of peripheral nervous system although Hodgkin's lymphoma shows a prevalence of polyradiculoneuritis.[108] Subacute sensory neuropathies, as an autoimmune disorder,[265] may result from the distant effects of lymphoma,[210,381,479] bronchogenic carcinoma, pancreatic carcinoma,[144] and, less commonly, tumors of the ovary, testes, penis, stomach, and oral cavity.[858] Both cytotoxic T-cell-mediated attack against neurons and humoral mechanisms play a role in this type of paraneoplastic syndrome.[1177] Anti-Hu antibody serves as a marker for such subacute sensory neuropathy. Some of these cases may also have encephalomyelitis or other upper motoneuron involvement.[803]Although rare, paraneoplastic manifestation of breast carcinoma include anti-collapsin response mediator protein 5 (anti-CRMP5)-positive sensory ataxic demyelinating neuropathy.[960]

Pathologic features include (1) neuronal degenerations with secondary peripheral or central axonal changes; (2) demyelination reminiscent of acute or chronic idiopathic polyneuritis; (3) microvasculitis with active wallerian degeneration causing mononeuritis multiplex[816]; (4) perineuritis defined as perineurial thickening and inflammation[1026]; and (5) opportunistic neuropathic infection. The cases of severe pain correlate to preferential loss of small myelinated and unmyelinated fibers.[820]

Patients have clinical findings of sensory or motor deficits or, more commonly, mixed involvement. Two main subgroups have emerged as the presenting symptoms: sensory ataxia and severe spontaneous pain, although occasional patients develop a pure motor neuropathy mimicking myasthenic syndrome. Other initial manifestations include the symptom of mental neuropathy causing numb chin[705] and intestinal

pseudo obstruction.[643] Thus, sensorimotor neuropathy represents a group of heterogenous conditions with overlapping clinical and histologic features.[35,161] The same type of progressive sensory neuropathy, termed *chronic idiopathic ataxic neuropathy*, may develop without evidence of cancer.[231] Distinguishing between paraneoplastic and nonparaneoplastic sensory neuronopathies can tax the clinician, but prominent neuropathic pain and neurologic dysfunction involving more than the peripheral sensory system should prompt a careful search for a cancer, especially if associated with an increased cerebrospinal fluid protein.[161] Despite generally disappointing therapeutic attempts, some patients with anti-Hu-associated paraneoplastic sensory neuropathy will respond to early aggressive immunotherapy.[810]

Quantitative sensory testing may uncover subclinical abnormalities involving both large and small fibers.[652] The conduction studies reveal a substantial reduction in SNAP[886] and CMAP amplitude with only mild slowing of conduction velocity. Despite the traditional emphasis on an inflammatory process in the dorsal root ganglia, electrophysiologic studies may also reveal motor conduction abnormalities.[811] Inmost cases, EMG typically shows fibrillation potentials and high-amplitude, long-duration motor unit potentials (MUPs) in atrophic muscles. Small, short-duration polyphasic potentials occasionally seen in wasted proximal muscles probably result from neuropathic abnormalities of the intramuscular axonal twigs.[59]

Vasculitic Neuropathy

In necrotizing angiopathy, probably related to autoimmune hypersensitivity, patients have systemic or nonsystemic vasculitic neuropathy (Collins, Periquet, Mendell, et al, 2003).[823] The inflammatory process, possibly through endothelial cell activation,[843] involves the small- and medium-sized arteries in multiple organ systems, including the thoracic and abdominal viscera, joints, muscles, and the nervous system. Necrosis of the media gives rise to small aneurysms and thrombosis of the vessels with palpable nodules along the affected arteries. This type of neuropathy also accompanies connective tissue disease such as rheumatoid arthritis, systemic sclerosis, nonvasculitic, steroid-responsive mononeuritis multiplex,[660] and Sjögren's syndrome,[410,823] or other multisystem diseases such as Wegener's granulomatosis,[475,783] cryoglobulinemia with an IgM Kappa M protein,[1089] and livedoid vasculitis, a dermatologic condition characterized by chronic, recurrent ulceration of the lower limb.[1100]

The clinical symptoms and signs, which may appear either abruptly or insidiously, consist of malaise, fever, sweating, tachycardia, and abdominal and joint pain. Approximately one-half of the patients develop either diffuse polyneuropathy or mononeuritis multiplex, which presumably results from ischemia caused by thrombosis of the nutrient arteries heavily infiltrated with inflammatory cells. The disease may remit spontaneously despite a generally poor prognosis with survival of only a few months to a few years after the onset of clinical symptoms. In one series, 6 of 16 patients had a distal symmetric sensorimotor polyneuropathy and 10, features of mononeuritis multiplex.[537] In a series of 106 histologically proven cases, 17 (16%) had clinical, electrophysiologic, and pathologic features of sensory neuropathy.[979] In another study of 23 patients with giant cell arteritis, 11 had a generalized neuropathy; 9, a mononeuritis multiplex; and 3, a mononeuropathy.[148] Other types of neuropathy described in association with this syndrome include acute motor axonal neuropathy.[49] Hepatitis C–associated vasculitic neuropathy may show exacerbation after interferon therapy.[93]

In the affected limbs, NCS shows a slow velocity in proportion to the reduced CMAP and SNAP amplitude. Nonuniform axonal regeneration may give rise to pathologic temporal dispersion and phase cancelation (see Chapter 11-5), mimicking demyelinating neuropathy.[10] In addition, a conduction block (see Fig. 5-11A,B in Chapter 5) may result from subinfarctive nerve ischemia affecting the segment outside the usual sites of compression.[110] Serial studies, however, usually demonstrate conversion of the electrophysiologic findings to those most consistent with severe axonal loss. Needle studies reveal spontaneous activities in atrophic muscles as expected in acute or subacute axonal neuropathy.

Superficial peroneal nerve and peroneus brevis muscle biopsy using direct immunofluorescence helps establish the diagnosis of vasculitic neuropathy.[200,1168] Epidermal nerve density studies indicate small-diameter sensory neuropathies.[624] Some patients with sensory-predominant, painful, idiopathic neuropathy have inflammatory changes in sural nerve, the finding consistent with autoimmune vasculopathy that may respond to immunotherapy.[504]

Sarcoid Neuropathy

Patients develop distal sensorimotor polyneuropathy as a rare complication of sarcoidosis. Typical neuropathies associated with this disorder include GBS, mononeuritis multiplex, lumbosacral plexopathy and purely sensory neuropathy.[413,1236] Histologic studies reveal granulomata or inflammatory changes in the epineural and perineural spaces, leading to periangitis, panangitis, and axonal degeneration.[808] Abnormal warm and cold sensation thresholds suggest small-fiber neuropathy in some patients with sarcoidosis.[429] Electrophysiologic abnormalities include reduced CMAP and SNAP amplitudes with mild slowing in NCS[162,808] and prominent fibrillation potentials and positive sharp waves in EMG. In one case, morphologic studies confirmed the electrodiagnostic impression of an acute axonal and demyelinating neuropathy.[772] Differential diagnosis should include rare nerve root involvement of sarcoidosis, causing polyradiculopathy.[546]

Neuropathy in Sjögren's Syndrome

Sjogren's syndrome characterized by dryness of the eyes, mouth, and other mucous membranes also involves various other anatomic structures such as joints, blood, internal organs, skin, muscle, and central and peripheral nervous systems. Peripheral neuropathy occurs in a large proportion of patients, in most cases as a subclinical demyelinating neuropathy.[369] Other forms include mononeuropathy multiplex, distal sensory neuropathy, distal sensorimotor neuropathy, and small-fiber sensory neuronopathy.[160,496,497,663,1169] In one series of 33 cases,[722] symmetric sensorimotor polyneuropathy ranked the first in incidence, followed by symmetric sensory neuropathy. Approximately one-fourth of patients had superimposed autonomic neuropathy, mononeuropathy, or cranial neuropathy. In another series, most patients with neuropathy and a positive lip biopsy for Sjögren syndrome had a painful, distal, axonal sensory neuropathy.[371] Some of the clinical and neurophysiologic findings suggest the involvement of the spinal ganglion and postganglionic sympathetic ganglion cells.[575] The symptoms, generally mild at the onset, slowly progress.[1169] Electrophysiologic and sural nerve biopsy studies reveal evidence of necrotizing vasculitis with axonal degeneration more than demyelination.[871] The symptoms may respond to intravenous immunoglobulin therapy (IVIG).[538]

Critical Illness Neuropathy

Critically ill patients may develop a severe motor and sensory polyneuropathy of unknown cause[90] and other neuromuscular diseases with prolonged ventilator dependency.[1032] Some investigators advocate the term *critical illness neuropathy* as a useful clinical concept,[87] whereas others argue that the enormous complexity encountered in critical illness weakness makes the implication of a neuropathy as the sole cause of syndrome untenable.[105] The first reported case had difficulty in weaning from the ventilator after being critically ill. These patients usually have sepsis and multiple organ failure for at least 30 days. This type of polyneuropathy may escape clinical detection because a thorough assessment on such ill, bedridden patients often proves difficult.[136] Incomplete recovery frequently occurs within 1–2 years after the onset of disease.[1233]

In one series of 48 cases,[514] most patients with acquired neuromuscular dysfunction after sepsis had both myopathy and neuropathy, with changes in NCS developing early in the course of severe sepsis. In another study,[1106,1108] critically ill patients demonstrated normal motor unit number estimate (MUNE) despite reduced CMAP amplitude, suggesting predominantly myopathic injury with small motor unit potential (MUP) in the setting of severe weakness (see Chapter 27-7). Limb compression during unattended coma may also cause multiple peripheral nerve injuries.

The unique combination of swollen limbs, pressure blisters, and myoglobinuria constitutes the compartment syndromes. In one study,[426] 68% of GBS patients admitted to the intensive care unit develop features of axonal degeneration, not related to the usual precipitants of critical illness neuropathy. Histologic investigations of muscle atrophy in two critically ill patients with generalized weakness revealed marked Type I and Type II muscle fiber atrophy and only minor axonal degeneration of sural nerve and intramuscular nerve fibers.[1202]

EMG examination reveals the evidence of partial denervation with fibrillation potentials, positive sharp waves, and occasional complex repetitive discharges (CRDs) in a widespread distribution. Conduction studies show relatively well-preserved nerve conduction velocities and distal latencies, but with considerable reduction of CMAP and SNAP amplitudes. Although not well defined at present, the major features suggest an axonal polyneuropathy without conduction block or pathologic temporal dispersion. Direct muscle stimulation,[914] in comparison to nerve stimulation, may help differentiate neuropathic and myopathic process.[1106] This semiquantitative method, however, falls short of establishing a conclusive diagnosis as both types of changes may coexist.[88]

Other Disorders Associated with Neuropathies

Sensorimotor neuropathy may accompany some multisystem atrophy like Shy-Drager syndrome, Crow-Fukase, or syndrome of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) (see Chapter 24-3),[253,1060,1163] the syndrome of skin pigmentation, edema, and hepatosplenomegaly[1109] and hypo or hyperthyroidism.[272,558,769] Systemic lupus erythematosus may accompany predominantly demyelinating polyneuropathy at times as the presenting feature.[712,827,828] Sensory neuropathy develops as part of the cerebellar ataxia neuropathy vestibular reflexia syndrome.[1067]

Patients with the Churg Straus syndrome have a vasculitic neuropathy associated with the hypereosinophilic syndrome.[322,1205] It affects both the sensory and motor fibers with multifocal conduction abnormalities (see Fig. 5-11A,B in Chapter 5) and evidence of severe axonal degeneration. Demyelinating neuropathy may also occur as a rare manifestation of Creutzfeldt-Jakob disease.[774] Patients with mitochondrial neurogastrointestinal encephalomyopathy may develop mixed axonal and demyelinating neuropathy, which mimics CIDP.[60] The eosinophilia-myalgia syndrome[569] associated with L-tryptophan preparations may cause a sensorimotor neuropathy characterized by segmental demyelination and distal axonal degeneration.[127,262,331] Patients with polymyalgia rheumatica with muscle aching, tenderness, and weakness, often attributed to steroid-responsive myositis[116] may also have a peripheral neuropathy.[950,977]

The neuropathy associated with polycythemia vera involves large and small myelinated fibers with mild slowing of motor and sensory conduction.[1216] Distal axonal degeneration follows ischemia produced by thromboembolic occlusion of a major proximal limb artery,[1190] especially in patients at risk with uremia, diabetes,[919] or peripheral arterial disease.[300] Chronic peripheral arterial occlusive disease also gives rise to an axonal neuropathy characterized by abnormalities of sural nerve SNAP and peroneal and tibial nerve F-wave latencies.[635,1181] Tourniquet paralysis could also mimick acute demyelinating neuropathy.[1050]

Multiple sclerosis occasionally accompanies hypertrophic demyelinating neuropathy with typical nerve conduction changes.[348,983] Denervation of the rectal sphincter characterizes multisystem atrophy with an autonomic neuropathy.[907] Burn patients may have undiagnosed neuropathy.[698] Polyneuropathy may also result from lightning injury,[411] severe hypothermia[6] and graft-versus-host disease.[25]

Other systemic disorders sometimes associated with a polyneuropathy include acromegaly,[469] β-thalassemia,[1037] celiac sprue,[181,917] cerebrotendinous xanthomatosis,[1167] chronic mountain sickness,[1096] Crohn's disease,[442] Ehlers-Danlos syndrome,[1166] hemophagocytosis syndrome,[431] hemophilia,[166] insulinoma,[414] Leigh's disease,[198,466] liver disease,[715] Machado-Joseph disease (SCA3),[199] maple syrup urine disease,[541] multiple symmetric lipomatosis,[764] multiple system atrophy,[2]

Parkinson's disease,[818] scleroderma,[883] sickle cell anemia,[927] tyrosinemia,[362] Wernicke-Korsakoff syndrome,[459] Whipple's disease[222] and xeroderma pigmentosum.[418]

3. INFLAMMATORY, INFECTIVE, AND DYSIMMUNE NEUROPATHIES

Immune-Mediated Neuropathies

This category of neuropathy, traditionally called the GBS, consists of a wide range of disorders: acute inflammatory demyelinating polyneuropathy (AIDP) as the prototype and its variants, Miller Fisher syndrome (MFS), acute motor axonal neuropathy (AMAN) prevalent in China and Japan, acute motor sensory axonal neuropathy (AMSAN), acute sensory ataxic neuropathy (ASAN), and acute motor conduction block neuropathy (AMCBN).[137,691,1135] In paraproteinemia and those associated with infection, immunoglobulin M (IgM) or immunoglobin G (IgG) antibodies against specific gangliosides block functionally relevant epitopes for nerve conduction or neuromuscular transmission.[612,1206]

In general, IgM autoantibodies accompany chronic progressive neuropathies, and IgG antibodies, acute onset neuropathies or a variant of GBS. Of these, IgM autoantibodies include anti-MAG antibodies associated with distal, predominantly motor neuropathies, and antibodies to GD1b and disialosyl gangliosides found in ataxic, large-fiber sensory neuropathy. In contrast, IgG autoantibodies comprise anti-GQ1b antibodies seen in over 90% of patients with MFS and anti-GM1, GM1a, GalNac-GD1a, and GM1b antibodies associated with acute motor axonal neuropathy (AMAN).[232] Antisulfatide antibodies accompany axonal neuropathy, mixed sensory, or sensorimotor axonal neuropathies and predominately sensory demyelinating neuropathy. Anti-GM1 antibody IgG subclass may serve as a predictor for clinical recovery of GBS patients.[584] The IgG1 subclass associated with preceding gastroenteritis and campylobacter jejuni serology tends to indicate slow recovery, whereas the IgG3 subclass associated with preceding respiratory infection may suggest rapid recovery.[549] In GBS patients without ophthalmoparesis, the presence of IgG anti-GQ1b antibody may serve as a factor predictive of respiratory failure.[482] The genetic polymorphism of campylobacter jejuni may determine autoantibody reactivity as well as the clinical presentation of GBS.[548,1203]

In this category of neuropathy, the segment of maximal involvement varies from one patient to the next. This helps explain the diversity of clinical and electrophysiologic abnormalities seen in a number of subtypes of GBS, showing different pathologic features. Classification of these subtypes based on NCS correlate closely with pathologic changes seen in sural nerves—almost complete sparing of sural nerve in AMAN and macrophage-mediated demyelination and lymphocytic infiltration in AIDP.[669] Electrophysiologic studies also reveal sensory conduction abnormalities, more frequently for the median and ulnar nerves than sural nerves in AIDP but not in AMAN.[594] Immunomodulatory treatments, alone or in combination with other medication, provide an effective immunotherapy for most of these autoimmune disorders.[104,365]

The pathophysiology of demyelination and its clinical consequences include (1) elevated thresholds, giving rise to slowed impulse propagation and prolonged refractory periods; (2) conduction block with clinical weakness and sensory loss; (3) increased desynchronization of volleys causing temporal dispersion of waveforms, loss of reflexes, and reduced sensation; (4) exaggerated hyperpolarization after the passage of impulse, inducing frequency dependent conduction block, possibly as the cause of fatigue after sustained effort; and (5) steady or bursts of ectopic discharges at sites of focal demyelination considered responsible for facial myokymia and spontaneous or mechanically induced paresthesias.

Of these, slowing of conduction by itself induces little, if any, clinical deficits, as long as all the impulses arrive at the target organ. A prolonged refractory period for transmission also causes no symptoms because voluntarily induced repetitive discharges have a substantially longer time interval. The types of nerve conduction abnormalities,[283] however, offer potentially important clues to differential diagnoses. For example, hereditary demyelinating neuropathies

like hypertrophic type of Charcot-Marie-Tooth (CMT) disease show uniform slowing along the length of the nerve. In contrast, acquired demyelinating neuropathies such as GBS show nonuniform involvement with pathologic temporal dispersion and conduction block in certain parts of the nerve. Unlike reduced conduction velocity, a complete or intermittent conduction block often accompanies major loss of strength. In fact, this feature, if assessed quantitatively, correlates best with the degree of weakness in patients with demyelinating diseases.[483,1128]

Acute Inflammatory Demyelinating Polyneuropathy

PATHOGENESIS AND GENERAL CHARACTERISTICS

Although of unknown etiology, AIDP and related demyelinative neuropathies closely resemble experimental allergic neuritis [974] either by active immunization with extracts of peripheral nerve [408] or by repeated transfer of P2-protein reactive T cell lines.[611] Infectious agents associated with this syndrome include human immunodeficiency virus (HIV),[208] herpes zoster virus,[830] hepatitis B virus, West Nile virus,[11] campylobacter jejuni,[407,580,984] mycoplasma with anti-Gal-C or anti-GM1 antibody,[582,1063] cyclospora [915] and falciparum malaria.[1019] In the majority, however, repeated attempts have failed to isolate infective agents. These findings support an autoimmune pathogenesis rather than direct invasion of the nerve by infectious agents.[516,1193] Genetic factors may impose a risk[752] as evidenced by rare familial GBS.

Serum and cerebral spinal fluid (CSF) anti-GM1 antibodies may play a key role in the pathogenesis of demyelination[890,1002] as well as axonal degeneration.[467] The serotypic determinant of PEN 19 of campylobacter jejuni may aide in the production of anti-GM1 antibody by a GM1-like lipopolysaccharide.[1229] A child born to a mother with ongoing GBS developed the disease 12 days postpartum, suggesting a delayed effect of transplacentally transferred blocking antibodies.[124] Similarly, IgG anti-GM antibodies raised in rabbits can reversibly block the voltage-gated sodium channels of nerve cells.[1180]

The adjusted AIDP incidence rate varied between 1.65 and 1.79 per 100,000 with the in-hospital molarity rate of 2.58% during the years 2000 through 2004.[16] The incidence rate from different countries showed no significant differences,[184] although occasional epidemics have occurred in China.[1215] This inflammatory demyelinative neuritis affects all levels of the peripheral nervous system, occasionally with retrograde degeneration in the motor cells of the spinal cord or brainstem. In mild cases, pathologic changes may consist of slight edema of the nerves or roots with only minimal inflammatory infiltrates.[929,975] In contrast, the fulminant syndrome may show universal inexcitability of the peripheral nerves with axonal degeneration secondary to inflammation.[70,312]

CLINICAL FEATURES

Although clinical and pathologic findings vary even among patients with the classical AIDP, certain diagnostic criteria have emerged (Table 24-1).[42,430,1133] In about two-thirds of the cases, neurologic symptoms follow a mild, transient infectious process of either the respiratory system or, less commonly, the gastrointestinal system. A single infectious agent causes more than one type of pathology, implying interaction with additional host factors.[387] Some patients seem to have other precipitating events such as polio,[536] hepatitis B vaccination, yellow fever vaccination,[1164] rabies vaccine treatment [134] and allogeneic bone marrow transplantation.[1185]

The first symptoms of neuropathy usually appear in about 1–2 weeks, when the infection has resolved. Weakness initially involves the lower limb, sometimes rapidly progressing to the upper limb and the face within a few days. Paralysis of proximal muscles and facial diplegia stand in contrast with the distal weakness characteristic of other forms of neuropathy. Patients may have myokymia and even involuntary contraction resulting from continuous motor unit discharges.[887] Occasionally, the disease takes the form of encephalomyeloradiculoneuropathy with progressive central nervous system disease,[760] papilledema,[775] bilateral deafness [771] and severe sensorimotor neuropathy.[1186] For example,

Table 24-1 Nerve Conduction Study Criteria for Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Acute Motor Sensory Axonal Neuropathy (AMSAN), and Acute Motor Axonal Neuropathy (AMAN)

AIDP
One or more of the following in two or more nerves, or two or more of the following in one nerve if all others inexcitable and CMAP (distal) ≥10% LLN
Motor conduction velocity < 90% LLN (85% if CMAP [distal] <50% LLN)
Distal motor latency >110% ULN (120% if CMAP [distal] <100% LLN)
CMAP (distal)/CMAP (proximal) ratio <0.5 and CMAP (distal) ≥20% LLN
F-response latency >120% ULN
AMSAN
None of the features of AIDP except one demyelinating feature allowed in one nerve if CMAP (distal) <10% LLN
Sensory action potential amplitudes < LLN
AMAN
None of the features of AIDP except one demyelinating feature allowed in one nerve if CMAP (distal) <10% LLN
Sensory action potential amplitude >LLN
Inexcitable
CMAP (distal) absent in all nerves or present in only nerves with CMAP (distal) <10% LLN
Definitions:
CMAP (distal)—compound muscle action potential amplitude after distal stimulation
CMAP (proximal)—compound muscle action potential amplitude after proximal stimulation
LLN—lower limit of normal
ULN—upper limit of normal

(Modified from Cornblath and Hughes.[206])

campylobacter jejuni infection can cause not only an acute polyradiculoneuropathy but also an encephalomyelitis.[493] The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), a common electrolyte disorder, has significant association with AIDP severity as an indicator of poor prognosis.[954] Rarely, seizures and other signs of cerebral involvement may signal the onset of illness in pediatric population.[1192] In preschool children, refusal to walk and complaint of pain, as the presenting symptoms, often mislead the physician, delaying the diagnosis.[926]

The initial symptoms may include unilateral involvement of the cranial and phrenic nerves[956] or nerves supplying the oropharynx, neck, and proximal upper-limb muscles.[38,139] Respiratory problems develop in approximately one-half of the patients,[270] especially in the primary demyelinating group,[269] sometimes requiring emergency intubation.[1188] Predicting respiratory failure must rely more on clinical features and vital capacity than electrophysiologic studies of phrenic nerve.[271] Occasional patients have an acute, severe, progressive illness with quadriplegia in 2–5 days, requiring mechanical ventilation over 2 months.[335]

Pain, often severe, may dominate the symptoms in the whole spectrum of GBS, including MFS and pure motor patients.[370, 945] It frequently occurs as the first symptom but may even last for at least 1 year despite minimal sensory loss. Careful testing usually reveals deficiencies in vibratory sense, two-point discrimination, and pain perception. The autonomic dysfunction mainly

results from axonal degeneration of the vagus and splanchnic nerves as seen in experimental allergic neuritis. It primarily involves sympathetic vasomotor and parasympathetic cardiovascular fibers but also sudomotor, gastrointestinal, and other systems.[1034] Thus, the patient may have transient elevation or fluctuation of blood pressure and heart rate,[324] ileus,[128] and urinary retention from internal sphincter obstruction induced by sympathetic hyperactivity.[955]

The disease follows an acute or subacute course with usual progression up to 6 weeks after onset.[438] The symptoms and signs then plateau for a variable period of time followed by gradual improvement. Some authors distinguish an intermediate form between AIDP, which requires less than 4 weeks of progression, and CIDP, which shows progression exceeding 2 months.[813] Patients with acute CIDP, however, may initially have a course of disease compatible with that of AIDP and later develop exacerbations and remissions.[947] The CSF typically contains high protein and no cells with the exception of some lymphocytes in occasional cases. Marked CSF pleocytosis or the presence of polymorphonuclear granulocytes, though rare, does not rule out the diagnosis of AIDP.[906] Glial fibrillary acidic protein may serve as a marker.[794]

Although some patients improve dramatically following corticosteroid therapy,[807] prednisone may adversely affect the eventual outcome of the disease.[446] Plasma exchange[43,473] has the beneficial effect, but not universally.[724] Some patients show antibody rebound after the therapy, with deterioration of NCS results.[925] Treatment with intravenous immunoglobulin (IVIG) usually,[258,260,905] but not always,[151] provides a beneficial effect by blockade of blocking antibodies.[122,232] Side effects of IVIG, though rare, include stroke[133] and myocardial infarction.[1036]

The time course of recovery depends on the extent of demyelination and, more important, axonal degeneration.[184] In one series, severe residual deficits developed in the patients with highly elevated anti-GM1 activity,[1131] and in another, in those with high IgG antibody titers against GD1a ganglioside.[1230] Some patients have severe axonal loss without inflammation or demyelination[310,1225] or secondary to demyelination.[217,312] Such patients may not regain motor function for 1–2 years. Although specific treatment has shortened the duration of mechanical ventilation, elderly patients with preexisting pulmonary disease tend to require tracheostomy.[616] Other factors associated with poor prognosis included advanced age, preceding diarrhea, and low Medical Research Council sum score.[1176]

In some patients, impaired joint mobility,[1027] severe residual fatigue,[347] neuropathic pain,[860] and psychosocial dysfunction[77] may become a disability despite an improving neurologic status,[236] attesting to the importance of supportive care.[441] Residual motor and sensory dysfunction endures in approximately half of patients.[264] Pulmonary morbidity predominates in patients with AIDP admitted to the intensive care unit.[417] In some patients, physical training improves functional outcome and quality of life.[346] The presence of residual signs in patients with mild disease may advocate the use of early treatment in mildly affected patients.[1138] Rasch-built Overall Disability Scale[1140] specifically captures activity and social participation limitations in patients with immune-mediated peripheral neuropathies. In one study,[1139] a simple scoring system based on age, history of diarrhea, and GBS disability score at 2 weeks accurately predicted outcome at 6 months. Disability measures must address the arms as well as the legs in evaluating immune-mediated polyneuropathies.[727]

ELECTRODIAGNOSTIC FINDINGS

Electrodiagnosis plays a key role in the evaluation. In advanced stages, an NCS usually shows substantially reduced velocities and a pathologically dispersed CMAP (see Figs. 5-10A,B in Chapter 5). In milder forms, studies may reveal less dramatic changes because initial weakness commonly results from proximal conduction block without distal abnormalities. Indeed, 15%–20% of cases have entirely normal studies distally during the first 1–2 weeks, which by no means preclude the diagnosis.[295,531] Thus, neurophysiologic abnormalities seen early in AIDP[1172] often relate to H reflex (see Chapter 9-2), F waves (see Chapter 7-4), and blink reflex (see Chapter 8-6). In one series, ectopic A wave, or proximal

re-excitation of motor axons (see Chapter 7-5), constituted the most common late discharges seen during early stage.[935]

The initial absence and later delay of the F wave with normal distal conduction (see Figs. 7-7 and 7-10 and Table 7-4 in Chapter 7) characterizes a typical pattern of abnormalities. These findings indicate the vulnerability of the most proximal, possibly radicular, portions of the motor fibers with little changes along the main nerve trunk at the onset of illness.[363,526,531,535,717] Isolated absence of F wave may result from proximal conduction block or axonal degeneration.[596] Alternatively, F waves may disappear with impaired excitability of motoneurons or motor axons.[1072,1217]

As in any neuropathy, the early changes may also selectively involve the common sites of compression[591] and the most terminal segment, presumably reflecting the longest distance from the cell body. The involvement of this segment results in increased duration of a distally elicited CMAP as a marker of pathologic temporal dispersion.[899] Immune-mediated attacks on the axolemma of motor fibers may also give rise to rapidly resolving conduction slowing and conduction block in the absence of demyelination.[598] Electrophysiologic signs of axonal loss abound in a follow-up study of AIDP.[263] Early and severe demyelination with secondary axonal damage may mimic AMAN variant clinically and electrophysiologically showing inexcitability of motor nerves.[485,704,1162] Children, who tend to recover sooner, otherwise, have similar neurophysiologic evaluation.[242]

Despite the clinical pictures of predominantly motor involvement, sensory or mixed NCSs[670] show distinct, albeit milder, abnormalities of the median and ulnar nerves. Interestingly, the disease tends to spare the sural nerve sensory action potential, often regarded as one of the first affected in other neuropathies.[17] In fact, patients with AIDP typically show relative preservation of the sural sensory response, associated with absent or prolonged F waves.[15] Quantitative thermal threshold measurements may uncover early abnormalities of small nerve fibers.[1087] Phrenic nerve conduction time may provide a sensitive measure in predicting impending ventilatory failure.[220] Studies of the blink reflex frequently reveal conduction abnormalities as expected from clinical facial palsy (see Figs. 8-4 and 8-7 and Table 8-4 in Chapter 8). Although less sensitive than F wave,[824] SEP studies may demonstrate a proximal conduction delay between Erb's point and the cervical cord despite normal sensory conduction distally.[363]

Facial or limb myokymic discharges (see Fig. 14-12B in Chapter 14) may appear early, sometimes persisting during the course of illness.[708] Rare spontaneous activities include continuous motor unit discharges, or neuromyotonia.[887] Otherwise, EMG usually shows only a reduced interference pattern indicating neurapraxia without axonal degeneration. Occasional patients with typical clinical features, however, may have a primarily axonal neuropathy and prominent denervation first detectable 2-3 weeks after onset.[717] Single muscle fiber studies may show concomitant blocking of the two muscle fibers, implicating an axolemmal dysfunction.[1030]

Sequential conduction studies show a great variability among different patients and even from one nerve to another in the same patient.[530] Relatively common patterns of conduction failure include a length-dependent and uniform reduction of CMAP presumably based on a random distribution of lesions.[1134] Reversible proximal conduction block often underlies a rapid recovery.[74] In contrast, reduction in amplitude of CMAP with distal stimulation generally suggests axonal degeneration, especially when accompanied by normal conduction velocities.[209,225,382,731] Here, functional recovery depends on axonal regeneration, which takes considerably longer than remyelination. Very small distally evoked potentials, however, may also result from primary demyelination of terminal branches.[389,335] Thus, this finding does not necessarily imply a poor prognosis, especially in children.[1221] The nerve conduction velocity often becomes slower while the patient begins to improve, demonstrating again the lack of a strong correlation between clinical and this aspect of electrophysiologic assessments.

Miller Fisher Syndrome and Sensory Ataxia Neuropathy

This syndrome[323] consists of ataxic gait, absence of the muscle stretch reflexes, and ophthalmoplegia. In one series of 50 consecutive patients,

features frequently seen, in addition to the triad, included pupillary abnormalities, blepharoptosis and facial palsy, and no sensory loss despite the presence of profound ataxia.[749] Despite immunologic peculiarities of this subgroup[689] as evidenced by its association with serum antibodies to GQ1b ganglioside,[123,583,845] it probably constitutes a cluster within the overlapping spectrums of the GBS. Some patients with anti-GQ1b antibody syndrome have Bickerstaff brainstem encephalitis[805] characterized by drowsiness, extensor plantar responses, and hemisensory loss, in addition to ophthalmoplegia and ataxia.[655,801] Others have acute ophthalmoplegia without ataxia, manifesting various combination of external and internal involvement.[626]

Some patients with chronic ophthalmoplegia of unknown cause also show high titers of IgG anti-GQ1b antibodies typically found in patients with acute ophthalmoplegia.[908] Some of these cases also show electrophysiological evidence of neuromuscular transmission defects.[656,657] Occasional patients with the ataxic form of AIDP may also have the same antibodies, which suggest that these two syndromes form a continuous spectrum.[1228] Haemophilus influenzae infection may precede MFS much as campylobacter jejuni enteritis associated with AIDP.[550]

To compound the issue, some patients with AIDP associated with IgG nonspecific to ganglioside GD1b may show clinical characteristics of acute cerebellar or sensory ataxia.[739,842] Also, some patients develop severe sensory ataxia and demyelinating polyneuropathy associated with IgM anti-GM2 and GalNAc-GD1a antibodies.[662] Patients with ASAN, which resembles this syndrome, have severe sensory loss, no motor deficits, and a poor prognosis.[1070] Antibody against QD1b may play a role in the pathogenesis of this condition.[737,795,798] Despite the absence of muscle weakness, some of these patients show evidence of demyelination in motor NCS, which plays the key role for the diagnosis.[814]

Electrophysiologic studies of MFS usually reveal characteristics of an axonal neuropathy or neuronopathy with prominent sensory nerve changes in the limbs and motor damage in the cranial nerves.[334] Serial studies in such a case may show a time course of conduction changes similar to that seen in AIDP.[1119] Needle studies usually uncover only slight abnormalities in the limbs and evidence of facial denervation. Serial transcranial magnetic stimulation (TMS) may document reversible corticospinal tract conduction abnormalities.[658] Quantitative cardiovascular autonomic function tests reveal abnormalities of both sympathetic and parasympathetic functions at the height of MFS.[678]Plasmapheresis may[180] or may not[748] improve ophthalmoplegia and ataxia.

Chronic Inflammatory Demyelinating Polyneuropathy

Ad Hoc Committee of the American Academy of Neurology[27] recommended clinical and research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP)[962] based on symptoms and signs, electrodiagnostic studies, lumbar puncture and cerebrospinal fluid examination, laboratory tests appropriate to the specific clinical situation, and, when available, results from nerve biopsy. Research criteria designed for selection of patients to clinical trials does not apply in clinical practice as it excludes a substantial number of patients who could otherwise qualify. The clinical criteria for the diagnosis will serve as a guideline for clinicians, even though it does not encompass all cases that neurologists will diagnose as CIDP.[115] Diagnostic criteria of probable and possible cases should help categorize the patients who had neither a lumbar puncture nor a nerve biopsy. This recommendation lists a set of mandatory features required for a definite diagnosis, supportive features, which, though helpful in clinical diagnosis, by themselves do not make a diagnosis, and exclusionary features, which strongly suggest alternative diagnoses. Table 24-2 summarizes the mandatory criteria for CIDP. Epidemiologic data include the prevalence of 1.97 per 100,000 based on 1991 American Academy of Neurology criteria as compared to 4.77 established by 2006 European Federation of Neurological Societies/Peripheral Nerve Society criteria, which provide a higher diagnostic sensitivity.[902]

Current knowledge supports an autoimmune etiology of CIDP,[1102] although its heterogeneity with a wide spectrum of the phenotypes precludes the elucidation of the specific cause.[1016]

Table 24-2 Criteria for the Diagnosis of Chronic Inflammatory Demyelinative Polyneuropathy (CIDP)

Clinical features for the mandatory criteria consistent of:

1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of a peripheral nature involving more than one limb, developing over at least 2 months
2. Hypo- or areflexia, usually involving all four limbs

Physiologic studies confirm the predominant process of demyelination by documenting three of the four findings listed below:

1. Reduction in conduction velocity in two or more motor nerves:
   a. Less than 80% of lower limit of normal (LLN) if amplitude is more than 80% of LLN
   b. Less than 70% of LLN if amplitude is less than 80% of LLN
2. Partial conduction block or abnormal temporal dispersion in one or more motor nerves, e.g., peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow
   a. Criteria suggestive of partial conduction block comprises less than 15% change in duration and more than 20% drop in negative-peak area or peak-to-peak amplitude between proximal and distal sites
   b. Criteria for abnormal temporal dispersion and block consist of more than 15% change in duration and more than 20% in amplitude between proximal and distal sites. These criteria are derived from studies of normal individuals
   c. Additional studies, such as stimulation across short segments or recording of individual motor unit potentials are required for confirmation
3. Prolonged distal latencies in two or more nerves:
   a. More than 125% of upper limit of normal (ULN) if amplitude is more than 80% of LLN.
   b. More than 150% of ULN if amplitude is less than 80% of LLN.
4. Absent F waves or prolonged minimum F-wave latencies (10–15 trials) in two or more motor nerves:
   a. More than 120% of ULN if amplitude more than 80% of LLN.
   b. More than 150% of ULN if amplitude less than 80% of LLN.

Nerve biopsy shows unequivocal pathologic evidence of demyelination and remyelination:

1. Demyelination by either electron microscopy (more than 5 fibers), or teased fiber studies (more than 12% of 50 teased fibers, minimum of four internodes each, demonstrating demyelination/remyelination)

Cerebrospinal fluid studies reveal:

1. Cell count less than 10/mm^3 if HIV-seronegative or less than 50/mm^3 if HIV-seropositive
2. Negative VDRL

(Modified from Sander and Latov.[962])

Some authors distinguish the patients with only distal symptoms as having distal acquired demyelinating symmetric polyneuropathy (DADS), and they further classify DADS into those with and without circulating benign immunoglobulin monoclonal protein (M protein).[757] Those with M protein often have pathogenic antibodies against myelin-associated glycoprotein (MAG) causing MAG neuropathy (see subsequent section of this section). Systemic passive transfer of immunoglobulin causes demyelinative disease with substantial reduction of conduction velocity.[415,1212] Anti-MAG antibodies may develop later during the course of the disease.[1125]

The GM1 and GM3 autoantibodies may play a role in the pathogenesis of CIDP in systemic lupus erythematosus.[1004]

Apart from its chronicity reflecting axonal changes,[332] CIDP continues to worsen with persistent evidence of ongoing demyelination beyond 2 months.[56,714] Some patients may initially develop features similar to the AIDP.[747] In fact, up to 20% of patients have acute onset characterized by rapid, progressive weakness with a nadir of the first episode of weakness within 2 months from onset of disease and a consecutive chronic course.[945,946] Some acute-onset CIDP patients have more prominent sensory signs and less autonomic dysfunction, facial weakness, and preceding infectious illness compared to AIDP patients.[252] Others have prominent cranial nerve involvement, dysautonomia, respiratory failure, and autoantibodies.[396]

The disease may affect only upper limbs or follow a progressive course over several years with severe generalized disability.[373,1093] Other possible features include fatigue,[98] dropped head syndrome,[428] dysautonomia,[453] tonic spasm,[1146] phrenic nerve palsy,[1049] ventilatory failure,[523] and hypoglossal nerve involvement.[1211] Clinical features vary based on the patient's age at the onset of illness, which, therefore, should play a role in considering the diagnosis, therapy, and prognosis.[409] The risk of relapse increases during pregnancy.[713] Familial occurrence may indicate genetic predisposition.[450]

The clinical spectrum includes, in addition to classical CIDP, asymmetric, pure MMN, asymmetric, multifocal acquired demyelinating sensorimotor neuropathy (MADSAM), distal acquired demyelinating symmetric sensorimotor neuropathy,[967] and an ataxic form of CIDP.[1214] Although rare, focal neuropathy may precede the onset by several years,[1149] or asymmetrical polyneuropathy may show a stepwise progressive course.[1161] Chronic motor axonal polyneuropathy (CMAN) associated with antibodies against N-acetylgalactosminyl GD1a,[486] pure sensory presentation,[73,182,812,998] and chronic immune sensory polyradiculopathy[1006] may constitute a variant of CIDP.[193,373,485,1120] Steroid-responsive hereditary sensory neuropathies may imply a superimposed acquired demyelination.[83,287]

Children may have clinical features, which mimic a genetically determined disorder,[1009] or atypical pattern with more proximal weakness.[742] Compared with adults, they tend to have more precipitous onset, a higher incidence of gait abnormalities, greater neurologic deficits,[999,1000] good response to corticosteroids, and a benign course with full recovery.[922]

The onset of CIDP may rarely follow the treatment of chronic viral hepatitis C with interferon-α, sometimes associated with the occurrence of a number of autoimmune disorders.[653,725] Patients receiving tumor necrosis factor γ blockers may also develop a neuropathy resembling CIDP.[13,916] A peripheral neuropathy indistinguishable from CIDP[1044,1116] may accompany a systemic disease such as IgG or IgA monoclonal gammopathy of unknown significance (MGUS)[470] and diabetes mellitus,[729] although they tend to show more severe axonal loss reflecting additive effects of the underlying disorders.[374] Presence of prominent motor symptoms and subacute worsening help recognize these patients who may potentially benefit from immunosuppressive therapy.[397,472,901] Epidemiologic studies[185,614] do not support a pathogenetic correlation between the two disorders. Other disorders described in association with CIDP include CMT[700] membranous glomerulonephritis,[1013] Hashimoto's thyroiditis,[52] and liver transplantation.[291]

A chronic demyelinating neuropathy may also accompany a relapsing multifocal central nervous system disorder, mimicking multiple sclerosis[314,761] and subclinical central nervous system involvement,[819,831] sometimes with hypertrophic nerves producing mass effect.[568,1033] In these cases, electrophysiologic studies reveal a slowing of peripheral conduction velocity as well as an increased central conduction time (CCT). The occurrence of both peripheral and central demyelination bears resemblance to chronic relapsing experimental allergic encephalomyelitis and neuritis.

In patients with CIDP, NCS reveals multisegmental demyelination with characteristics quite similar to those of AIDP, except for chronicity.[528] Other electrophysiologic abnormalities include dispersion of the distal CMAP.[1085] The electrophysiologic signs of axonal loss and the

associated length-dependent muscle weakness suggest secondary axonal loss.[399] Phrenic nerve stimulation tends to show a delayed latency and a reduced CMAP amplitude in CIDP as also seen in MMN.[681] Not only motor but also sensory nerves may show slowing[103] and evidence of conduction block and temporal dispersion, which serve as useful markers.[900] Focal neuropathies at common sites of compression may result from concomitant entrapment, not necessarily as part of CIDP.[837,898] Distribution patterns of conduction abnormalities correlate well with clinical weakness.[595,897] The use of tibial nerve far-field potential may allow segmental evaluation of proximally dominant slowing in patients with CIDP.[586,1110] Other studies have shown myokymic or continuous motor unit discharges[726] and abnormalities of cardiovascular autonomic function and sympathetic skin response.[679]

The CSF cell count may exceed the usual low limit of 10/mm^3 in HIV-seropositive patients. Nerve root hypertrophy,[266,710,740] seen as an enhancement in MRI, may cause lumbar stenosis.[366] Nerve biopsy may reveal a pattern of axonopathy in addition to unequivocal pathologic evidence of demyelination and remyelination.[1124] The presence of clusters of macrophages around endoneurial vessels in sural nerve biopsies may serve as a useful marker for establishing the diagnosis.[1023] Reduced epidermal nerve density indicates sensory and autonomic small-fiber neuropathies.[179]

Prednisone causes a small but statistically significant improvement over no treatment.[284,310] Additional modes of therapy include cyclosporin,[55] immunoglobulin,[196,728,894] methotrexate,[249] and interferon-α 2a.[375] Plasma exchange also works especially in cases with features of demyelination rather than axonal degeneration, suggesting a role of pathogenic humoral factors. Although corticosteroid and plasmapheresis work equally well as a therapeutic measure, IVIG suits best as the first choice of treatment because of its ease in administration and a smaller number of reported side effects.[261,439,623,728,1150] The same may or may not hold in pediatric population.[1008,1078] Nonresponders often show axonal degeneration as evidenced by muscle atrophy and decreased CMAP amplitudes, which usually signals unfavorable long-term prognosis.

In a multicenter study of 312 patients consisting of 199 responders and 113 nonresponders, additional clinical features related to IVIG unresponsiveness included male gender, longer disease duration, and slow progression of symptoms.[446] In a 5-year follow-up study,[589] CIDP patients generally had a favorable prognosis, although 38% still required immune treatments and 13% had severe disability. In another study,[163] neurophysiologically definite and probable patients responded to immunotherapy equally. Treatment with cyclosporin may free some patients from repeated IVIG administration.[800] In one series,[758] good prognostic signs included acute or subacute onset and presence of proximal weakness. In one series,[111] improvement in averaged CMAP amplitude correlated with dominant-hand grip strength and Medical Research Council sum score. Studies of minimal F-wave latency and isokinetic strength help document the acute motor response following a single IVIG treatment course.[400] Clinical and functional assessment suggests IVIG modulates membrane function and promotes axonal recovery.[648]

Multifocal Motor Neuropathy with Conduction Block

Usually considered as a unique variant of CIDP (Table 24-3), this potentially treatable condition[786,853] deserves special mention in the differential diagnosis of amyotrophic lateral sclerosis (ALS) and other motoneuron syndromes.[630,786] Affected patients typically develop chronic, asymmetric, predominantly motor neuropathy with multifocal conduction delay and persistent conduction block.[825,1051,1056] Acute, generalized presentation, if seen as an exception to the rule, may mimic features of AIDP.[629,691] Although MMN typically causes distal upper-limb weakness and atrophy, proximal muscles, biceps brachii in particular, may show hypertrophy possibly associated with continuous motor unit activity.[822] The long-lasting conduction block suggests chronic demyelination as the pathologic basis.[483] The patients often have normal or occasionally even increased stretch reflexes.[485] Some patients develop cranial[490,863,1183] and phrenic nerve involvement[79,92,599] and others,

Table 24-3 Characteristics of Multifocal Motor Neuropathy with Conduction Block (MMN) and Chronic Inflammatory Demyelinative Polyneuropathy (CIDP)

	MULTIFOCAL MOTOR NEUROPATHYWITH CONDUCTION BLOCK (MMN)	CHRONIC INFLAMMATORY DEMYELINATIVE POLYNEUROPATHY (CIDP)
Pure motor manifestation	Frequent	Rare
Multiple mononeuropathy	Yes	No
Remission and exacerbation	No	Yes
Generalized areflexia	No	Yes
CSF protein level	Often normal	Elevated
Sites involved in conduction block	Forearm brachial plexus	Entrapment sites, root
Elevated anti-GMl antibody	Frequent	Rare
Choice of therapy	Immunosuppressants, immunoglobulin	Steroids, plasma exchange

CSF, cerebrospinal fluid.

central demyelination.[646,863] These features make it difficult to diagnose the condition solely on the basis of clinical examination.[527] Table 24-4 summarizes the criteria for definite and probable diagnosis of MMN. The diagnostic criteria proposed by AAEM require clinical weakness without objective sensory loss or upper motoneuron signs in the distribution of two or more named nerves, showing conduction block outside of common entrapment sites.[825]

Conduction blocks typically involve unusual sites such as the median nerve in the forearm or

Table 24-4 Criteria for the Diagnosis of Multifocal Motor Neuropathy (MMN)

Criteria for definite MMN consist of:

1. Weakness without objective sensory loss in the distribution of two or more named nerves. During the early stages of symptomatic weakness, the historical or physical finding of diffuse, symmetric weakness excludes the diagnosis.
2. Definite conduction block in two or more nerves outside of common entrapment sites such as median nerve at the wrist, ulnar nerve at the elbow, and peroneal nerve at the knee
3. Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block
4. Normal results for sensory nerve studies on all tested nerves, with a minimum of three nerves tested.
5. The absence of each of the following upper motor neuron signs: spastic tone, conus, extensor plantar response, and pseudobulbar palsy

Without the evidence of definite conducton block above, the diagnosis becomes probable MMN in the presence of either:

1. Probable conduction block in two or more motor nerve segments outside the common eatrapment sites, or
2. Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, outside the common entrapment sites

(Modified from Olney, Lewis, Putnam, et al.[825])

brachial plexus[251,489] rather than the common sites of compression seen in multiple entrapment neuropathies.[78] Some patients have pure motor mononeuropathy with distal conduction block as the presenting symptoms[318,1174] or as a variant called monofocal motor neuropathy.[692] Conversely, progressive, predominantly motor, symmetric demyelinating neuropathy may also qualify as a variant of MMN associated with anti-GM1 antibodies.[802] Most patients have selective involvement of motor fibers with normal sensory conduction through the sites of lesions, although some patients, who initially fulfill the criteria, may subsequently develop a sensory loss associated with electrophysiologic sensory abnormalities.[603] In some otherwise typical cases, diagnostic studies may fail to document apparent motor conduction block.[174,243] Pathologic temporal dispersion (see Chapter 11-5) also implies demyelination as an inherent feature of this entity.[360] Magnetic fatigue test may uncover activity-dependent conduction block located in a proximal nerve segment, which would otherwise escape detection.[787] In another series of 19 MMN patients,[1052] however, maximal voluntary contraction induced pathologic temporal dispersion, but no activity-dependent conduction block. Both motor conduction block and abnormally increased threshold probably reflect a chronic focal demyelination that, for yet undetermined reasons, becomes persistent.[484,528,786,1218] Axonal degeneration[1127,1171] may become prominent, if untreated.[609] Pregnancy may worsen MMN.[173]

As a variant of MMN or as a distinct clinical entity, some adult[640,896,1132,1152,1157,1170] and rarely pediatric patients[1175] have asymmetric sensory or sensorimotor involvements. This entity, also referred to as MADSAM or Lewis-Sumner syndrome, shares histologic features with CIDP and MMN,[815] although showing different disease progression and no benefit with steroid therapy.[47] Some patients with features indistinguishable from ALS have NCS abnormalities suggestive of MMN.[5,1200] In one series, 17 of 169 patients clinically diagnosed as having motoneuron disease (MND) had some abnormalities in motor NCS, including 10 with conduction block.[608] Demonstration of motor conduction block at multiple sites differentiates this potentially treatable clinical entity from the small subgroup of ALS patients with only lower motoneuron involvement.[605] Ultrasonography shows extensive nerve enlargements along the course of the brachial plexus, or median, ulnar, or radial nerve in the majority of patients.[61]

Electrophysiologic studies must confirm the diagnosis before initiating therapeutic trials with, for example, immunosuppressants such as cyclophosphamide. Several authors have documented a successful treatment with IVIG.[359,490,565,785,852] In 94% of 88 patients with MMN, IVIG improved strength in at least two muscle groups without decrease in other muscle groups.[153] Outcomes of therapy with either immunosuppressants or immunoglobulin, however, vary considerably among different reported cases.[1011] Some patients improve without returning to normal, others stabilize, some require long-term therapy, and still others become refractory to any form of treatment.[1076] In one series,[607] the evidence of A waves in pretreatment electrophysiologic study signaled IVIG-responsive lower motor neuron syndrome even in the absence of conduction block. Most studies suggest better results with cyclophosphamide or IVIG therapy[313] compared to prednisone or plasmapheresis. Subcutaneous infusion, as an alternative option, adds flexibility to the treatment schedule.[398]

In our series,[489,490] two patients with MMN had focal conduction block involving motor but not sensory fibers at the site of nerve swelling (see Fig. 11-17A,B in Chapter 11). A nervebiopsy taken adjacent to the enlargement in one patient revealed subperineurial edema and slight thickening of the perineurium under low-power light micrographs.[489] The perivascular area at the center contained scattered large-diameter axons almost devoid of myelin or with very thin myelin. These thinly myelinated axons usually had small onion bulbs. The presence of cytoplasmic processes covered with basement membrane suggested their Schwann cell origin. A nerve biopsy specimen from another patient also revealed a perivascular area containing scattered demyelinated axons surrounded by small "onion bulbs." Morphometric studies with high-power light micrographs showed a fiber density of 6458 fibers/mm^2, compared with 7906 fibers/mm^2 in the control.

Axonal diameter and myelin thickness had a linear relationship in the normal subjects. In contrast, the patient had numerous large-diameter axons with thinner myelin, although some normally myelinated large axons remained.

The underlying pathogenic mechanism centers on elevated titers of anti-GM1 antibodies found in a wide variety of neuromuscular conditions,[152,367] but more commonly in some lower motoneuron disorders and in MMN.[559] Antibodies may have a predilection for the GM1 component of the motor fibers, which have a longer carbon chain than the sensory fibers.[804] Anti-GM1 antibodies may[966] or may not [425,485,846] cause motor dysfunction by binding to the nodal and paranodal regions. Surface-bound antibodies directed against a major axoplasmic antigen may interfere with remyelination rather than causing demyelination.[484,485] The pathogenesis of MMN in most patients does not seem to involve an antecedent campylobacter jejuni infection held responsible for induction of antiganglioside antibodies by a mechanism of molecular mimicry.[1080]

In an extraordinary case,[966] a patient had received a duck embryo rabies vaccine 3 months before the onset of her MND. She had multifocal conduction block, elevated levels of anti-GM1 IgM antibodies, and deposits of IgM at nodes of Ranvier. Aside from attacking motoneurons guided by the abundant GM1 on the cell surface, anti-GM1 antibodies may cause conduction block in peripheral nerves by binding to the nodes of Ranvier. An autopsy study in another patient showed findings consistent with both ALS and MMN.[1156] Secondary amyloidosis developed as a life-ending event in a patient with established diagnosis of MMN.[80] Conditions associated with MMN or MADSAM include West Nile virus infection, which more commonly causes poliomyelitis-like motor neuropathy,[1057] and administration of antitumor necrosis factor α as therapy for rheumatoid arthritis.[433]

Acute Motor Axonal Neuropathy

Annual summer epidemics of acute-onset flaccid paralysis occur in northern China. Based on an historical analysis of more than 3200 patients with this syndrome, called acute motor axonal neuropathy (AMAN), distinctive features include a high incidence in children and young adults residing in rural areas.[344,380,1207] Patients develop, without fever, systemic illness, or sensory involvement, a rapidly progressive ascending tetraparesis or rarely paraparesis[393] followed usually by a satisfactory recovery. Other early signs include diminished or lost muscle stretch reflexes, although occasional patients may have hyperreflexia,[592,1062] as in some cases of AIDP.[879] Compared to AIDP, AMAN patients tend to have a more rapid progression and an earlier nadir.[423] Almost all AMAN patients who had slow recoveries over the first 6 months could eventually walk independently, although it may take several years to achieve this goal.[424] Occasionally acute relapses occur after long asymptomatic intervals.[12,1189] These patients tend to have an antecedent illness and show no response to immunosuppressive therapy.[378] The CSF shows no cells with elevated protein content in the second or third week of illness.

Electrodiagnostic studies show a reduced CMAP associated with normal distal latencies and limb conduction velocities, as well as normal SNAP. In one study, motor unit number estimates (MUNEs) remained decreased despite a return of CMAP amplitude, indicating collateral reinnervation, rather than nerve regeneration, as the main mechanism for the eventual clinical recovery.[597] Nerve terminal degeneration-regeneration presumably provides a mechanism for good recovery.[1071] When elicitable, F waves also fall within the normal range in latency. Increased refractoriness to the second of a pair of electrical stimuli supports the hypothesis of sodium channel dysfunction.[587] Massive leakage of driving current through the loose paranode may explain reversible conduction block sometimes seen in this condition,[1226] which may overlap with the entity called by some as AMCBN.[137,1227] Patients with camplylobacter jejuni–associated AMAN can show transient slowing of nerve conduction, mimicking demyelination[593]. In one series of 18 patients of AMAN,[556,593]a serial NCS revealed reversible conduction block, degeneration without conduction block, and conduction block followed by axonal degeneration, constituting a continuum of electrophysiologic abnormalities.

Conduction blocks seen during the first 3 weeks of illness may create confusion in making early disease classification, leading to underestimation of AMAN diagnosis.

Autopsy studies have shown wallerian-like degeneration of motor fibers. Thus, AMAN, mostly seen in China, Japan, Mexico, and elsewhere,[461] seems to constitute a syndrome either as a distinctive entity[464] or a variant of AIDP.[759,1007,1226] A similar relationship exists between CIDP and its presumed variant, steroid-sensitive CMAN.[1120] Serologic evidence suggests association of anti-GD1a antibody with AMAN but not AIDP.[427] For the IgG anti-GM1-positive subgroup of GBS patients, who tend to develop axonal degeneration, IVIG therapy may serve more efficaciously than plasmapheresis.[590] The use of IVIG in an AMAN model also reveals that it may prevent axonal degeneration.[782] In one study of Japanese children,[762] AMAN and AIDP patients had a similar proportion, both showing generally favorable recovery.

Other Autoimmune Neuropathies

Many peripheral neuropathies with prominent and selective involvement of autonomic fibers have an identified cause such as diabetes, amyloidosis, and inherited autonomic neuropathy. In contrast, spectrum of idiopathic autonomic neuropathy with ganglionic acetylcholine receptor autoantibodies has no definable cause. These include pandysautonomic and pure autonomic failure.[540] More than 50% of patients with high level of ganglionic acetylcholine receptor (AChR) autoantibodies have a combination of sicca complex characterized by dry eyes and dry mouth, abnormal pupillary light response, upper gastrointestinal tract syndrome, and neurogenic bladders.[964] Acute neuropathies may develop after peripheral blood stem cell and bone marrow transplantation, possibly as the result of autoimmune phenomenon directed against specific nerve antigens.[892]

Neuropathies Associated with Paraproteinemia

A number of studies have demonstrated a clear association between IgM and IgG[1055] and, to a lesser degree, immunoglobulin A (IgA)[996] monoclonal proteins and peripheral neuropathy.[868] Most affected patients have otherwise benign monoclonal gammopathy, sometimes with a genetic predisposition, but some have various systemic syndromes. These include primary systemic amyloidosis, osteosclerotic myeloma, and, less frequently, osteolytic multiple myeloma, Waldenström's macroglobulinemia, cryoglobulinemia, gamma heavy chain disease often associated with hepatitis C infection,[37,235] angiofollicular lymph node hyperplasia with vasculopathy, papilledema, organomegaly, endocrinopathy and paraproteinemia, or Castleman's disease[256] and the syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes, or POEMS.[953,1001,1112] In POEMS syndrome, NCS shows characteristic patterns of lower-limb involvement, primarily affecting the intermediate rather than distal nerve segments.[732] Table 24-5 summarizes the main clinical and laboratory features of these entities. In multiple myeloma and macroglobulinemia, neuropathy may develop as a feature of the underlying disorder or as the result of paraproteins. In some of these cases, immunoglobulin deposits in the endoneurial space, as determined by examination of nerve biopsy specimen, may play a role in the pathogenesis of peripheral neuropathy.[1123]

MONOCLONAL GAMMOPATHY

Benign monoclonal gammopathy of unknown significance (MGUS) occurs in 10% of all patients with idiopathic peripheral neuropathy.[508] Conversely, 30%–70% of those with MGUS develop chronic sensorimotor neuropathy.[707] The majority of patients with polyneuropathy associated with this entity have an IgM monoclonal protein (M protein). These patients develop risk factors for hematological malignancy with or without associated polyneuropathy.[307]The clinical features closely mimic those of CIDP with progressive sensorimotor loss and occasional tremor.[613,884] Electrophysiologic and morphologic studies show evidence of demyelination, although a few have axonal loss as a major finding.

In one series,[791] MGUS patients had slowly progressive symmetric sensory symptoms and signs with no cranial nerve involvement, whereas

Table 24-5 Main Features of Monoclonal Protein-Peripheral Neuropathy Syndromes

TYPE OF PN	TOPOGRAPHY	WEAKNESS	SENSORY LOSS	AUTONOMIC LOSS	COURSE	CSF PROTEIN	MNCV	PATHOLOGY
Benign monoclonal gammopathy (IgG, IgA)	Distal, rarely proximal	++	++	+	Chronic progressive	++	Mild slowing	SD + AD
Benign monoclonal gammopathy (IgM)	Distal, symmetric	++	++	0	Chronic progressive	++	Very slow	SD
Amyloidosis, light-chain type	Distal, symmetric	+/++	+++	++	Chronic progressive	+	Mild slowing	AD
Osteosclerotic myeloma	Distal, symmetric	+++	+	0	Chronic progressive	+++	Very slow	SD(+AD)
Waldenström's macroglobulinemia	Distal, symmetric	++	++	0	Chronic progressive	++	Very slow	SD(+AD)

AD, axonal degeneration; CSF, cerebrospinal fluid; MNCV, motor nerve conduction velocity; PN, peripheral neuropathy; SD, segmental demyelination.
(Modified from Kelly.[507])

CIDP patients tended to have preceding infection, asymmetric motor features, cranial nerve involvement, and abnormal median and normal sural nerve sensory potentials. The association with a central lesion,[633] though uncommon, includes cerebral lymphoma.[298] The characteristic laboratory findings include IgM and IgG and, less commonly, IgA gammopathy and a high level of CSF protein.

Plasma exchange rapidly lowers the level of monoclonal antibody, with some recovery of motor function.[821] Some patients also respond to high-dose IVIG therapy[233,694] and immunosuppressive treatment.[792] Higher age at onset and demyelination increase the risk, whereas anti-MAG antibodies decrease the risk of developing a Rankin Scale score ≥3.[781]

MYELIN-ASSOCIATED GLYCOPROTEIN NEUROPATHY

This category also includes various polyneuropathy syndromes associated with IgM monoclonal gammopathy showing antibodies binding to myelin-associated glycoprotein (MAG), peripheral myelin protein (PMP) 22, myelin protein zero (MPZ), or sulphated glycolipids.[170,572,637,784,1130] Slowly progressive sensorimotor neuropathies of this type tend to show a uniform and predictable pattern characterized by fiber length–dependent demyelination mediated by circulating antibodies and axonal degeneration of distal terminals. Some patients have predominant motor symptoms with extensive muscle atrophy.[502] Increased signal intensity and swelling of the brachial plexus on MRI imply more generalized involvement.[308] A combined syndrome of polyneuropathy and gait ataxia[500,867] and axial myoclonus[1155] often improves after IVIG or plasmapheresis therapy.

Electrophysiologic abnormalities may lead to disproportionate prolongation of distal motor latency as evidenced by an increase in residual latency and a decrease in terminal latency index (TLI) (see Chapter 5-4 and 6-3),[46,140,491] showing a higher correlation with anti-MAG than anti-SGPG titers.[1107] In one study,[462] electrophysiologic features suggestive of MAG neuropathy included low median and ulnar terminal latency index and absence of CMAP in the lower limb. Findings of axon loss also increase with nerve length as part of a length-dependent process.[328] In another series,[674] all 21 patients with median nerve TLI <0.26 had MAG/SGPG neuropathy.

SYSTEMIC AMYLOIDOSIS

Primary systemic amyloidosis characterized by a plasma cell dyscrasias and amyloidogenic immunoglobulins affects multiple organ systems with symptoms similar to those of malignancy or collagen vascular disease. When patients with this disease manifest polyneuropathy as a main symptom, their clinical picture closely resembles that of hereditary transthyretin amyloidosis [65,416,709,997] and gelsolin-related familial amyloidosis.[204] Diffuse peripheral neuropathy develops as the result of metabolic or ischemic changes or direct infiltration by amyloid. The clinical features consist of a painful sensorimotor neuropathy with prominent autonomic dysfunction affecting multiple systems. Atypical presentations include MND, asymmetric polyradiculopathy, cranial nerve palsies, painful sensory neuropathy, mononeuritis multiplex,[1104] and primary demyelinating polyneuropathy.[1173] Electrophysiologic abnormalities include slight slowing of the motor nerve conduction velocity; mild reduction in CMAP amplitude; absent or reduced ulnar, median, and sural nerve SNAP; and focal median nerve slowing at the wrist by amyloid deposits accumulated in the flexor retinaculum. In EMG studies, the evidence of denervation abounds diffusely but more conspicuously in the distal muscles of the leg.

Axonal degeneration predominates in small myelinated and unmyelinated fibers,[1094] usually sparing the large myelinated fibers, or the reverse of the findings seen in large fiber type diabetic neuropathy. This accounts for the typical dissociated sensory loss with predilection for pain and temperature sense and relative preservation of vibratory and position sense. An in vitro study of sural nerve SNAP has shown a selective reduction in C and delta potentials in familial amyloid neuropathy (see Chapter 24-5).[281] This supports the view that amyloid neuropathy predominantly causes distal axonal damage first in the sensory and then in the motor fibers, although

transthyretin amyloidosis may rarely present with multifocal demyelinating mononeuropathy.[109] Neuropathic symptoms may improve with high-dose melphalan followed by autologous stem cell transplantation.[498]

MULTIPLE MYELOMA

Skeletal osteosclerotic lesions, although seen only in less than 3% of myeloma patients as a whole, develop in at least 50% of those with myeloma neuropathy.[511] This type of myeloma commonly affects younger individuals. Despite a generally benign clinical course, the patients often develop a demyelinating neuropathy that resembles CIDP. Symptoms may improve following surgery, radiation, or chemotherapy.[936] Electrophysiologic and histologic evidence of prominent demyelination suggests an immunologic effect of the monoclonal protein on a myelin antigen as a precipitating cause.[509,706] Intraneural injection of patient serum into rat sciatic nerve, however, produces no demyelinative lesion.[511] Instead, the morphologic features suggest axonal attenuation or distal axonal degeneration with secondary demyelination.[817]

Osteolytic multiple myeloma may accompany amyloid neuropathy much like the type seen in systemic amyloidosis without multiple myeloma. These cases show, in addition to prominent distal axonal loss and CTS, atypical features such as radiculopathy and mononeuritis multiplex. In this condition, a peripheral neuropathy also develops without amyloidosis in 30%–40% of cases, based on electrophysiologic and histologic findings.[158,507] Diverse clinical and electrophysiologic features resemble various subgroups of carcinomatous peripheral neuropathy. Sensorimotor types show distal axonal degeneration and mild decrease in nerve conduction velocity. The patients with primary sensory involvement characteristically have a loss of proprioception but few deficits in the motor system.[506] Those with primary motor abnormalities have features similar to CIDP with prominent slowing of nerve conduction velocities. Some patients also develop multifocal neuropathy related to infiltration of the peripheral nerves by malignant plasma cells.[245] Demyelinating polyneuropathy may improve remarkably during treatment of myeloma with lenalidomide, a structural derivation of thalidomide with lower neurotoxicity.[618] A mild sensorimotor peripheral neuropathy related to multiple myeloma, however, may worsen slightly during treatment with thalidomide.[877]

Patients with Waldenström's macroglobulinemia may develop a primarily demyelinating sensorimotor neuropathy of the type commonly associated with MGUS.[636] Occasional patients, however, have axonal degeneration and amyloid infiltration, as in osteolytic multiple myeloma. Electrophysiologic studies typically reveal predominant segmental demyelination and, less frequently, evidence of axonal changes as a major finding.

CRYOGLOBULINEMIA

In cryoglobulinemia,[158] two types of neuropathy develop: (1) a mild distal neuropathy probably caused by vasa nervorum microcirculation occlusion with intravascular deposits of cryoglobulins, and (2) a severe distal symmetric sensorimotor neuropathy with necrotizing vasculitis.[351] Persistent multifocal conduction block reported in one patient probably resulted from superimposed immunomediated demyelination.[793] Hepatitis C virus may play a role in nonsystemic vasculitic mononeuropathy multiplex[773] associated with[28] or without[211] cryoglobulinemia. Sural nerve biopsies and EMG show the evidence of axonal degeneration. A preferential loss of large diameter fiber confirms a major role of ischemia in the pathogenesis.[352] Treatment consists mainly of plasmapheresis.[1086] A reversible sensory autonomic neuropathy seen in cold agglutinin disease may have similar pathogenesis to those proposed for cryoglobulinemia.[1098]

Infective Neuropathies

HIV-RELATED NEUROPATHY

Patients with AIDS develop various types of neuropathy as evidenced by conduction studies.[357,604,664,921] In this entity, cell-mediated tissue destruction results from HIV infection and serves as the pathogenetic mechanism of AIDS neuropathy.[106,870] Peripheral neuropathy may

complicate all stages of HIV infection.[207,606,631] These include AIDP,[891] sensory and sympathetic ganglia neuritis,[305] and acute cranial nerve palsy, which may occur 2–3 weeks after acute HIV infection, sometimes in otherwise asymptomatic patients.

Cytomegalovirus, a common pathogen in AIDS, also causes a wide spectrum of peripheral nervous system disorders, including multifocal demyelinative polyneuropathy.[102,746] In AIDS-related Burkitt's lymphoma, primary peripheral nerve involvement, although rare, may result from compression by a lymphomatous mass.[1209] Neuropathy, as one of the most common neurologic manifestations, also affects as many as 20% of patients with AIDS-related complex.

In contrast to the autoimmune basis of demyelinative neuropathy,[1053] less clearly established pathogenetic mechanisms of distal symmetrical sensory polyneuropathy include inflammatory, toxic, and nutritional causes.[696,1003,1179] Polyradiculopathy most likely results from infections with such agents as cytomegalovirus and herpes simplex virus, which selectively destruct the motoneurons and motor cranial nerves.[62,293] The prevalence of neuropathy in HIV-infected patients has increased substantially since the introduction of highly active antiretroviral therapy, like stavudine, an effective agent available in relatively inexpensive generic form. Stavudine neuropathy risk increases with patient age and height.[178] Zidovudine may induce mitochondrial myopathy but causes no clear neurotoxicity.[628]

Needle studies reveal severe, distally prominent denervation despite only mildly slowed nerve conduction velocities. Multifocal or distal symmetric inflammatory neuropathy may herald the onset of AIDS in some homosexual men with lymphadenopathy.[703] In these patients, reduced sural nerve action potentials may constitute the sole electrophysiologic abnormality.[1015] Reduced intraepidural nerve fiber density shows association with increased neuropathic pain and higher plasma viral load in HIV-sensory neuropathy.[882]

DIPHTHERIC NEUROPATHY

Prophylactic immunization and early use of immune sera and antibiotics in infected patients have drastically lowered the incidence of diphtheritic polyneuropathy, which occurs in about 20% of patients. Diphtheria initially causes a primary infection followed by biphasic early local and late remote secondary toxic effects. Local effects occur by direct spread of toxin, resulting in the early problems, whereas the ensuing generalized neuropathy arises from hematogenous dissemination.[711] The exotoxin of Corynebacterium diphtheriae becomes fixed to the nerve and produces segmental demyelination after several weeks. Local paralysis of the palatal muscles may immediately follow an infection of the throat. Sensorimotor axonal neuropathy may also develop in adults after contracting cutaneous diphtheria, which still prevails in the tropics.[910]

Compared to the AIDP, which clinical signs resemble,[215] diphtheric neuropathy tends to have a bulbar onset, respiratory feature, slow evolution, biphasic course, and death or long-term disability.[661] The symptoms typically develop 2–4 weeks after the initial infection. Patients have a high incidence of lower cranial nerve dysfunction, most notably palatal and pharyngolaryngoesophageal weakness.Blurring of vision results from paralysis of accommodation. Other autonomic abnormalities include cardiac vagal dysfunction.[445], The involvement of sensory and motor nerves causes paresthesias and weakness of the affected limbs. A rapidly descending paralysis may lead to respiratory problems. The primary pathologic change consists of segmental demyelination involving the sensory and motor fibers.[1021] Conduction abnormalities usually begin a few weeks after the onset of neurologic symptoms, peaking when the clinical recovery has already begun.[579] F-wave studies also help establish serial changes in motor conduction.[354]

NEUROPATHY IN LEPROSY

An acid-fast bacillus, Mycobacterium leprae, transmits leprosy by close and prolonged contact. Although rare in the United States, this chronic infectious disease still prevails in Africa, India, and South and Central America. The World Health Organization classification uses the number of skin lesions to divide leprosy into two major groups: paucibacillary with strong cell-mediated

immune response and multibacillary with poor cell-mediated immune response.[844]

Of the two corresponding clinical forms, the lepromatous or neural type with five or fewer skin lesions causes extensive and widespread granulomatous infiltration of the skin, leading to characteristic disfiguration. The diffuse sensory neuropathy seen in this variety results from direct invasion of the nerve trunks by the bacillus.[99] The thickened perineurium by an overgrowth of connective tissue compresses the myelin sheath and the axons. In the other type called the tuberculoid form with greater than five skin lesions, more focal involvement of the skin causes patches of the depigmented maculoanesthetic areas. Here, swelling of the nerves does not necessarily imply direct invasion by the organisms.

Clinical features suggest mononeuritis multiplex or slowly progressive diffuse distal sensory polyneuropathy.[980] The organism seems to have predilection for great auricular, ulnar, radial, peroneal, facial and trigeminal nerves. Common manifestations include facial palsy involving the upper half of the face, wristdrop, footdrop, and claw hands. Neural leprosy may begin with a small erythematous macule that soon enlarges, forming anesthetic depigmented areas. The loss of pain and temperature sensation causes ulcerated necrosis of the skin. Palpation of the affected nerve reveals characteristic fusiform swelling caused by an infective granulomatous process. Clinical presentation commonly overlaps without clear separation between the neural and tuberculoid forms, giving rise to an intermediate or mixed form.

Electrophysiologic abnormalities consist of moderately to markedly slow motor and sensory conduction not only across enlarged segments[684,1065] but also along the unpalpable portions.[719] In one series, radial nerve sensory abnormalities correlated best with the clinical findings,[978] whereas, in another, ulnar sensory studies revealed more prominent changes.[118] A normal SNAP seen despite clinical sensory loss implies the early involvement of small nerve fibers, which contribute little in the routine NCS. Nearnerve recording from nerve fibers as small as 4–6 μm, however, failed to detect such abnormalities, probably because regenerating myelinated fibers have electrophysiologic characteristics similar to that of normal unmyelinated fibers.[699] Needle studies show the evidence of denervation in the atrophic muscles. Electrodiagnostic studies also help monitor for toxicity secondary to therapy, particularly thalidomide-associated neuropathy.[829]

The denervated muscle shows histopathologic changes of fascicular atrophy and inflammatory nodules. Nerve biopsy material taken from sites remote from skin lesions reveals subperineurial edema and various losses of myelinated and unmyelinated fibers. Similarities in some of the pathologic changes observed in the two types of leprosy suggest a common mechanism of nerve damage in the early stages.[986] Teased fiber studies in each leprosy type also reveal paranodal demyelination affecting successive internodes.[468]

OTHER NEUROPATHIES ASSOCIATED WITH INFECTIONS

Lyme borreliosis causes a severe, predominantly axonal polyradiculoneuropathy typically with cranial neuropathy and lymphocytic meningitis.[390,685,756,1084] The syndrome of acute sensory and autonomic neuropathy often shows a focal onset, suggesting an immune-mediated or vascular process at the level of the posterior root or the dorsal root ganglion.[859,1197]

In paralytic rabies, the central nervous system shows vascular and inflammatory changes while the peripheral nerves have segmental demyelination, remyelination, and Wallerian degeneration with variable axonal loss.[190] Electrophysiologic abnormalities include slowing of motor and, to a lesser extent, sensory conduction velocity, and a reduced number of MUP and fibrillation potentials.[1064] An overlap of both clinical and pathologic features in paralytic rabies and AMAN raises the possibility that infections and autoimmune etiologies can lead to similar changes in the nerves.[985]

Tick paralysis results from a neurotoxin secreted by engorged female ticks, Ixodes holocyclus in Australia and Dermacentor andersoni or virabilis in North America. Patients develop ascending paralysis or, less commonly, focal weakness followed by spontaneous recovery.

EMG evidence of denervation, prolongation of distal motor latency, and low sensory amplitude suggests axonal degeneration.[1122] An abrupt increase in refractoriness detected during early stage by nerve excitability studies suggests impairment of distal neural transmission.[567]

Subacute sensory neuropathy develops as a rare complication of Epstein-Bar virus infection.[941] Varicella zoster causes cranial polyneuritis in the absence of rash,[753] in addition to more common postherpetic neuralgia.[744,745] Risk factors for postherpetic neuralgia include older age, female gender, presence of prodrome, rash severity, and acute pain severity.[480] Other viral infection, which may cause sensory polyneuropathy or mononeuritis multiplex during acute stages include hepatitis B virus[197] and hepatitis C virus.[965] Other infective diseases occasionally associated with neuropathy include rickettsial disease,[391] Chagas disease, trypanosomiasis,[991] and various types of insect and spider stings.[216]

4. METABOLIC AND TOXIC NEUROPATHIES

Metabolic neuropathies consist of two groups: those representing nutritional disturbances and those resulting from toxic causes. Neuropathies attributable to a specific nutritional deficiency include beriberi, pellagra, and pernicious anemia. Toxic neuropathies develop after the administration of various drugs or the exposure to chemical substances such as lead or arsenic. Many neuropathies associated with general medical conditions also belong to this broad category.

Nutritional Neuropathies

Children with insufficient protein or caloric intake suffer from retarded myelination or segmental demyelination.[191] They have abnormalities of motor and sensory nerve conduction related to the severity of malnutrition. Severe malabsorption from blind loop syndrome also causes vitamin E deficiency. Alcoholic and paraneoplastic neuropathies may result, at least in part, from inadequate food and vitamin intake, although some toxins may also interfere with the metabolism of the nerves.[226] In particular, alcoholic neuropathy, distinct from the pure form of thiamine-deficiency neuropathy, may result from toxic effect of ethanol or its metabolites.[553,1232] Disorders of the alimentary system[175] in general and diets deficient in vitamins and other nutritional factors in particular play a major role as a cause of polyneuropathy associated with beriberi, pellagra, pernicious anemia, dysentery, and cachexia.

Thiamine deficiency causes Beriberi with signs and symptoms similar to those of alcoholic polyneuropathy,[554] which include pain, paresthesias, distal weakness and sensory loss, and absent stretch reflexes. A similar neuropathy may develop during intended weight reduction or anorexia nervosa. Following bariatric surgery for obesity,[547] patients may develop sensory-predominant polyneuropathy, mononeuropathy, or radiculoplexopathy,[1082] which good nutritional control may prevent.[1083] Histologic studies reveal conspicuous axonal degeneration and less prominent demyelination. Pellagra, another deficiency disease involving the vitamin B1 complex, often affects malnourished patients with chronic alcoholism. The clinical features consist of gastrointestinal symptoms, skin eruptions, and disorders of the peripheral and central nervous systems. Neuropathic characteristics include paresthesias, loss of distal sensation,tenderness of the nerve trunks, hyporeflexia, and mild paralysis.

Pernicious anemia results from a deficiency of intrinsic factors in gastrointestinal secretions that mediate absorption of vitamin B12. Pathologic changes primarily involve the dorsal and lateral funiculi of the spinal cord, hence the name *combined system disease*. The peripheral nerves also show fragmentation of myelin sheaths and degeneration of axons.[560] The presenting clinical symptoms consist of paresthesias, dysesthesias, and loss of vibration and position sense. The patients commonly have spastic paraparesis during the early stages, followed by areflexia as the disease progresses. Peroneal and, to a lesser degree, median nerve SEP shows marked abnormalities in addition to peripheral conduction changes consistent with sensorimotor axonopathy[321,912] or rarely demyelinating neuropathy.[18] Most untreated patients have reduced conduction velocity in part because of thiamine deficiency seen in the

majority of cases.[212] Patients with prominent axonal degeneration have diffuse spontaneous discharges in EMG but nearly normal motor nerve conduction velocities.[560] Appropriate treatment arrests the progression of neuropathy, but residual neurologic abnormalities persist.[763,968]

In primary biliary cirrhosis, a sensory neuropathy develops from poor nutrition, xanthomatous infiltrates, or immunologic abnormalities.[169] Celiac disease, a chronic inflammatory enteropathy, results from sensitivity to ingested gluten. Approximately 10% of patients have an associated neurologic disease, most often peripheral neuropathy or ataxia.[183] Isolated vitamin E deficiency, in the absence of lipid malabsorption, may cause ataxia and peripheral neuropathy.[463] Peripheral neuropathy may also develop from a serum proteinase inhibitor deficiency[330] and hypophosphatemia as a rare postoperative complication.[993]

Alcoholic Neuropathy

Alcohol, a major cause of peripheral neuropathy in the United States, primarily affects those who drink large quantities for a number of years, and improves, albeit to a limited extent, once a person abstains.[421] In addition to its possible toxic effect, dietary insufficiency and impaired absorption may play important roles. Indeed, many patients have a vitamin B1, or thiamine, deficiency,[226] which alone can cause similar clinical findings. The pathologic changes include reduced density of large and small myelinated fibers and acute axonal degeneration and regeneration with secondary paranodal demyelination involving the most distal segment.[63] In alcoholic polyneuropathy with normal thiamine status, sensory-dominant involvement with prominent neuropathic pain supports the role of direct effect of alcohol or its metabolites, distinct from nutritional causes of beriberi neuropathy.[555]

Alcohol-related neuropathy may affect up to half of patients who suffered from alcoholism, and in studies that employ clinical and electrophysiologic criteria, 25%–66% of chronic alcoholics may have the disease.[723] Clinical symptoms usually appear insidiously over weeks or months but sometimes more acutely over a period of a few days. The initial sensory complaints consist of distal pain, paresthesias, and dysesthesias, first in the legs and later in the arms. Burning sensations in the limbs resemble those in diabetic neuropathy. Neurotrophic changes predominate in chronically weak and atrophic muscles. Plantar ulcers develop when patients subject insensitive tissues to unusual amounts of trauma. More advanced cases have bilateral footdrop, associated with distal muscular atrophy involving the extensors more than the flexors. Sensory symptoms may respond to daily administration of vitamin B1, but muscular atrophy tends to persist despite therapy.

Electrophysiologic evaluations demonstrate impaired functions of small-caliber motor fibers and large cutaneous sensory fibers. Despite the traditional emphasis on the role of conduction velocity, early abnormalities consist of decreased amplitude of SNAP and CMAP. Thus, NCSs initially reveal either normal or only slightly reduced velocities in most patients. As in other axonal neuropathies, conduction velocity decreases in proportion to the loss of evoked sensory and motor responses. Conduction abnormalities may involve not only the distal but also the proximal segments of the nerve. Assessments of sural nerve and late responses improve the diagnostic yield.[228] In most patients, EMG reveals fibrillation potentials and other neuropathic changes. Usually abnormalities involve the lower limbs earlier and more prominently than the upper limbs, reflecting the length-dependent degeneration of axons. Other reported abnormalities include those seen in sympathetic sudomotor responses, sympathetic skin responses, and cardiorespiratory reflexes,[767]as well as visual evoked potentials (VEPs).[168]

Toxic Neuropathies

Toxic neuropathies may have three presumed sites of cellular involvement: (1) neuronopathy affecting cell bodies, especially those of the dorsal root ganglion; (2) distal axonopathy causing dying-back axonal degeneration; and (3) myelinopathy or Schwannopathy with primary segmental demyelination. Of these, neuronopathy includes rare acute sensory neuronopathy following antibiotic treatment. The sensory neurons in the spiral ganglion give off a unipolar coiled

axon, which divides into medial portion directed toward the spinal cord and the lateral portion directed peripherally. Distal axonopathies, the most common form of toxic neuropathy, often involve both of these portions thus causing central peripheral distal axonopathy. In experimental acrylamide neuropathy, recovery begins in the largest peripheral axons, perhaps at the expense of central axons.[487]

The common types of neuropathies generally affect the large-diameter fibers, first in the distal segments with subsequent progression proximally toward the cell body. The pathologic process then spreads to small-diameter axons. The sudden development of clinical symptoms in distal axonopathy reflects the acuteness of intoxication. In contrast, an insidious onset suggests a chronic low-level exposure. Toxins often affect the longer and more vulnerable nerves of the lower limb initially. Early signs include distal weakness, hypesthesia, or paresthesia in a glove-and-stocking distribution, as well as reduced ankle stretch reflexes. Symptoms may worsen after termination of exposure. Despite this phenomenon, referred to as "coasting," the removal of the neurotoxin eventually leads to a gradual recovery. The axons, once degenerated, regenerate slowly over months to years, with incomplete return of function.

The selection of proper electrophysiologic tests depends largely on the nature of the condition under study. A few specific toxins such as perhexiline maleate result in demyelination as evidenced by NCS.[95] Toxic exposure to n-hexane causes a primarily axonal polyneuropathy with secondary demyelination[806,1012] and pathologic features consistent with giant axonal neuropathy.[165] Most other toxins lead to axonal loss, showing reduced amplitude of CMAP and SNAP. In these cases, substantial degeneration of large, fast-conducting fiber accounts for a slight increase in distal latency and a decrease in conduction velocity. Needle studies show fibrillation potentials and positive sharp waves.

Administration of tetanus toxoid[911] may also cause myelinopathy. Ciguatera poisoning transmitted by fish flesh contaminated by ciguatoxin causes, in addition to gastrointestinal effects, symptoms of peripheral neuropathy.[132] Acute tetrodotoxin-induced neurotoxicity may follow ingestion of puffer fish.[488,515] Conventional NCSs demonstrate marked conduction slowing of motor and sensory nerves, consistent with reduced sodium current, which prolongs internodal conduction time. Unleaded gasoline sniffing may cause mononeuropathy multiplex superimposed on a background of sensorimotor polyneuropathy.[129]

Some drugs show a characteristic pattern of neuropathic involvement. For example, pyridoxine abuse leads to a pure sensory central peripheral distal axonopathy.[854] Vincristine causes a dose-related sensorimotor neuropathy with unexpected off-therapy worsening.[1153] Studies in chick embryos show that exogenous administration of gangliosides may attenuate the neurotoxicity of vincristine in vitro.[435] Cisplatin, used to treat malignant tumors, induces an axonopathy that bears a great resemblance to sensory neuropathy sometimes associated with such a neoplasm.[564] This dose-dependent sensory neuropathy primarily causes a distal lesion affecting the large sensory neurons as well as the spinal cord and brainstem.[566] Psychiatric patients treated with the phenothiazine derivative, perazine, may develop a subacute axonal neuropathy after intense sun exposure.[923] Perhexiline maleate, used for therapy of angina pectoris, may cause segmental demyelination.[95] Cancer therapy gives rise to hematological as well as neurotoxic side effects. Severity of chemotherapy-induced neuropathy increases with the duration of treatment and the symptom usually stops with the completion of drug therapy.[1198] Total neuropathy score validated for patients with diabetes also serves in grading chemotherapy-induced peripheral neurotoxicity.[157]

A variety of other drugs cause distal axonopathy.[958] Functionally disabling toxic symptoms can occur in patients with preexisting neuropathy at standard doses.[171] Drugs with known neurotoxicity include amantadine,[888] allopurinol,[50] amiodarone,[329,465] cisplatin,[918,924] colchicine,[944,1222] dapsone,[557] diphenylhydantoin,[904] 2′,3′-dideoxycytidine,[72] disulfiram,[34,826] FK506,[1195] gold,[499] heroin,[230] interferon beta,[296] isoniazid,[36,1039] lithium,[167,1142] L-tryptophan,[358] melarsoprol,[356] metronidazole,[1234] isonidazole,[721] nitrofurantoin, nitrous oxide,[619,948] oxaliplatin,[632] paclitaxel,[851] penicillamine,[862] perhexiline maleate,[95,949] phenytoin,[988] pyridoxine,[75,854,1199]

statin,[86,254,342,634,903] suramin,[1022] taxol,[294,651,1129] thalidomide,[156,172,336,] and valacyclovir.[856]

Lead and arsenic, two specific agents responsible for distal axonal neuropathies, merit special attention. The general features of lead poisoning include abdominal cramps, encephalopathy, and the occasional appearance of a blue lead line along the gingival border. Laboratory tests reveal the presence of basophilic stippling of erythrocytes and elevated lead levels. Neuropathy occurs primarily in adults occupationally exposed to lead or following accidental ingestion of contaminated food, but it may also affect children with known plumbism or pica. In the classic form, predominant involvement of motor fibers innervating the extensor muscles of the upper limbs produces bilateral radial nerve palsies without sensory loss. In chronic occupational inorganic lead exposures, typical toxic neuropathy develops, with distally prominent sensory and motor involvement.[1099] The traditional motor syndrome associated with subacute lead poisoning may result from lead-induced porphyria.[940] The removal of the toxin initiates a gradual recovery over a period of several months. Lead produces segmental demyelination in some animal species, possibly because extravasated lead in the interstitial fluid injures the Schwann cells directly.[755] This type of pathologic change does not necessarily characterize the neuropathy seen in human cases, which may show severe axonal loss.[1208] A group of workers exposed to lead had a temporally dispersed CMAP but normal maximal conduction velocity.[154]

Arsenic poisoning usually results from accidental ingestion of rat poison or exposure to industrial sprays.[316]The administration of melarsoprol, an organo-arsenic compound, may also cause toxic arsenic accumulation in the presence of renal and hepatic dysfunction.[356] Polyneuropathy develops several weeks after acute poisoning or more slowly with chronic low-level exposure. Pale transverse bands bearing Mee's lines appear parallel to the lunula in all fingernails and toenails about 4–6 weeks after arsenic ingestion. Arsenic, found in the urine during acute exposure and in the hair and nails later, confirms the diagnosis. The clinical features resemble those of alcoholic neuropathy with early loss of stretch reflexes and painful paresthesias and sensory loss in a glove-and-stocking distribution (see Fig. 19-20 in Chapter 9). Flaccid paralysis may develop later, beginning in the lower limbs and eventually affecting the upper limbs. In one study, serial examination revealed maximal sensory and motor loss within 4 weeks of the estimated time of exposure, and only partial improvement 2 years after the onset of illness.[754] Electrophysiologic studies show marked sensory abnormalities indicative of axonal degeneration,[809] progressive slowing of motor conduction velocity,[754] and evidence of denervation in EMG. Timely removal of the toxin leads to a nearly complete recovery of conduction abnormalities. A demyelinating polyneuropathy may develop following acute exposure in contrast to the distal predominantly sensory axonal involvement associated with chronic low-level toxicity.[379]

Industrial chemicals causing toxic axonal neuropathy include acrylamide,[487,768] carbon disulfide,[841] cobalt-chromium,[449] isofenphos,[155] inorganic mercury,[21,39] methyl n-butyl ketone,[23,1031] n-hexane,[588,806,857,1012] nitrous oxide,[1160] organophosphate ester mecarbam,[1035] organophosphate parathion,[665,1144] polychlorinated biphenyl,[159] pyrethroid,[9] tellurium,[1118] thallium,[578,1219] triorthocresyl phosphate,[1143] and vinyl chloride.[866]

5. INHERITED NEUROPATHIES

Hereditary motor and sensory neuropathies (HMSNs) consist of several types: hypertrophic and neuronal varieties of CMT, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas disease, Refsum disease, and those associated with spinocerebellar degeneration, optic atrophy, and retinitis pigmentosa. Other inherited polyneuropathies include Friedreich's ataxia, acute intermittent porphyria, cerebral lipidosis, hereditary sensory and autonomic neuropathy (HSAN), lipoprotein neuropathy, giant axonal neuropathies, Fabry's disease, and familial amyloid neuropathy.

Patients with some demyelinative neuropathies characteristically have uniform conduction slowing of all nerves without signs of major conduction

block (see Chapter 5-4). These include CMT1A, CMT1B, Dejerine-Sottas, metachromatic leukodystrophy, Cockayne's disease, and Krabbe's disease.[641] In contrast, inherited disorders usually associated with multifocal conduction block comprise HNPP, CMTX, adrenomyeloneuropathy, Pelizaeus-Merzbacher disease, and Refsum disease. These disorders may mimic an acquired demyelinative neuropathy, which also typically shows multifocal slowing, temporal dispersion, and conduction block.

Genetic Classification of Inherited Neuropathies

Clinical classification of CMT with prevalence ranging from 1 in 3500 to 8000 population centers on two major varieties, CMTI and CMTII, or hypertrophic and neuronal varieties corresponding to demyelinating and axonal types. Genetic linkage studies provide evidence for this division and further heterogeneity.[84,101,455,847,878]

The most common CMTI, which has an autosomal dominant inheritance, comprises CMT1A, 1B, and 1C (Table 24-6).[403,778] Of these, CMT1A, the most prevalent form estimated to affect 85% of Type I families, has a tandem duplication of chromosome 17p11.2–12 with trisomic expression of the peripheral myelin protein-22 (PMP-22) gene[673] or, less frequently, a missense mutation of PMP-22.[164] Men tend to have a more severe form of the disease than women, who may have formes frustes.[404] The less common CMT1B has a linkage to chromosome 1q21–23,

Table 24-6 Genetic Classification of Hereditary Motor and Sensory Neuropathy

	LOCUS	GENE	MECHANISM
CMTI (HMSN Type I)			
CMT1A	l7pl1.2–12	PMP-22	Duplication/point mutation
CMT1B	lq21–23	P_0	Point mutation
CMT1C	Unknown	Unknown	Unknown
CMTII (HMSN Type II)			
CMT2A	Ip35–36	Unknown	Unknown
CMT2B	3ql3–22	Unknown	Unknown
CMT2C	Unknown	Unknown	Unknown
CMTX (X-linked HMSN)			
CMTX1	Xq13.l	CX32	Point mutation
CMTX2	Xp22.2	Unknown	Unknown
CMTX3	Xq26	Unknown	Unknown
Dejerine-Sottas disease (HMSN Type III)			
DSD Type A	l7p11.2–12	PMP-22	Point mutation
DSD Type B	Iq22–23	P_0	Point mutation
Hereditary neuropathy with pressure palsies			
HNPP Type A	17p11.2–12	PMP-22	Deletion/point mutation
HNPP Type B	Unknown	Unknown	Unknown

CMT, Charcot-Marie-Tooth disease; CMTX, X-linked dominant or recessive; CMT, DSD, Dejerine-Sottas disease; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with pressure palsies; PMP, peripheral myelin protein; P_0, myelin protein zero (MPZ); CX, connexin

showing point mutations in myelin protein zero (MPZ).[292,602,1028] The other type, CMT1C, has no linkage to either chromosome 1 or chromosome 17.

Genetic linkage analysis has identified at least four different forms of CMTII, CMT2A mapping to chromosomes 1p35–36, CMT2B with loci at 3q13–22, CMT2C linked to 12q 23–24.[177] and CMT2D mapping to 7p14.[617] Other reported sites of mutation include MPZ of chromosome 1q21–23 [702] and mutofusin2 (MFN2).[880] Thus, mutations in the gene that encode for MPZ can produce different phenotypes: CMT1B with low conduction velocity, CMTII with unaffected conduction velocity, and CMT1D with intermediate conduction velocity[53] and other varieties of sensorimotor symptoms.[976] A neuronal type with onset in early childhood shows none of the regenerative features considered characteristic of autosomal dominant CMTII.[337]

Occasional patients have an autosomal recessive,[797] X-linked dominant or recessive patterns.[458] Clinical, electrophysiologic, and histologic findings also support primary axonal or demyelinating neuropathy in the X-linked disorder CMTX, which includes X-linked dominant CMTX1 with gap-junction beta-1 protein (GJB1), or connexin 32(CX32) point mutations of chromosome Xq13.1,[385,1068] and X-linked recessive CMTX2 with loci at Xp22.2 and CMTX3 with loci at Xq26 having no CX32 point mutations.[455] Another form, X-linked distal hereditary motor neuropathy, previously called spinal forms of CMT and distal spinal muscular atrophy, maps to chromosome Xq13.1-q21.[513] Demyelinating CMT4A[200] and axonal CMT with vocal cord paralysis, both autosomal recessive in inheritance, show mutations in the ganglioside-induced differentiation–associated protein 1 gene (GDAP1).[770] Patients with CMT and giant axons have a pathologic and genetic entity distinct from classic CMT.[675] Simultaneous MFN2 and GDAP1 mutations caused major mitochondrial defects in a patient without CMT.[149]

To facilitate the genetic analyses in CMT families with clearly dominant inheritance shown by male-to-male transmission, the patient with a demyelinating neuropathy needs screening for PM22 to diagnose CMT1A and, if negative, MPZ mutation to diagnose CMT1B. In contrast, the patient with an axonal neuropathy should have screening for MFN2 mutation to diagnose CMTII. The use of neurophysiologic measurements also helps select probable CMTX families as having slow nerve conduction velocities in the absence of male-to-male inheritance or chromosome 17DNA duplication. In this setting, one may screen the connexin 32 gene first, before MPZ or PMP22. In one study, the yield of connexin 32 mutation increased from approximately 6% of all CMTI families to 91% of nonduplicated, nondominant families with characteristic electrophysiologic changes of CMTX.[780] Figure 24-2 summarizes the role of genetic testing in the diagnosis of suspected hereditary polyneuropathies.[302]

Some families with autosomal dominant HMSN have calf enlargement caused by muscle fiber hypertrophy predominantly of Type I fibers,[240,957] and others have neuropathy with optic atrophy.[1025] In one family with HMSN, some members had features of myotonic dystrophy, and others had only its genetic markers on chromosome 19.[1029] A large group of clinically unequivocal cases shows a bimodal distribution of nerve conduction velocities.[404] In addition to the neuronal and hypertrophic types, some investigators emphasize the existence of an intermediate variety in some kinships.[96,355,872]

In HNPP with autosomal dominant inheritance,[622] slight traction or compression leads to motor and sensory deficits in an otherwise asymptomatic patient. In most families thus far studied, patients have a 1.5 Mb deletion in a segment of chromosome 17p11.2–12 that contains the PMP-22 gene.[494,695,779,1220] Genetic studies have shown another hereditary recurrent focal neuropathy, hereditary neuralgic amyotrophy (HNA) with genetic loci at chromosome 17q25. Brachial plexus involvement (see Chapter 23-3) may occur as the only expression of HNPP, requiring its distinction from HNA by DNA analyses to test for 17p11.2 deletion.[832]

The duplication in CMT1A and deletion in HNPP in the same region probably result from consequences of unequal crossing-over during germ cell meiosis.[164] Both neuropathies result from an imbalance of PMP-22 protein expression.[341] In one series, DNA analysis detected the

deletion of 17p11.2 in 24 of 51 patients with multifocal neuropathies, establishing the diagnosis of HNPP.[1113] In another study, underexpresssion of PMP-22 mRNA correlated with disease severity and with mean axon diameter.[972] Kinships without the typical 1.5 Mb deletion usually have distinct mutation in the PMP-22 gene, suggesting genetic heterogeneity.[26,1047]

Linkage analyses in autosomal dominant cerebellar ataxia have demonstrated genetic heterogeneity and subclassification, spinocerebellar ataxia (SCA) Type I to Type VII (SCAI to SCAVII) with five identified genes all showing expanded and unstable CAG repeat[570,1126] SCAI on 6p22-p23, SCAII on 12q23–24.1, SCAIII/Machado-Joseph disease (MJD) on 14q24.3, SCAVI on 19p13, SCAVII on 3p11-p13, and SCAIV and SCAV on two unidentified genes of chromosomes 16 and 11. Mutations in the HSP27 gene also cause dominant, recessive, and sporadic HMN/CMTII.[368,437]

Autosomal Dominant Charcot-Marie-Tooth I (Hereditary Motor Sensory Neuropathy Type I)

The hypertrophic variety of CMTI affects both sexes, but men more commonly than women. Histologic studies reveal enlargement of the peripheral nerves, segmental demyelination and remyelination with onion bulb formation and axonal atrophy.[1141] Despite some studies suggesting a primary neuronal disturbance based on axonal atrophy, morphologic and morphometric investigations reveal a lack of small- and large-diameter myelinated axons at an early stage and a demyelinating process followed by axonal loss.[339]

The symptoms usually begin insidiously during the first two decades sometimes with subtle clinical signs appearing even in children before 1 year of age.[71] These include pes planus, distal foot wasting, weakness of ankle eversion and

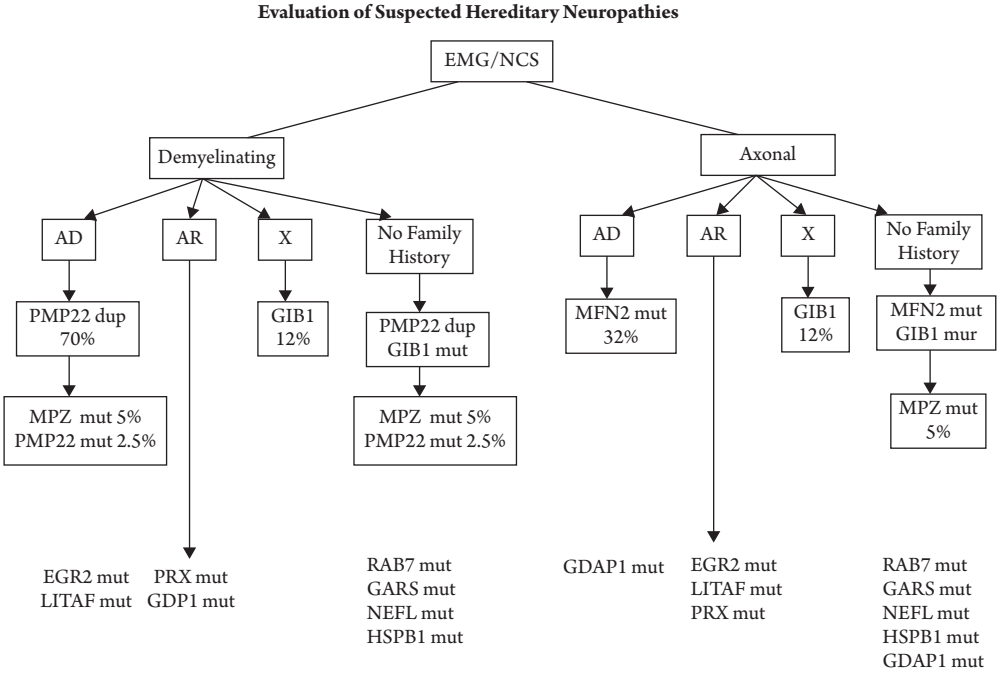

FIGURE 24-2 Evaluation of Suspected Hereditary Neuropathies. PMP22, peripheral myelin protein 22; MPZ, myelin protein zero; PR, periaxin; GDAP1, gagnlioside-induced differentiation-associated protein 1; GJB1, gap-junction beta-1 protein (connexin32); MFN2, mitofusion 2; EGR2, early growth response 2; LITAF, lipolysaccharide-induced tumor necrosis factor α; RAB7, small guanosine triphosphatase late endosomal protein; GARS, glycyl-transfer RNA synthetase; NEFL, neurofilament light change; HSPB1, heat shock protein beta-1. (Modified from England, Gronseth, Franklin, et al.[302])

dorsiflexion, fatigue,[85] and, most consistently, lower-limb areflexia.[311] Atrophy initially involves the peroneal musculature and then, the thigh and the upper limbs, sparing the trunk and girdle musculature. Rare manifestations include predominance of proximal upper-limb weakness,[48] diaphragmatic paralysis with respiratory or cardiac failure,[401] and cranial nerve involvement.[849] The classic stork leg configuration develops only rarely in the hypertrophic type. Bilateral footdrop causes a characteristic gait difficulty. The patient has paresthesias, dysesthesias, and muscle pain associated with foot deformity. Typical findings include palpable nerves, the loss of vibratory and position senses, reduced cutaneous sensations, and diminished stretch reflexes first at the ankle and later diffusely. Many investigators consider Roussy-Levy syndrome with a static tremor of the hands as a variant of CMT1B.[141,875]

The disease progresses very slowly over many decades at times showing spontaneous arrest. Muscle atrophy and weakness may incapacitate the patient. They may suffer from temporary worsening of otherwise stable symptoms during pregnancy.[943] Neurologic deficits may result from compression of the spinal cord, vertebral arteries, or neural foramina by the hypertrophic nerve roots.[130,937,1231] Like any chronic illness, CMT disease impairs quality of life (QOL).[990,1158] The ability to ambulate independently and do toe and heel walk correlate well with QOL measures.[839] The CMT neuropathy score, which combines symptoms, signs, and electrophysiology, and the Neuropathy Score based solely on the neurologic examination complement each other in detecting progression of CMT1A.[989]

Coincidence of two genetic mutations in parents caused an early and severe compound form of HMSN.[720,1151] In a kindred displaying a dominant inheritance, marriage between two heterozygotes resulted in two homozygous offspring. The homozygotes had clinical features reminiscent of the classic Dejerine-Sottas disease. Occasionally a patient with CMTI develops superimposed CIDP, which may respond to immunosuppressive therapy [735] or corticosteroids.[83] Although not universally accepted,[1178] this association may support a genetic susceptibility of certain CMT kindreds to inflammatory demyelinating process.[340,1165] Unusual and sometimes devastating clinical features may result from a rare chance association of CMT1A with such disorders as facioscapulohumeral muscular dystrophy (FSHD),[131] myasthenia gravis (MG),[176] Noonan syndrome,[994] and posterior interosseous nerve syndrome.[146] Patients with CMT1B may develop clinical features resembling amyloid neuropathy, which sural nerve biopsy can distinguish.[107]

As a hallmark of the CMTI, NCS shows a marked, diffuse, and uniform slowing with median motor conduction velocity of around 20 m/s in PMP22 duplications, higher in CX32 mutations and lower in the demyelinating form of MPZ mutations.[247] The uncommon recessive forms have slower conduction than the dominant form.[405] The motor conduction velocities in affected family members average less than one-half those of normal individuals, varying from 9 to 41 m/s with a mean of 25 m/s.[282] The range of conduction velocities found in affected individuals show no overlap with those of their clinically normal relatives, indicating complete penetrance of the gene from early childhood.[777] Slowing of conduction shows a complete concordance with the presence of the segmental duplication in CMT1A.[492] The great variation in conduction velocity emphasizes the influence of factors apart from the shared genetic mutation on phenotypic expression. Prolonged terminal latencies in the early stages indicate distally prominent slowing. The disease affects both peripheral and central sensory fibers as evidenced by delay and reduction of sensory potentials as well as SEP.

Despite slowing, a limited degree of temporal dispersion indicates a homogeneity of the pathologic process. The extent of the conduction abnormality varies little not only among members in the same family but also from one nerve to another in the same patient.[478] Such uniformity helps differentiate this entity from acquired inflammatory polyneuropathy. Conduction abnormalities may herald clinical onset of neuropathy. Motor nerve conduction velocities attain maximal slowing over the first 3 to 5 years of life and remain relatively stable thereafter,[520] whereas CMAP amplitudes decline with progressive axonal loss.[938] Both measures, despite an inverse relationship to clinical severity, show no correlation with age,[432] probably

because the primary pathologic process remains inactive after childhood.[309] Serial electrophysiologic studies can detect the conduction abnormalities in infancy and early childhood.[345] For purposes of genetic counseling, a clinically and electrophysiologically normal subject at 6 months of age has a very small risk of having inherited the CMT1 gene,[67] although the florid clinical picture may not occur until the second decade of life.[345]

Other electrophysiologic abnormalities include absent or delayed F waves,[530] a finding that matches the slowing of motor nerve conduction in the distal segment (see Figs. 7-8 and 7-10 and Table 7-3 in Chapter 7).[525] Studies of the facial nerve[364,524] and phrenic nerve[145] also show increased latencies despite relatively normal strength of the mimetic muscles and diaphragm (see Figs. 8-7 and 8-8 and Tables 8-2 and 8-4 in Chapter 8). Patients may also have impaired central conduction[1020] and autonomic dysfunction[1020] but not universally.[452] The reduction in MUNE shows a stronger correlation with clinical weakness than CMAP amplitude probably, reflecting extensive motor unit reconfiguration.[639] In one study,[1136] MUNE values declined with age equally in both patients and controls, indicating limited motor unit loss. Recording isometric force during fastest voluntary contraction shows a prolongation in contraction time and a reduction in maximal rate in rise of tension.[659] In many patients, studies of evoked potentials detect a minor degree of involvement of visual[142] and auditory pathways.[562,970]

An interval-training exercise with cycling can improve functional capacities and alleviate fatigue in CMT patients.[297] Early foot and ankle intervention may prevent long-term disability and morbidity in CMT1A.[125] Intramuscular injection of botulinum toxin, though safe and well tolerated, did not affect the progression of pes cavus.[126] Possible surgical therapies for upper-limb neuropathy include standard tendon transfers, nerve compression release, soft tissue releases, and joint fusions.[117]

Autosomal Dominant Charcot-Marie-Tooth II (Hereditary Motor Sensory Neuropathy Type II)

In the neuronal variety of CMT, patients have neither hypertrophic nerves nor prominent segmental demyelination. Inherited as an autosomal dominant disorder, symptoms and signs appear in early adulthood or later. Rarely the disease appears in early childhood sporadically or with autosomal recessive or dominant inheritance.[836] The spectrum of this type includes CMTII patients with Thr124Met mutation in MPZ, who characteristically have marked sensory abnormalities, deafness, pupillary abnormalities, and severe dysautonomia[1048] and those with a BSCL2 Ser90Leu mutation, who have pyramidal signs as a unique feature.[672] Most consider a third type of CMT disease, designated as the spinal form, as a variant of the neuronal type or of distal SMA. In addition, TRPV4 mutation causes CMT2C with short stature, vocal cord paresis, and axonal neuropathy.[177] Individuals with the same mutation may have no distinct CMTII or have phenotypic CMT2C with vocal cord and diaphragmatic involvement.[51,539]

The clinical features, although much less generalized, resemble those of CMTI with less conspicuous sensory disturbances. As the name *peroneal muscular atrophy* indicates, affected patients develop selective muscular wasting of the legs with limited involvement of the upper limbs in early stages. A prospective study showed a slow deterioration of muscle strength and increase in disability during a 5-year follow-up period.[1081] An almost total loss of muscle bulk below the knee gives rise to a stork leg appearance. Despite footdrop with severe weakness of the plantar flexors and clubfeet, patients often walk fairly well, rarely showing total incapacitation. Some affected individuals have tremors of the hands but much less commonly than those with CMTI. Differential diagnoses include plexiform neurofibroma of the cauda equina, which may mimic peroneal muscular atrophy.[69]

Electrophysiologic studies reveal mild slowing of the nerve conduction velocities consistent with a reduction in amplitude of the CMAP and SNAP.[68,405] Needle studies typically show a large MUP, fasciculation potentials, fibrillation potentials, and positive sharp waves. Studies of macro-EMG and muscle biopsy revealed only minor collateral reinnervation and prominent muscle fiber hypertrophy in CMTII in contrast to the opposite finding in CMT I.[304] Some patients

have a nonuniform slowing of motor conduction velocities and dispersion of CMAP reminiscent of acquired chronic demyelination.[1068]

Autosomal Recessive Charcot-Marie-Tooth (Recessive Hereditary Motor Sensory Neuropathy)

Clinical and genetic analyses have identified nine forms of autosomal recessive HMSN associated with defects in seven loci and six genes. Electrophysiologic findings, available only in some cases, support the notion of demyelination. In a gypsy family with HMSN-L, for example, studies revealed the presence of A waves, a three-component blink reflex, and changes in hypoglossal nerve conduction velocity.[460] Patients with periaxin gene mutations have early-onset autosomal recessive demyelinating CMT disease (CMT4F) or Dejerine Sottas neuropathy.[693]

X-Linked Charcot-Marie-Tooth (X-Linked Dominant Hereditary Motor Sensory Neuropathy)

The genetically heterogeneous group of CMTX includes a rare variant with X-linked dominant inheritance,[939] which represents at least 10%–15% of all HMSN.[320,833] In a large Canadian kindred traced through six generations,[388] affected fathers had no male-to-male transmission, whereas all their daughters expressed the disease. The typical clinical features consist of onset in early childhood, pes cavus, distal muscular atrophy, and sensory abnormalities. Other features seen in some cases of X-linked HMSN include pyramidal signs and cerebral white matter lesions,[376] deafness,[625] and abnormalities in the cerebellum and central somatosensory pathway.[503]

Electrophysiologic observations may indicate a heterogenous pattern with demyelinative features or substantial loss of distal motor and sensory nerve fibers with primary axonal degeneration. Some CMTX patients, usually women, show a nonuniform involvement between and within nerves,[386,638] mimicking acquired demyelinating neuropathies, probably because of short internodes as the specific effect of the mutations.[138]

Hereditary Neuropathy with Liability to Pressure Palsies

Autosomal dominant HNPP[622] shows, as the most prominent feature of the disease, pressure-induced reversible motor weakness, although sensory symptoms may also appear.[642] Compression palsy commonly affects the ulnar, radial, and peroneal nerves, with recovery occurring slowly over weeks and months. Occasional patients may develop acute anterior interosseus neuropathy,[317] recurrent familial brachial plexus palsies,[1046] or other acute painless mononeuropathies[848] as the only or predominant clinical manifestation. Others may have acute recurrent polyneuropathy,[621] acute multiple mononeuropathies,[218] or chronic sensorimotor neuropathy as the presenting symptoms.[319,690]

Irreversible axonal damage may occur at entrapment sites in motor nerves, progressing with age[552] or triggered by physical exercise.[434] Rare associated features include central nervous system (CNS) demyelination[24] and the syndrome of moving toes and myoclonus.[981] The presence of mild symptoms and the marked phenotypic variability leads to underrecognition of HNPP.[574] Cranial MRI and electrophysiologic studies may reveal subclinical or overt CNS myelin damage.[961,1069,1077]

Motor and sensory NCS shows focal conduction changes at the usual compression sites in paretic limbs[1117] but also in some clinically unaffected nerves.[1105] Evaluations of clinically normal nerves reveal electrophysiologic abnormalities in approximately one-half of the patients and some asymptomatic relatives.[224] Some patients have diffuse slowing of sensory nerve conduction and delay of distal motor latencies with relatively minor reduction of motor nerve conduction velocity.[30] Accentuated distal slowing found primarily in the segments liable to pressure palsies or repetitive trauma support the concept of pressure palsy rather than a distal myelinopathy.

Histopathologic changes include focal, sausage-like or tomaculous thickening of the myelin sheaths and noncompacted "loose" myelin lamellae together with segmental demyelination and remyelination.[683,1105] Other entities associated with focal thickening of myelin sheath include IgM paraproteinemic neuropathy and

HMSN.[963] A reliable screening method to detect clinically unaffected carriers comprise evaluation of motor conduction across usual entrapment sites, especially the ulnar nerve, and sensory conduction in the sural nerve. Molecular analysis confirming the chromosome 17p11,2 deletion establishes the specific diagnosis.[451]

Hypertrophic Polyneuropathy of Dejerine Sottas (Hereditary Motor Sensory Neuropathy Type III)

Dejerine and Sottas[241] described a very severe, generalized form of demyelinating sensorimotor neuropathy inherited as an autosomal recessive trait.[876] The disorder shows a considerable genetic heterogeneity[677] with a mutation in either PMP-22[457,701] or MPZ[412] or linkage to chromosome 8.[456] The affected nerves have marked thickening, onion bulb formation, segmental demyelination, and thinning of the myelin surrounding the nerve. Symptoms appear in infancy with delayed development of motor skills, especially in walking. Clinical features consist of pes cavus, muscle cramps, incoordination, kyphoscoliosis, weakness, sensory loss, and abducens and facial nerve palsies. Adult patients often have paraparesis and severe truncal ataxia, requiring the use of a wheelchair. Patients with this disorder have a higher incidence of ataxia, areflexia, and hypertrophic nerves than those with CMTI. Pathologic analysis reveals a greater loss of myelinated fibers, a larger number of onion bulbs with more lamellae per each, and a higher ratio of the mean axon diameter to the fiber diameter.[835] Characteristic features include NCS, abnormalities showing a marked slowing of velocity for both motor and sensory fibers. In one series of 11 patients, all but one had median and ulnar motor conduction velocities less than 6 m/s.[66]

The differential diagnosis should include congenital demyelinating sensorimotor neuropathy with focally folded myelin sheaths.[338]In this condition, nearly all teased fibers have an abundance of focal myelin thickenings, or tomacula, which serve as a striking discriminating feature. The clinical, genetic, and electrophysiologic characteristics otherwise resemble those of Dejerine-Sottas disease. In contrast to the generalized form, rare localized hypertrophic neuropathy consists of isolated mononeuropathy with focal nerve enlargement.[1014] This entity usually represents a localized form of Dejerine-Sottas disease, an entrapment neuropathy, or an intraneural neurofibroma. In some patients, morphologic findings in the localized areas of enlarged nerves consist primarily of perineurial cell hyperplasia or perineurioma.[738] In this disorder, NCS findings suggest severe sensorimotor axonal loss with no evidence of slowed conduction velocity. Needle studies also indicate a focal axonal loss with evidence of severe denervation limited to the territory of the affected nerve.

Hereditary Ataxic Neuropathy of Refsum (Hereditary Motor Sensory Neuropathy Type IV)

Hereditary ataxic neuropathy of Refsum, a rare disorder transmitted by an autosomal or a recessive gene, has characteristic pathologic changes in the olivocerebellar tracts, anterior horn cells, and the peripheral nerves. The typical clinical features comprise deafness, anosmia, night blindness with retinitis pigmentosa, ichthyosis-like skin, cerebellar signs, and nystagmus. Involvement of the peripheral nerve causes lightning pain in the legs, wasting of muscles, hyporeflexia, hypotonia, and diminished vibration and position sense. A metabolic defect in the oxidation of branched chain fatty acid elevates serum phytanic acid, which for unknown reasons leads to a hypertrophic neuropathy. Patients develop recurrent segmental demyelination and motor and sudomotor axonal losses in parallel with exacerbations of weakness, showing an apparent long-term clinical stabilization.[577,1091] Electrophysiologic studies reveal decreased sensorimotor conduction velocities in all limbs.[259] Severe axonal involvement in the lower limb may characterize other cases.[350] Dietary restriction of phytol results in considerable improvement of symptoms. Some patients with retinitis pigmentosa and ataxia have a syndrome that clinically resembles Refsum disease without detectable biochemical abnormalities. In these cases, electrophysiologic studies reveal a mildly delayed, low-amplitude SNAP, but no evidence of hypertrophic neuropathy.[1111]

Spino-Cerebellar Ataxia

Autosomal dominant spino-cerebellar ataxia (SCA) often accompanies a neuropathy that superficially resembles CMT with distal wasting and weakness involving the legs more than the arms.[120,327,649,1041] Some patients show muscle wasting presumably reflecting the loss of motoneurons.[1] Others have an extensor planter response with normal or increased stretch reflexes in the upper limbs and at the knee despite frequently absent ankle jerks. In one series,[570] clinical studies showed sensory or sensorimotor polyneuropathy in 42% of SCAI, 80% of SCAII, and 54% of SCAIII patients. Furthermore, SCAI patients with polyneuropathy had significantly higher CAG repeats than those without polyneuropathy.

Electrophysiologic abnormalities include lower-than-normal mean motor and sensory nerve conduction velocities and a reduced SNAP amplitude.[406,543,718] Median nerve SEP reveals a decrease in amplitude of N13 and N20 with increased interpeak latencies, implicating central and peripheral sensory pathways.[743] Sural nerve biopsies show fewer number of myelinated fibers and normal unmyelinated fibers.[718] Peripheral neuropathy also develops in some patients with infantile[561] and late-onset SCA[306,796] sometimes associated with ceroid lipofuscinosis.[1201]

A predominantly sensory axonal neuropathy seen in olivopontocerebellar atrophy affects those patients with glutamate dehydrogenase deficiency but not those with normal enzymatic activities.[187]Such distinction may serve as an electrophysiologic marker for differentiating the subtypes. The postmortem examination of one patient revealed olivopontocerebellar atrophy, demyelination of the posterior columns, degeneration of anterior horn and dorsal root ganglion cells, and a reduced number of myelinated fibers in the sural nerve.[188]

Friedreich's Ataxia

Friedreich's ataxia shows an autosomal recessive inheritance associated with a GAA trinucleotide repeat expansion in the first intron of the X25 gene on chromosome 9q13–21.1. Patients with limited GAA expansions may develop mild symptoms later than the usual onset without cardiomyopathy.[349,353,680] The disease primarily affects the spinocerebellar tracts, corticospinal tracts, and posterior columns of the spinal cord. In advanced cases, the degeneration also involves the dorsal roots and peripheral nerves. Despite the traditional emphasis on the severe loss of large myelinated fibers and well-preserved unmyelinated C fibers,[834]studies of cutaneous nerve fibers show involvement of small epidural nerve fibers.[790]

The only constant clinical findings within 5 years of presentation comprise limb and truncal ataxia and absent stretch reflexes in the legs.[402] All patients eventually develop dysarthria; signs of pyramidal tract dysfunction in the legs; and loss of joint, position, and vibration sense. Other less frequent clinical features include cardiomyopathy, kyphosis, scoliosis, pes cavus, distal amyotrophy, optic atrophy, nystagmus, and deafness. On the average, patients lose the ability to walk by the age of 25 years and become chair-bound by the age of 44 years.[402] Common variabilities include late onset, preservation of the lower-limb tendon reflex, and slow progression.[219]

Electrophysiologic studies show an absent or considerably reduced SNAP,[716,959] abnormal SEP with peripheral as well as central conduction delay,[246,861] and essentially normal motor NCS except for modest slowing in some patients.[834] Abnormal CCT measured by TMS progressively worsens as the disease advances.[223] Patients rarely complain of visual impairment, but VEP studies usually show an increased latency or reduced amplitude.[143,654,861] Nerve biopsy reveals a severe loss of large myelinated fibers but no demyelination.[147]

Porphyria

An acute, primarily motor neuropathy characterizes several forms of porphyria, a rare hereditary disorder that belongs to the category called *inborn errors of metabolism*.[869] These include acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria.[58] A partial defect in hepatic heme synthesis results in overproduction of delta aminolevulinic acid and porphobilinogen. The disease shows a higher incidence in women,

autosomal dominant inheritance, and variable degrees of expression. Clinical features include abdominal pain, vomiting, peripheral neuropathy, neurogenic bladder, seizures, and mental status changes, but no skin photosensitivity. Excessive quantities of porphyrin intermediates excreted in the urine impart a deep red color with formation of polypyrroles from porphobilinogen on exposure to light. Patients experience acute attacks either spontaneously or after inadvertent ingestion of barbituates, sulphonamides, or certain other drugs. In one reported case using aminolevulinic acid during photodynamic therapy, the patient developed acute neuropathy with neurological features mimicking hepatic porphyria.[1066]

Acute axonal neuropathy affects motor fibers regularly and sensory fibers in about 50% of patients.[20] Weakness progresses rapidly, involving the axial muscles more than the distal muscles sometimes mimicking GBS, although other features such as seizure help establish the clinical diagnosis. The sensory loss, although relatively mild, may also predominate proximally. Reflecting axonal loss, NCS shows a low-amplitude CMAP with slightly slow conduction velocities. Needle studies reveal prominent fibrillation potentials and positive sharp waves in the proximal muscles 1–2 weeks after onset.

Cerebral Lipidosis

Polyneuropathy accompanies at least two types of cerebral lipidosis: Krabbe's disease and metachromatic leukodystrophy. In both entities, a marked slowing of nerve conduction suggests the diagnosis, although the confirmation comes from a nerve or cerebral biopsy.[697]

Krabbe's disease, an autosomal recessive disorder, affects the white matter of the central and peripheral nervous systems.[751]A galatocerebrosidase (GALS) deficiency causes the accumulation of undegraded psychosine, leading to the pathologic hallmarks of globoid cell leukodystrophy. Identification of a homozygous point mutation in the GALS gene establishes the diagnosis.[969] Histologic studies in Krabbe's globoid cell leukodystrophy reveal diffuse loss of myelin throughout the cerebral white matter and peripheral nerves. Prominent perivascular cuffs appear consisting of greatly enlarged cells with the accumulation of cerebroside. Affected infants, normal at birth, develop severe neurologic disturbances within the first few months of life. The disease often follows a fulminant course with rigidity, head retraction, optic atrophy, bulbar paralysis, a decorticate posture, and finally death before the end of the first year. Neuropathy, usually an early manifestation affecting the nerve uniformly,[992] may occasionally herald the disease as one of the presenting features.[221,644] In one series of 26 children, NCS showed abnormalities in all early infantile form with the onset of disease in the first 6 months of life, but only in 20% of the remaining cases with later onset.[443]

In metachromatic leukodystrophy,[135,201,333] a deficiency of arylsulfatase leads to an abnormal breakdown of myelin. Metachromatic staining properties result from cerebroside sulfate, which accumulates in the nervous tissue. Neurologic signs include spasticity, ataxia, dementia, and neuropathy. The disease usually affects infants but rarely children[194,392] and adults.[94] Electrophysiologic studies reveal a substantially slowed conduction as expected in a demyelinative neuropathy. Morphometric studies show a marked reduction in sheath thickness, particularly in the large myelinated fibers.[54]

Hereditary Sensory and Autonomic Neuropathy

Hereditary sensory and autonomic neuropathy (HSAN) consists of five distinct entities. The most common, HSAN Type I, has an autosomal dominant inheritance with a locus assigned to chromosome 9q22.1-q22.3. It shows degeneration of the dorsal root ganglia, early loss of SNAP, and preservation of the sympathetic skin responses.[64,776,987] In one family, sural nerve biopsies showed a marked loss of all myelinated fibers and a comparable loss of unmyelinated fibers.[234] Clinical findings include loss of pain and temperature sensation, areflexia, and development of ulcers in the lower limbs with nearly complete sparing of the upper limbs. The disease tends to progress slowly after its onset in the second decade of life. Deafness, diarrhea, and ataxia occasionally develop in affected individuals.

Type II has autosomal recessive inheritance with onset in infancy or early childhood. It affects both upper and lower limbs equally with a higher incidence of chronic ulceration than in Type I. Characteristic features include progressive sensory neuropathy, spastic paraplegia, and a mutilating lower-limb acropathy.[1079,1097] In this type, NCS shows an absent SNAP and borderline slow conduction. Some families with HSANI have prominent muscle weakness[267] with possible implication of overlap with HMSNII.[276]

Other entities in this category include Type III, or familial dysautonomia of the Riley-Day syndrome[920,1090]; Type IV, a rare congenital loss of C fibers with complete insensitivity to pain and anhidrosis[627,666,789,1154]; Type V, congenital insensitivity to deep pain without anhidrosis[436,733]; and familial sensory autonomic neuropathy with arthropathy in Navajo children.[476] Studies of sympathetic skin response (SSR), preserved in Type III and lost in Type IV, can differentiate the two.[422]

Lipoprotein Neuropathies

Two types of lipoprotein disorders accompany neuropathies. Patients with Bassen-Kornzweig syndrome, seen mostly in Jewish children, have malabsorption, cerebellar signs, retinitis pigmentosa, acanthocytosis, and virtual absence of betalipoprotein in the serum, or abetalipoproteinemia. Diminished stretch reflexes and the absence of position and vibratory senses suggest a peripheral neuropathy. Neurologic signs resemble those of Friedreich's ataxia and Refsum syndrome. The fiber diameter spectrum of the sural nerve indicates a loss in the 8–12 μm diameter range. In one histologic study, the sural nerve showed a decreased number of large fibers with diameters greater than 7μm, axonal regeneration, and paranodal demyelination.[1187]

In typical cases, NCS reveals a reduced SNAP amplitude with a slight delay in distal latency[1187] and a normal or slightly reduced CMAP amplitude with normal conduction velocities.[668,730] Needle studies show signs of chronic denervation in distal limb muscles such as a large-amplitude, long-duration MUP and poor recruitment. Other electrophysiologic abnormalities may include prolonged VEP and SEP latencies.[114]

Patients with Tangier disease have a low level of high-density lipoprotein and cholesterol in the serum. Their enlarged tonsils have a characteristic bright orange color from the deposition of cholesterol esters. The skin and rectal mucosa display similar changes. Both myelinated and unmyelinated fibers show degeneration.[544] Dissociated losses of pain and temperature sensation, not unlike those seen in syringomyelia, suggest selective involvement of the small fibers.[277] Patients may have a relapsing and remitting mononeuropathy with prominent demyelination and remyelination, or slowly progressive neuropathy with advanced axonal degeneration.[881] Conduction studies may reveal abnormal velocities in some patients but not in others.[343] Differential diagnosis of trophic ulcers in the setting of sensory or autonomic neuropathy include, in addition to Tangier disease, leprosy, diabetic small-fiber neuropathy, vasculitic neuropathy, and HSAN.[1005]

Giant Axonal Neuropathy

Children with giant axonal neuropathy (GAN)[255,1088] usually have white matter abnormalities of the CNS and intellectual dysfunction.[244] The disease shows an autosomal recessive inheritance trait localized to chromosome 16q24 with causative point mutations in a gene called gigaxonin.[325,571] The spectrum of pathogenic mutations in the gigaxonin gene accounts for the allelic heterogeneity of GAN.[119] The accumulation of neurofilamentous material leads to ballooning and degeneration of the axons,[384,573] affecting the motor fibers more than the sensory fibers.

The clinical features in a large kindred include infantile onset, progressive distal amyotrophy of four limbs, brisk reflexes, diffuse fasciculations, bulbar signs, and deep sensory loss in both lower limbs.[394] Patients characteristically have tightly curled, reddish hair in contrast to the sparse hair seen in Menke's kinky hair disease. Electrophysiologic studies suggest the presence of secondary demyelination triggered by axonal enlargement, although available data fall short of characterizing the condition. Abnormalities demonstrated by evoked potential studies confirm clinical and pathologic findings of CNS dysfunction.[686]

Fabry's Disease

Fabry's disease, a multisystem X-linked recessive disorder, results from an inborn error of glycosphingolipid metabolism, caused by a deficiency of lysosomal α galactosidase A, which causes the accumulation of ceramide trihexose in various tissues. The enzymatic defect of ceramide trihexosidase affects the skin, blood vessels, cornea, and cell bodies of the dorsal ganglia. Both the central and peripheral nervous systems show lipid depositions in endothelial and perithelial cells of the vessel walls or perikaryon.[995] Axonal degeneration primarily involves small myelinated and unmyelinated fibers.[545,1073]

The presenting clinical features include severe burning sensations of the hands and feet, and thermal afferent fiber dysfunction in a length-dependent fashion.[671] Corneal confocal microscopy may help diagnose this neuropathy by assessing loss of corneal sensation.[1074] Although ordinarily normal, NCS may show some slowing especially at the common sites of compression in affected men and occasionally in female carriers.[645] Some, but not all, patients with Fabry's disease have shortened cutaneous silent period in the lower limb associated with a reduced SNAP.[22] Needle studies reveal no abnormalities in most cases. Enzyme replacement therapy leads to a modest but significant improvement in the clinical manifestations of the small-fiber neuropathy associated with this disorder.[973]

Familial Amyloid Neuropathy

The most common familial amyloid polyneuropathy, Type I, has a variant transthyretin (TTR) with a single amino acid substitution.[32,237] These mutations include a most frequent methionine-for-valine reported from Portugal, Italy, Sweden, and Japan, an alanine-for-valine in a family of German origin, a leucine-for-valine seen in Japanese pedigrees,[1121] and a serine-for-alanine documented in Taiwain.[1213] The familial amyloid polyneuropathy Type IV phenotype in Finnish as well as Japanese kinships results from a single base substitution, guanine to adenine, at nucleotide position 654 in the gelsolin gene located on chromosome 9q32-q34.[676]

Familial amyloid neuropathies, unlike primary, or nonfamilial, amyloid neuropathies associated with paraproteinemia (see Chapter 24-3), have relentless progression of neurologic and cardiac impairment, leading to death within 7–15 years after disease onset. Signs and symptoms of amyloidosis result from deposits of amyloid around blood vessels and connective tissues in multiple systems. Clinical features depend on the organs involved, which commonly include the heart, tongue, gastrointestinal tract, skeletal muscles, and kidney. Amyloid deposits in the flexor retinaculum may cause CTS in about one-fourth. Some patients develop sensorimotor polyneuropathy without other systemic symptoms of amyloidosis.[889]

Compared to HSAN, familial amyloid neuropathy shows a greater motor and autonomic involvement with an early loss of SSR,[987] which therefore serves well in detecting the condition.[203] One study [522] showed the usefulness of quantitative sensory and autonomic test for assessing the disease severity. Liver transplantation may offer hope for arresting the progression of sensorimotor neuropathy.[76]

A form of autosomal dominant amyloidosis prevalent in northern Portugal produces progressive neuropathy involving the legs in young adults. Another, milder form of autosomal dominant amyloidosis with neuropathy of the upper limbs primarily affects Swiss families with the onset later in life. Familial amyloid neuropathy has also involved kinships of German,[799] Japanese,[31,448,1017] Northwest Irelands,[1038] Taiwanese,[1210] and English ancestries.[534] The mutations of the TTR gene, found in some of these hereditary cases,[522,1114] have also affected British and French patients without a family history.[82]

Other Inherited Neuropathies

Other rare inherited neuropathies or systemic disorders associated with peripheral neuropathy include adrenomyeloneuropathy (see Fig. 7-9 in Chapter 7),[81,750,913,1137,1191] arthrogryposis multiplex congenita,[495] cerebrotendinous xanthomatosis,[874] Cockayne's syndrome,[383] chorea-acanthocytosis,[647] congential cataracts facial dysmorphism neuropathy syndrome,[1101] congenital

hypomyelination polyneuropathy,[100] distal hereditary motor neuropathy,[192] familial demyelinating sensory and motor polyneuropathy,[971] HMSN associated with agenesis of corpus callosum,[268] HMSN with treatable extrapyramidal features,[474] hereditary tyrosinemia,[736] infantile neuroaxonal neuropathy,[1194] lethal neonatal autosomal recessive axonal sensorimotor polyneuropathy,[1145] multiple endocrine neoplasias,[274] mitochondrial disorders,[97,741,1184] neurofibromatosis,[521,1095] sialidosis Type I or the cherry-red spot myoclonus syndrome,[1040] late-onset Tay-Sachs diseases,[982] Waardenburg-Hirschsprung disease accompanied by congenital hypomyelinating neuropathy,[454] and Wilsons disease[229,481] sometimes in the context of copper deficiency induced by treatment with zinc and chelators.[326]

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25

Mononeuropathies and Entrapment Syndromes

Abbreviations: AIDS—acquired human immunodeficiency syndrome, CIDP—chronic inflammatory demyelinating polyneuropathy, CMAP—compound muscle action potential, CMT—Charcot-Marie-Tooth disease, CRPS—complex regional pain syndrome, CSF—cerebral spinal fluid, CTS—carpal tunnel syndrome, EMG—electromyography, GBS—Guillain-Barré syndrome,

HNPP—hereditary neuropathy with liability to pressure palsy, HSV—herpes simplex virus, MEP—motor evoked potential, MMN—multifocal motor neuropathy, MUP—motor unit potentials, NCS—nerve conduction study, SEP—somatosensory evoked potentials, SNAP—sensory nerve action potential, NMDA—N-Methyl-D-aspartic acid, TMS—transcortical magnetic stimulation

1. INTRODUCTION

Despite the unpredictable nature of traumatic injuries, individual nerves commonly predisposed to isolated damage include long thoracic, suprascapular, musculocutaneous, and axillary nerves in the shoulder girdle, and lateral femoral cutaneous, femoral, and sciatic nerves in the pelvic girdle.[127,572] An injury resulting from acute or chronic repetitive external pressure produces a compressive neuropathy, whereas chronic distortion or angulation of the nerve from an internal source causes an entrapment neuropathy. Entrapment syndromes develop at the common sites of chronic or recurrent constriction of the radial, median, ulnar, common peroneal, and tibial nerves.[572] Certain types of peripheral nerve disorders may develop occupationally. For example, instrumentalists may suffer from the symptoms of cervical radiculopathy, thoracic outlet syndrome, or mononeuropathy involving the median, ulnar, or digital nerve.[342,343] A number of different nerve lesions also result from stretch, ischemia, compression, or laceration during a surgical procedure.

The diagnosis of a focal nerve lesion depends on elucidation of weakness and atrophy of all muscles supplied by the nerve distal to the lesion. Sensory findings, which usually appear earlier, provide less reliable localizing signs than motor deficits, particularly in the upper limbs, where sensory dermatomes overlap considerably. Electrodiagnostic studies help localize and characterize a focal lesion if performed as an extension of the physical examination in a proper clinical context. Needle studies delineate the exact distribution of denervated muscles in assessing a focal nerve lesion. In demyelinative or other neurapraxic conditions, a reduced recruitment of motor units signals a conduction block. The pattern of distribution here also helps elucidate the zone of involvement despite the preservation of the axons. Partial focal nerve lesions, however, can produce restricted clinical deficits and EMG abnormalities that defy the classic rules of localization if a proximal lesion selectively involves a bundle of nerve fascicles destined to innervate a distal muscle.[570]

Conduction abnormalities usually precede axonal degeneration in a compression neuropathy. Stimulation above and below the suspected site of lesion will document not only a localized slowing of conduction but also changes in amplitude and area of the muscle or nerve action potential as indices of functional block. Such a pattern of abnormalities often helps differentiate an entrapment syndrome from a diffuse neuropathy. This distinction, however, may blur in certain types of polyneuropathy that, in early stages, mimic a restricted pathology at the common sites of compression. Focal conduction block (see Chapters 4-6 and 11-5), although usually attributable to demyelination, may also result from other factors such as ischemia and toxic insults,[248,285] initially affecting slow-conducting, small-diameter fibers as shown by experimental focal compression.[586]

2. CRANIAL NERVES

Isolated cranial nerve palsies may result from lesions of the respective nerves along their extra-axial courses or as the sole manifestation of brainstem lesions. Cranial nerves most commonly assessed in an electrophysiologic laboratory include the facial, trigeminal, and accessory nerves. They travel superficially, which allows easy access to electrical stimulation from the surface, and innervate the muscles readily approachable for needle studies. Clinical diagnosis of multiple cranial neuropathies represents a diversely heterogenous entity, although a tumor composes more than one-quarter of cases.[276]

Facial Nerve

Bell's palsy develops sporadically in an isolated incidence without household clustering or preceding viral infections.[196,507,521] Accumulating evidence, however, implicates herpes simplex virus type I (HSV-1) reactivation at least in some cases.[181,377] This gives a rationale for the use of acyclovir, which may[130,234] or may not[156,197,198,579] show additional therapeutic benefit. Swelling and hyperemia in the intraosseous portion of the facial nerve suggests a focal pathology during the acute stage. Paralysis of the upper and lower portions of the face develops suddenly, often associated with pain behind the ear. Additional features may include loss of taste in the anterior two-thirds of the tongue, hyperacusis, and rarely numbness on the affected side of the face.[612] At least 80% of patients have the demyelinative form, improving quickly and completely over several weeks without specific therapy. The remaining 20% develop substantial axonal degeneration with functions returning slowly and poorly after many months. Such recovery nearly always accompanies aberrant regeneration, which results in synkinesis (see Fig. 8-15 in Chapter 8).[298] The same principles apply to the electromyography (EMG) of facial and limb muscles. In the face, however, physiologically small motor unit potentials (MUPs) may mimic fibrillation potentials. Signs of denervation appear early in less than 3 weeks following injury, presumably reflecting the short nerve length. Serial electrodiagnostic studies help delineate the course of the illness (see Fig. 8-3 and Tables 8-2 and 8-3 in Chapter 8).[606] The presence of the direct response, or compound muscle action potential (CMAP) elicited by stimulation of the facial nerve, after the fourth to fifth day of onset usually indicates a good prognosis, although late axonal degeneration can still occur. Preservation or return of Rl or R2 of the blink reflex also serves as a reliable measure in predicting a satisfactory recovery (see Fig. 8-13 in Chapter 8) with reasonable assurance that the remaining axons will survive. The reflex, however, rarely returns during the first few days after onset. In a series of 56 patients who recovered without distal degeneration, the R1 reappeared by the latter half of the first week in 57%, by the second week in 67%, and by the third week in 89%.[298] Other signs for good outcomes include incomplete clinical paresis and MUP discharge with voluntary effort during EMG.[649]

In the absence of substantial nerve degeneration, the latency of the direct response remains unaltered throughout the course on the affected side. In these patients, R1 of the blink reflex, if present, shows a relatively normal latency initially, a delay during the second to the fourth week, and a notable recovery during the second to third month with a return to the normal range during the fourth month (see Fig. 8-14 in Chapter 8). The time course of this recovery indicates a focal demyelination of the facial nerve, which characterizes most cases of Bell's palsy. In the remaining cases, facial nerve undergoes substantial degeneration followed by reinnervation, sometimes from contralateral unaffected nerve crossing the midline.[199] The ultimate recovery then depends on the completeness of regeneration. This process generally takes a few months to a few years, resulting almost always in an aberrant reinnervation[300] usually associated with hyperexcitability[116] and occasionally blepharospasm on the nonparetic side.[85]

Peripheral facial paresis secondary to herpes zoster infection, or Ramsay Hunt syndrome,[580] carries a less favorable prognosis, although early administration of acyclovir and prednisone may reduce the nerve degeneration.[182] In one series,[233] children tended to have late appearance of vesicle, milder facial palsy, less association of cranial neuropathy, and a better prognosis, 79% achieving a full recovery. Diabetic patients may have a more severe form of facial palsy with evidence of substantial denervation. Facial palsy may develop as a rare complication of an inferior dental and, less commonly, upper dental anesthetic block[42] or internal carotid artery dissection.[384] Head trauma also causes various types of facial nerve injury often with a delayed onset of paralysis. A rare familial type may show recurrent episodes, which tend to leave increasing residual weakness after each attack.[6] Hyperostosis cranialis interna, a rare genetic bone disorder, also causes a recurrent facial palsy associated with impairment of the senses of smell, taste, and vision.[375]

Peripheral facial palsies may accompany systemic infection such as Lyme borreliosis[195,228] and acquired human immunodeficiency

syndrome (AIDS).[626] Patients with Guillain-Barré syndrome (GBS)[271] and chronic inflammatory demyelinating neuropathy (CIDP)[311] may develop bilateral, or rarely unilateral, facial paresis as the consequence of acute demyelinative conduction block (see Figs. 8-7 and 8-8 in Chapter 8). In contrast, the chronic insidious progression of neuropathic process in hereditary Charcot-Marie-Tooth (CMT) disease Type I allows preservation of motor function despite a marked delay of R1, indicating demyelination. Patients with Bannwarth's syndrome may have unilateral or bilateral facial palsy as part of multiple mononeuritis associated with erythema, pain, elevated cerebral spinal fluid (CSF) protein, and pleocytosis.[647] Hairy cell leukemia may lead to peripheral neurologic complications causing bilateral facial nerve palsy.[163]

An acoustic neuroma strategically located at the cerebellopontine angle may compress not only the facial nerve but also the trigeminal nerve and the pons, that is, the efferent, afferent, and central arcs of the blink reflex.[299,301,362,504] Thus, the electrically elicited blink reflex reveals various degrees of abnormality in a most patients (see Tables 8-3 and 8-4), showing a high correlation with the tumor size.[432] Sarcoidosis may also involve the facial nerve as a cerebellopontine angle tumor.[208] Transcranial magnetic stimulation and nasal muscle F-wave recording also show a delayed latency, although the degree of abnormalities does not predict surgical outcome.[627] Hypoglossal-facial nerve anastomosis may partially restore the function after sacrifice of the facial nerve for removal of a cerebellopontine angle tumor. Peripheral facial palsy may herald other symptoms of multiple sclerosis in young adults (see Fig. 8-16 in Chapter 8). In these cases, blink reflex studies usually show an absent or delayed R1, indicating demyelination of the central reflex arc, which includes the intrapontine portion of the facial nerve.[290,292,293] Myokymic discharges, although characteristic of this disorder, may also appear in other conditions such as pontine glioma,[224] and subarachnoid hemorrhage.[51] Progressive hemifacial atrophy may develop in scleroderma with or without associated hemiatrophy of the body.[63,333,370]

Weakness of the orbicularis oculi and frontalis usually suggests a peripheral as opposed to a central type of facial palsy. In equivocal cases, an increase in R1 latency will confirm a peripheral abnormality. Reduced excitability may cause an apparent delay of R1 during an acute stage of contralateral upper motoneuron involvement especially if elicited by the glabellar tap.[165] In doubtful cases, a paired shock technique counters the effect of reflex hypoexcitability induced by a supranuclear lesion, eliciting the minimum latency R1 as an accurate measure of the conduction time along the reflex arc (see Chapter 8-4). A hemispheric lesion may also reduce the excitability of polysynaptic R2 substantially, showing either an afferent or efferent pattern of abnormalities (see Chapter 8-5 and Fig. 8-11).

Trigeminal Nerve

Clinical diagnosis of atypical facial pain represents a heterogenous entity, forming a continuum to a trigeminal neuropathic pain.[173] Demyelinating lesions affecting pontine trigeminal pathways may cause trigeminal neuralgia in patients with multiple sclerosis.[186,293] Rare cases of familial trigeminal neuralgia may accompany contralateral hemifacial spasm.[145] Microvascular decompression for trigeminal neuralgia[59] restores normal conduction monitored by direct recording from the root entry zone and scalp-recorded trigeminal somatosensory evoked potential (SEP).[337]

Trigeminal sensory neuropathy characteristically evolves with unilateral or bilateral facial numbness sometimes accompanied by pain, paresthesia, and disturbed taste. This type of neuropathy may accompany anhidrosis, oral incoordination, esophageal achalasia,[164] systemic sclerosis, and mixed connective tissue disease.[339] Clinical features of facial-onset sensory and motor neuronopathy comprise sensory deficits in the trigeminal nerve territory followed by peripheral motor impairments involving the facial muscles and motor neuronopathy spreading downward to affect the neck and then upper limbs.[172] A mandibular fracture may result in an isolated lesion of the mandibular nerve.[147] Exposure to trichloroethylene causes a cranial neuropathy with peculiar predilection for trigeminal root damage.[338] Facial pain or paresthesias may develop secondary to perineural invasion of head and neck carcinomas.[53] Facial numbness

may also herald other symptoms of an expanding tumor involving the trigeminal nerve.[321]

The blink reflex helps establish abnormalities of the trigeminal nerve (see Chapter 8-6). Studies with laser-evoked potential (see Chapter 19-5) detect severe impairment of the nociceptive afferent system in idiopathic and symptomatic trigeminal neuralgia.[120] In an unusual patient with facial-trigeminal synkinesis after resection of a trigeminal schwannoma, stimulation of the supraorbital or facial nerve elicited reproducible responses in the masseter and pterygoid muscles.[509] Percutaneous balloon compression of the trigeminal ganglion for the treatment of trigeminal neuralgia induces a focal demyelination as evidenced by increased latencies of motor evoked potential (MEP) elicited by transcortical magnetic stimulation (TMS) and CMAP evoked by nerve stimulation.[104]

Accessory Nerve

Pressure from a tumor or surgical procedures of the posterior triangle can damage the spinal accessory nerve.[139] Other causes include stretch induced injury,[358] cargo loading,[121] coronary artery bypass grafting,[278] cervicofacial lift,[549] carotid endarterectomy,[645,648] and ligature injury during surgical exploration.[29]

In trapezius palsies following injury of the accessory nerve, the upper vertebral border of the scapula moves away from the spinal vertebrae. With the lower angle of the scapula relatively fixed by muscles supplied by the C3 and C4 roots through the cervical plexus, the whole scapula slips downward and the inferior angle rotates internally or clockwise for the right and counterclockwise for the left scapula as viewed from the back. This type of winging tends to worsen with abduction of the arm to the horizontal plane, which displaces the superior angle further laterally. In contrast, winging of the scapula caused by serratus anterior weakness worsens with the elevation of the arm forward (see Chapter 25-3). A unilateral paralysis of the sternocleidomastoid weakens the rotation of the face toward the opposite shoulder, whereas bilateral involvement causes difficulty in forward flexion of the neck. Improvement in the amplitude of the spinal accessory CMAP on serial nerve conduction studies predicts a good outcome.[176]

Other Cranial Nerves

Superior oblique palsies may implicate a trochlear nerve lesion, which may appear as part of brainstem involvement.[590] Hypoglossal nerve palsy may result from compression by kinking of the vertebral artery,[206] aneurysm,[8] or dissection of the vertebral [388] or internal carotid artery.[86] It may also occur as a complication of endarterectomies in approximately 5% of cases[642] and during intubation, bronchoscopy, or use of a laryngeal mask airway.[152]

3. NERVES IN THE NECK AND SHOULDER GIRDLE

The phrenic nerve originating from C3 to C5 and various other peripheral nerves derived from the brachial plexus have a predilection to isolated injury by compression or a stab wound. The most commonly affected include the long thoracic, dorsal scapular, suprascapular, musculocutaneous, and axillary nerves.

Phrenic Nerve

Phrenic nerve palsy usually develops with mediastinal malignancy, cervical trauma,[390] and as a complication of cardiothoracic surgery. It may constitute a spectrum of idiopathic immune brachial plexopathy often with subclinical involvement of limb muscles.[608] Other conditions associated with a relatively isolated diaphragmatic paralysis include monoclonal gammopathy,[141] HIV,[467] segmental motor paresis following herpes zoster,[27] and diabetic neuropathy.[585] Unilateral lesions may result in no symptoms unless a respiratory disease preexists. In symptomatic patients, electrophysiologic studies usually reveal dysfunction of the ipsilateral as well as contralateral diaphragm. Patients require total ventilatory support after rare bilateral paresis, which may develop subacutely unaccompanied by pain, arm weakness, or antecedent events.[353] Phrenic nerve conduction studies help identify the cause of respiratory failure (see Chapter 6-4).[103,515]

Long Thoracic Nerve

The long thoracic nerve lies superficially in the supraclavicular region, where it may sustain a stab injury or pressure from a heavy shoulder bag or braces during surgery. Radical mastectomy may damage the nerve. Its straight course from origin to insertion makes it vulnerable to a stretch associated with vigorous athletic activity[534] and chiropractic manipulation.[446]

The serratus anterior, the only muscle innervated by the long thoracic nerve, functions as a stabilizer of the shoulder in abduction of the arm. It holds the scapula flat against the back by keeping its inner margin fixed to the thorax. With paralysis of this muscle, the patient cannot raise the arm up straight. The unopposed action of the rhomboids and levator scapulae displaces the superior angle of the scapula medially and rotates the inferior angle laterally and externally or counterclockwise for the right and clockwise for the left scapula as viewed from the back. The vertebral border of the lower scapula projects backward, away from the thorax. This tendency, called scapular winging, worsens with the outstretched arm thrust forward. In contrast, winging of the scapula caused by trapezius weakness worsens with abduction of the arm laterally (see Chapter 25-2).

Lesions of the long thoracic nerve give rise to isolated EMG abnormalities in the serratus anterior muscle. Conduction studies provide valuable information not only in distinguishing partial from complete degeneration but also in assessing the degree of regeneration. Contrary to other focal neuropathies, the electrodiagnostic findings do not seem to predict functional outcome.[176]

Suprascapular Nerve

Injury may result from ganglionic cysts,[611] pressure on the shoulder, stab wounds above the scapula,[385] improper usage of crutches,[545] or stretching of the nerve while serving a volleyball.[406] The rupture of the rotator cuff [269] or downward displacement of the upper trunk may also stretch the nerve anchored at the notch,[69] a mechanism in part responsible for Erb's palsy (see Chapter 23-2). Injury to this nerve at the supraspinatus notch results in atrophy of the supraspinatus and infraspinatus muscles with weakness in initiating abduction of the arm and external rotation of the glenohumeral joint.[356] Isolated weakness and atrophy of the infraspinatus muscle may also result from a lesion at the spinoglenoid notch.[406] In either case the teres minor and deltoid innervated by the axillary nerve partially compensate external rotation of the arm at the shoulder. Compressive lesions often induce a poorly defined aching pain along the posterior and lateral aspects of the shoulder joint and the adjacent scapula supplied by the sensory branches.

Stimulation at the supraclavicular fossa may reveal an increased latency to the supraspinatus or infraspinatus muscles, although a reduction in amplitude of CMAP serves as a better measure of axonal degeneration. Needle studies show selective denervation in the supraspinatus or infraspinatus or both, sparing other muscles supplied by C5 and C6.

Dorsal Scapular Nerve

With entrapment or injury of the dorsal scapular nerve, which innervates the rhomboid major and minor and levator scapulae, the scapula tends to wing on wide abduction of the arm. The patient may complain of pain in C5 and C6 distribution. The diagnosis depends on EMG demonstration of abnormalities restricted to the muscles in question.

Anterior Thoracic Nerve

Of the two branches of the anterior thoracic nerve, the lateral pectoral nerve may sustain a selective injury as reported in a patient who had compression injury from a seat belt.[379] A traumatic injury may also occur during car accidents, after sports activities, or as a compression injury from repetitive muscle contraction.[184] Weight lifting and concomitant pectoralis minor hypertrophy may produce intramuscular entrapment of the medial pectoral nerve.[506]

Axillary Nerve

The axillary nerve may undergo degeneration as part of brachial plexus neuritis or as the result of

selective injury. A partial nerve palsy sustained in association with fracture or dislocation of the head of the humerus usually recovers fully.[355] A lesion after a blunt trauma to the shoulder has less favorable prognosis.[43] Other causes include the pressure of crutches[578] or hyperextension of the shoulder, as might occur in wrestling. A circumscribed area of numbness develops in the lateral aspect of the arm over the belly of the deltoid. Atrophy of this muscle, evident with flattening of the shoulder, limits abduction of the arm after the first 30 degrees subserved by the supraspinatus. In contrast, a lesion involving C5 weakens all 180 degrees with damage to both muscles. Isolated lesions of the teres minor often escape clinical detection, compensated by the infraspinatus, which also rotates the arm outward. Abnormalities of EMG confined to the teres minor and deltoid can establish the diagnosis of axillary nerve palsy. Selective study of each portion of deltoid helps localize a lesion to the anterior division, which supplies the anterior and middle deltoid,[555] and the posterior division, which subserves the posterior deltoid and teres minor, and the sensation over the lateral aspect of the shoulder (see Chapter 1-4).

Great Auricular Nerve

Common causes of great auricular nerve injuries include tumors, trauma, parotidectomy, cardiac pacemaker insertion, carotid endarterectomy, and hanging attempt.[20]

Musculocutaneous Nerve

Injuries of the musculocutaneous nerve result from fractures or dislocations of the humerus,[355] proximal humeral exostosis,[265] heavy exercise,[57] rare complications of surgery,[148] gunshot or stab wounds, compression of the arm, or entrapment by the coracobrachialis muscle. Sensory examination reveals numbness along the lateral aspect of the forearm supplied by lateral antebrachial cutaneous nerve. Paralysis of the biceps results in absent stretch reflex and weakness of elbow flexion, compensated in part by the brachioradialis innervated by the radial nerve. Needle studies show denervation in the biceps brachii, brachialis, and coracobrachialis. Nerve conduction studies may corroborate the diagnosis by showing a reduced motor response from the biceps, and a smaller or absent response of the lateral antebrachial cutaneous nerve.

Antebrachial Cutaneous Nerves

Vigorous arm exercise as in prolonged wind surfing may give rise to a compression syndrome of the lateral antebrachial cutaneous nerve (see Chapter 6-4), the distal sensory termination of the musculocutaneous nerve[256] (see Fig. 1-8 in Chapter 1). This nerve, located in the antecubital fossa, may also sustain isolated injury during venipuncture[652] or mechanical pressure from a heavy object carried with the forearm flexed. The patients have pain or numbness along the lateral aspect of the distal forearm and tenderness to palpation over the nerve. Nerve conduction studies may show a decreased sensory amplitude and a prolonged distal latency.

Less frequently described mononeuropathies include medial antebrachial cutaneous neuropathy after stretch or associated with arterial graft[89] and posterior antebrachial cutaneous neuropathy after an intramuscular injection (see Chapter 6-4).[87] Low-amplitude sensory action potentials help document the loss of the sensory axons seen in postganglionic as compared to preganglionic pathology. Ulnar nerve lesions at the elbow causing absent or reduced ulnar nerve sensory potentials, spare the medial antebrachial cutaneous nerve, which branches off more proximally.

4. RADIAL NERVE

Proximal Sites of Involvement

An incorrectly used crutch may injure the nerve at the axilla, causing weakness of all the radial-innervated muscles and loss of the triceps stretch reflex. External trauma at the spiral groove commonly injures the nerve with or without a concomitant supracondylar fracture of the humerus.[123,174,629] Fractures of the head of the radius involve the nerve more distally, as does the local compression from improper use of walkers and wheelchairs.[62] Subluxation of the head of

the radius may produce a radial nerve palsy. Focal damage at this level also results from crush or twisting injury to the wrist or forearm, repetitive pronation and supination at work,[133] or chronic injection-induced triceps fibrosis.[393] The lateral head of the triceps muscle may entrap the radial nerve following continuous repetitive arm exercise[576] in association with focal myositis[11] or spontaneously.[414] An individual, often intoxicated, may compress the nerve falling asleep leaning against some hard surface or with an arm draped over a bench as in the so-called Saturday night palsy. A honeymoon palsy also results from a similar sustained compression if the groom supports the bride's head with his arm wrapped under her neck. The designation *ghost hand*, which is commonly used in Japan to describe a wrist drop, does not apply in the United States (where apparitions appear handless).

The lesion at the spiral groove usually spares the triceps but involves all the remaining long extensor muscles of the hand, wrist, and fingers as well as the brachioradialis, the only flexor supplied by the radial nerve. A radial nerve palsy, which weakens the wrist and finger extensors, spares the extension at the interphalangeal joints subserved by the median- and ulnar-innervated lumbricalis. The sensory losses vary but most often affect the dorsum of the hand and the thumb and index fingers. After a radial nerve palsy, ulnar innervated muscles, which insert on the exterior expansion, may show some apparent weakness because of unopposed traction.[517] Pressure neuropathy from conduction block of the radial nerve usually resolves in 6–9 weeks, but the recovery takes considerably longer after loss of a substantial number of axons. Rarely, children also suffer from traumatic or atraumatic mononeuropathy involving the proximal or distal main radial nerve or the posterior interosseous nerve.[158] In newborn infants, postulated mechanisms include entrapment by the umbilical cord and reduced amniotic fluid volume.[237,361]

Conduction studies after a fracture of the humerus may reveal slowing across the compression site at the spiral groove or the absence of both motor and sensory potentials. The size of the muscle or antidromic sensory potential elicited by distal stimulation differentiates between neurapraxia and axonotmesis (see Fig. 6-16 in Chapter 6). Most cases have prominent conduction block and a varying degree of axon loss.[62] In one series of 33 patients,[371] 92% of those with a recordable CMAP and 65% of those with an absent response had a good outcome. Superficial radial nerve conduction studies should include comparison with the contralateral side and the ipsilateral lateral antebrachial cutaneous nerve.[564]

Posterior Interosseous Syndrome

The posterior interosseous nerve, the terminal motor branch of the radial nerve in the forearm, penetrates the supinator muscle in its entrance to the forearm.[476] The compression syndrome here may develop spontaneously or following closed injuries to the elbow. Other conditions associated with this syndrome include rheumatoid arthritis with synovitis, congenital hemihypertrophy of the arm,[146] therapeutic excision of the radial head for certain fractures,[118] lipoma or chondroma,[160] ganglion cysts arising from the proximal radicular joint,[386] and CMT1.[81] Additional possibilities include repeated supination and pronation of the forearm by athletes[136] and prolonged pronation of the forearm by violinists.[367] The entrapment usually involves the nerve at the arcade of Frohse between the two heads of the supinator.[183,500] Isolated posterior interosseous nerve palsy may also develop as a manifestation of other disorders such as brachial plexopathy, acute motor axonal neuropathy,[326] and motor neuropathy of acute intermittent porphyria.[303]

The patient complains of pain over the lateral aspect of the elbow but no sensory loss. A lesion at this level causes weakness in the extensors of the wrist and digits with a notable sparing of the supinator, which usually receives innervation proximal to the site of compression. The radial nerve proper supplies the extensor carpi radialis longus and brevis. Normal contraction of these muscles coupled with the weakness of the extensor carpi ulnaris results in the characteristic radial deviation of the wrist on attempted dorsiflexion. Constriction at the distal portion of the supinator muscle may result in selective injury of one of the terminal branches, causing isolated paralysis of the thumb abductor and thumb and index

extensors.[242] Conversely, a compressive lesion may predominantly involve the extensor digitorum communis, partially or entirely sparing the extensor indices proprius and, to a lesser degree, the extensor digiti minimi. In this case, selective finger drop of the long and ring fingers with the relatively intact digits on both sides results in the so-called longhorn sign. Operative neurolysis usually, but not always, results in good recovery from posterior interosseous nerve palsy.[21,247] The differential diagnosis includes a rupture of the extensor tendons, which may affect only the last three digits, with preservation of the thumb and index finger. In this case, weak muscles show no evidence of denervation, and passive palmar flexion of the wrist induces no extension of the metacarpophalangeal joints.

Other Manifestations

Compression of the recurrent epicondylar branch causes pain at the elbow, usually with simultaneous entrapment of the deep branch of the radial nerve. This syndrome, one of the many entities commonly known as tennis elbow, results from repeated indirect trauma by forceful supination as the predisposing factor. Pain and tenderness localized to the lateral aspect of the elbow resemble the symptoms of lateral epicondylitis, another condition referred to, by some, as tennis elbow. In the entrapment syndrome, however, additional dysfunctions indicate the involvement of the radial nerve.

Superficial radial neuropathy may develop after wearing a tight watchband. Handcuff-related compression injuries often involve the sensory fibers of the radial nerve with or without concomitant involvement of the median or ulnar nerve at the wrist.[219,575] Surgical maneuver for trigger release may cause iatrogenic laceration of the digital nerve, which supplies the base of the thumb.[80]

5. MEDIAN NERVE

Median nerve injuries proximal to the elbow, though uncommon, may result from penetrating trauma or fracture dislocation of the distal or, rarely, proximal humerus.[613] Further distally, the nerve traverses three common sites of constriction along its course: between the two heads of the pronator teres, at the origin of the anterior interosseous branch, and at the distal edge of the transverse carpal ligament or, less commonly, within the intermetacarpal tunnel.

Pronator Teres Syndrome

In 83% of dissections, the median nerve pierces the two heads of the pronator teres before passing under it. The pronator teres syndrome develops at this point with trauma, fracture, muscle hypertrophy, persistent median artery, or anomalous fibrous band connecting the pronator teres to the tendinous arch of the flexor digitorum sublimis. The clinical features include pain and tenderness over the pronator teres, weakness of the flexor pollicis and abductor pollicis brevis, and preservation of forearm pronation. Hypoesthesia over the thenar eminence helps differentiate this entity from carpal tunnel syndrome (CTS), which spares the sensory branch passing superficially to the flexor retinaculum. The conduction studies may reveal mild slowing in the proximal forearm with a normal distal latency. Test maneuvers, such as elbow flexion, forearm pronation, and finger flexion, generally fail to enhance conduction abnormalities across the entrapment site.[411]Injection of corticosteroids into the pronator teres may relieve the pain to aid in diagnosis, but definitive treatment requires a surgical decompression.

A similar but distinct entrapment may develop as the median nerve traverses the ligament of Struthers, a fibrous band attached to an anomalous spur on the anteromedial aspect of the lower humerus.[44] This ligament may compress the median nerve together with the brachial artery above the elbow, proximal to the innervation to the pronator teres. Compression of the brachial artery with full extension of the forearm obliterates the radial pulse. Similar proximal median neuropathies may result from entrapment by an enlarged communication vein[58] or an accessory bicipital aponeurosis[566] often involving the pronator teres and flexor carpi radialis in addition to the more distal muscles. Incremental short segmental stimulation (see Fig. 11-17 in Chapter 11) near the proximal portion of the aponeurosis localizes

the precise site of compression.[409,427] Weakness and EMG abnormalities of the pronator teres and flexor carpi radialis serve to differentiate these conditions from the classical pronator teres syndrome, which usually spares the proximal muscles.[222]

Anterior Interosseous Nerve Syndrome

Anterior interosseous nerve syndromes, also called the syndrome of Kiloh and Nevin,[287] result from selective injury of this branch of the median nerve originating just distal to the pronator passage, unilaterally or bilaterally.[632] The palsy occurs either spontaneously or as a complication of an injury such as a forearm fracture.[189] Unlike the pronator syndrome, examination reveals no distinct sensory abnormalities despite the common presenting symptoms of pain in the forearm or elbow. Pure motor weakness typically involves pronator quadrates, flexor pollicis longus, and the radial half of the flexor digitorum profundus,[23] sparing the more proximal pronator teres. Asked to make an OK sign (or money sign in Japan) with the first two digits, the patient will form a triangle as though he is trying to pinch, instead of making a circle. Spontaneous recovery takes place from 6 weeks to 18 months.

Neuralgic amyotrophy (see Chapter 23-3) may manifest as an anterior interosseous nerve palsy presumably because of a distally located lesion or alternatively with a more proximal involvement of the nerve bundle already grouped to form the terminal branch.[528] Similarly, the syndrome may appear acutely in a patient with hereditary neuropathy with liability to pressure palsies (HNPP)[162] or multifocal motor neuropathy (MMN).[543] A partial median nerve lesion at an antecubital level can also involve the nerve bundle destined to form the anterior interosseous nerve,[633] or even more selectively, only the branches innervating flexor pollicis longus.[114] The anterior interosseous nerve syndromes may develop bilaterally as an idiopathic case[128] or in association with cytomegalovirus infection.[149]

Ordinary nerve conduction studies of the median nerve reveal no abnormalities. A CMAP recorded from the pronator quadratus after the anterior interosseous nerve stimulation at the elbow may demonstrate a delayed latency.[420] Comparison of the median motor latency to this muscle and abductor pollicis brevis may prove useful.[503] Needle studies reveal the evidence of selective denervation in the flexor pollicis longus, flexor digitorum profundus I and II, and pronator quadratus. Although spontaneous anterior interosseous nerve paralysis may require surgical decompression, some of these lesions remit without therapy if they represent a form of neuritis. In one series, most patients treated by observation had signs of recovery in 6 months and full recovery within 1 year.[397]

Carpal Tunnel Syndrome

Of all the entrapment neuropathies, carpel tunnel syndrome (CTS) ranks first as the most prevalent, showing the lifetime risk of approximately 10%, although the incidence depends on case inclusion criteria and occupational activities of the population.[402] The median nerve passes, with nine extrinsic digital flexors, through the tunnel bound by the carpal bones and transverse ligament attached to the scaphoid, trapezoid, and hamate.[560] Anatomically the carpal tunnel narrows in cross-section at 2.0–2.5 cm distal to the entrance, rigidly bound on three sides by bony structures and roofed by a thickened transverse carpal ligament. An abnormally high intracarpal tunnel pressure peaks at this level.[360] Pathologic studies show that a striking reduction in myelinated fiber size takes place under the carpal ligament at this point.[589] Interestingly, even in normal subjects, the slowest nerve conduction occurs 2–4 cm distal to the origin of the ligament.[295] This finding suggests a mild compression of the median nerve at this particular level in some clinically asymptomatic hands.[213] In fact, a histologic study revealed focal abnormalities at this site in 5 of 12 median nerves at routine autopsy despite the absence of any symptoms suggestive of the CTS in life.[200]

Certain anatomic peculiarities may predispose some individuals to the entrapment neuropathy. These include a limited capacity for longitudinal sliding of the median nerve under the ligament,[607] a greater body mass index,[399]

greater anteroposterior diameter of the wrist,[216] external hand dimensions,[105] small hand [415] and the presence of palmaris longus and fifth flexor digitorum superficialis.[519]

Any expanding lesion in the closed space of the carpal tunnel enhances compression. Thus, symptoms may develop with extra tunnel pressure by an anomalous artery[635] or sudden growth of ganglion cysts.[283] Wrist flexion and extension also substantially alter the cross-sectional areas as estimated by magnetic resonance imaging[559] and the intratunnel pressure measured by a catheter.[582] A cross-sectional measurement by computerized axial tomography, however, revealed a paradoxically larger carpal tunnel area in patients than in the controls.[643] Studies of ultrasound imaging also suggest that enlarged nerve rather than compressive deformation, characterizes the idiopathic CTS.[417] Accordingly, wrist-to-forearm median nerve area ratio may have some diagnostic value.[83,243,617] Median nerve cross-sectional areas at the wrist also shows a strong correlation to slowed conduction velocity.[631]

This syndrome affects women more than men most commonly in the fourth to sixth decades[335] with a greater prevalence in older populations.[190] Age-related changes of median nerve conduction, however, also develop, not necessarily leading to the symptoms of compression.[425] The entrapment usually involves the dominant hand[424] and has a higher incidence in the hands used occupationally[472] or for ambulation with cane, crutch, or wheelchair,[497] but not necessarily in the hands of computer users.[444,568]

In typical cases of idiopathic CTS, paresthesias in the hand frequently awaken patients at night.[431] The pain often extends to the elbow and not uncommonly to the shoulder, mimicking the clinical features of cervical spine disease or high median nerve compression.[656] The differential diagnosis rests in part on the symptoms of proximal lesions, which typically worsen with manipulation of the neck or shoulder girdle and subside with the arm at rest. In contrast, moving the hand often alleviates the pain in the CTS. Compression can affect the peripheral autonomic fibers, causing defective vasomotor reflex.[637] Thus, Raynaud's phenomenon may develop, especially in patients with a systemic disease such as rheumatoid arthritis. If untreated, patients will develop progressive hand dysfunction, generally in parallel with increasing clinical symptoms.[454]

Sensory changes vary a great deal in early stages, but they apparently begin in large fibers as evidenced by quantitative current perception threshold testing.[429] Sensory complaints usually involve the thumb, index, and long fingers as well as the lateral half of the ring finger. In one large series, 83% of 384 patients had sensory disturbance mostly consisting of hypesthesia, often confined to the tip of the long finger.[466] Examination of the ring finger also reveals characteristic sensory splitting into median and ulnar halves, a pattern rarely seen in radiculopathies. Patients with a milder nerve damage may have a more diffuse sensory loss, including outside the median nerve distribution.[68,638] Ectopic activity from ulnar axons, possibly compressed in the Guyon's canal, may[202] or may not account for such sensory symptoms in the CTS.[584] In my personal experience, some patients with an otherwise typical CTS complain of "numbness" of the little finger and ulnar half of the ring finger, apparently in comparison to hyperesthesia of the affected digits, which they erroneously consider normal. The sensory changes spare the skin of the thenar eminence innervated by the palmer cutaneous branch that arises approximately 3 cm proximal to the carpal tunnel. Occasional patients, however, also have thenar numbness with the additional entrapment of this branch by the fascia of flexor digitorum superficialis.[249,619]

To test the abductor pollicis brevis in relative isolation, the patient presses the thumb upward perpendicular to the plane of the palm. For the assessment of the opponens, the patient presses the tip of the thumb against the tip of the little finger. The two heads of the flexor pollicis brevis receive mixed median and ulnar innervation with considerable variation. Thanks to early diagnosis, patients now seldom develop a distinctive feature of the syndrome, a major wasting of thenar muscles, which mimic a congenital thenar atrophy[225] Nonetheless, a comparison between the affected hand and the normal side often reveals slight weakness. Abnormal fatigue possibly on the basis of rate-dependent conduction block,[65,267,624] however, does not seem to play a major role in

the pathophysiology (see Chapter 11-5).[396] The Purdue Pegboard Test, developed in the 1940s to screen for hand dexterity, serves well as a valid and reliable tool to quantify functional impairment caused by the CTS.[13] Some investigators advocate clinical scales useful in CTS evaluation.[67,192]

Passive flexion or hyperextension of the affected hand at the wrist for more than 1 minute may worsen the symptoms whereas a gentle squeeze of the hand may ease the pain.[374] Hyperextension of the index finger may exacerbate the symptom with volar forearm pain.[328] Percussion of the median nerve at the wrist causes paresthesia of the digits, although it has no localizing value in CTS. In fact, electrophysiologic data show the focal abnormality about 2–3 cm distal to the traditional percussion site on the volar aspect of the wrist.[295] The phenomenon originally described by Tinel[593] relates to localizing the distal end of the regenerating sensory fibers by tap-induced paresthesia, and not for entrapment neuropathy. Ischemia worsens the symptoms of CTS, showing correlation to the severity of pain and paresthesia but not to the extent of muscle wasting or duration of symptoms.[179] These findings suggest rapidly reversible changes in the nerve fibers associated with ischemic attacks.[248,325] Sharply focal structural changes seen in entrapment neuropathy, however, indicate that mechanical factors must play an important role in the pathogenesis.[180,438]

The symptoms may appear during pregnancy, with reported incidences varying from a few percent to a majority, and persist for 1 or more years or resolve quickly after delivery.[405,449,450,628] The rare CTS seen during the early ages characteristically shows short-lasting but severe attacks of pain.[134,520] In contrast to the sporadic incidence in most adult cases, rare familial occurrence prevails in children,[217,345,481] sometimes with anomalous thickening of the transverse carpal ligament.[392] Other associated abnormalities include insensitivity to pain in the mutilated hand.[28,581]

The syndrome also accompanies a variety of polyneuropathies and systemic illnesses (see Chapter 24-2).[5] Among them, HNPP should rank high in the differential diagnosis of familial CTS.[605,654] Familial [416,502] and certain secondary amyloidosis, especially those associated with multiple myeloma, may also give rise to this syndrome (see Chapter 24-3). Among endocrine disorders, acromegaly stands out, one study reporting 35 of 100 patients with evidence of the entrapment neuropathy. The syndrome also occurs in a high proportion of patients with rheumatoid arthritis[171] often as the initial manifestation of the tenosynovitis affecting the wrist flexor. In these cases, however, thenar atrophy may also develop from disuse, cervical spine disease, or compression of the ulnar nerve at the elbow.

Other conditions associated with a high incidence of the CTS include eosinophilic fasciitis,[263] myxoedema,[526] lupus erythematosus,[551] hyperparathyroidism,[498] toxic shock syndrome,[518] Lymeborreliosis,[229]long-termrenalhemodialysis,[194] fibrolipomatous hamartoma,[391] torsion dystonia,[142] hypercholesterolemia, [418] and obesity in younger patients.[48]

Differential diagnoses include a handcuff neuropathy[348] high median nerve compression at the elbow, a C6 radiculopathy, and degenerative cervical spine diseases. The combination of CTS and cervical radiculopathy, called the "double-crush syndrome,"[604] probably represents a chance occurrence of two very common entities.[101,327,490] Nonetheless, awareness of this possibility underscores the need of adequate electrophysiologic assessments because the presence of one condition does not exclude the other. A nonspecific tenosynovitis also gives rise to the symptoms similar to those of idiopathic CTS[282] The patients often have other evidence of degenerative arthritis such as trigger fingers, bursitis, tendinitis, and tennis elbow.

In addition, traumatic conditions may result in acute compression of the median nerve at the wrist. These include Colles' fracture,[350] isolated fracture of capitatum[530] or hamate,[376] acute soft tissue swelling after crushing and intraneural hemorrhage,[236] and recreational or occupational hand activities.[244,272] Most of these cases require emergency decompression of the median nerve. The lateral border of the flexor digitorum superficialis muscle may compress the median nerve against the forearm fascia and other flexor tendons. This rare entity causes symptoms similar to those of CTS, with additional findings of local tenderness and firmness in the forearm.[185,531]

Simpson's original contribution on CTS,[558] demonstrating segmental slowing at the wrist,

paved the way for clinical conduction studies.[201,266,330,588] Early work yielded a higher sensitivity of sensory as compared to motor conduction testing.[64,389,588] In later series,[295,621] however, the sensory and motor axons showed a comparable incidence of abnormalities. To support this view, CTS patients with selective involvement of sensory conduction in conventional studies show abnormalities of motor axon recruitment induced by submaximal stimulus intensities.[205] In addition, some patients have selective involvement of motor fibers, with normal sensory conductions.[294,400,488] Testing the clinically affected digit or all the median nerve-innervated digits improves the likelihood of detecting sensory conduction abnormalities.[539] In one series,[364] long finger proved the most sensitive, whereas in other studies, index finger[314] and ring finger[587] fared better than others. Nerve conduction measures reveal more abnormalities in the elderly.[50,52] Electrophysiologic procedures have become so sensitive that they not only confirm the diagnosis in most clinically suspected patients but also detect an incidental slowing in some asymptomatic subjects, who may not necessarily become symptomatic over an extended time.[630] A sensible interpretation of the test results in the clinical context avoids unnecessary or premature surgical interventions.[1,501,524]

Diagnostic studies should establish selective conduction abnormalities across the wrist-to-palm segment of the median nerve for sensory or motor fibers.[94,125,135,294,295,344,347,452,505,549,621] In our series,[295] palmar stimulation elucidated antidromic sensory or motor conduction abnormalities in all but 13 (8%) of 172 clinically affected hands. Without palmar stimulation, an additional 32 (19%) hands would have escaped detection. A review of electrodiagnosis in 100 patients with CTS also confirmed the clinical values of transcarpal motor and sensory conduction studies, which served as the most useful measure.[92] The same applies for the orthodromic sensory studies, which reveal more abnormalities with the addition of palmar stimulation.[132,398] This technique also provides a simple means to differentiate compression by the transverse carpal ligament from diseases of the most terminal segment seen in a distal neuropathy.[344,447]

In advanced stages the axons may degenerate distal to the entrapment, and retrograde changes may also affect the forearm segment.[16,91,93,95,96] With loss of the fast-conducting fibers at the wrist, recording a CMAP and antidromic digital sensory nerve action potentials (SNAPs) would show a reduced amplitude and a slowed conduction velocity[235] even with the preservation of the forearm segment. Mixed nerve conduction study (NCS) in the forearm measures the segment of interest per se[97,464] although possible contribution from cutaneous palmar branch bypassing the carpal ligament confuses the issue.[231,485]

With serial stimulation from the midpalm to the distal forearm in 1 cm increments, sensory axons normally show a latency change of 0.16–0.21 ms/cm (see Fig. 6-8A, B in Chapter 6). Approximately one-half of the affected nerves show an abrupt latency increase across a 1 cm segment, most commonly 2–4 cm distal to the origin of the transverse carpal ligament.[295,423] In these hands, the focal latency change across the affected 1 cm segment averages more than four times that of the adjoining distal or proximal 1 cm segments (see Fig. 6-8C,D in Chapter 6). In the remaining hands, conduction delay also affects the same vulnerable site maximally but with spread of abnormalities to the neighboring 1 cm segments. Digital stimulation allows simultaneous multichannel recordings of the orthodromic SNAP across the carpal tunnel for short segmental latency studies.[250,296,540,541] This approach, however, invalidates the comparison of amplitude, which varies depending on the depth of the nerve at different recording sites (see Chapter 11-7). Short incremental studies of CMAP from thenar muscles, though technically more demanding because of the recurrent course of the nerve, yields an equally sensitive measure.[295,634] Recording from the second lumbricals helps alleviate this type of technical difficulty as the series of stimulation follows the motor branch along a relatively straight passage (see Fig. 11-5A,B).

A number of other variations improve the sensitivity of the motor and sensory conduction studies. Side comparison, although useful with unilateral lesions, provides limited help in assessing a bilateral disease. With palmar stimulation, the simultaneous recording of SNAP from the

digit and the median nerve trunk at the wrist has the advantage of instantaneously assessing the latencies over the two segments.[363] Recording from two different sites, however, does not allow amplitude comparison between the antidromic and mixed nerve potential. Other measures (see Chapter 6-3) include comparison of median sensory latency to radial, ulnar, or palmar cutaneous sensory latency,[79,88,463,603] and median to ulnar nerve motor latency recorded from the second lumbricals and first palmar interosseus or from the abductor and adductor pollicis of the thumb.[302,477,478,523,596,618] These comparison studies generally serve well as a useful test for the CTS even in patients with bilateral or diffuse abnormalities.[110]

An interesting approach along the same line takes advantage of simultaneous stimulation of the median and ulnar nerves or median and radial nerves and recording SNAP from the ring finger or the thumb.[99,262,452,602] Palmar stimulation, if adjusted properly, can also activate the median or ulnar nerve selectively to elicit respective SNAP over the ring finger. The affected median nerve typically shows a normal, synchronized response with palmer stimulation and a temporally dispersed, delayed potential with stimulation in the wrist. In contrast, ulnar nerve shows nearly identical responses with distal and proximal stimulation (see Chapter 6-3). Combined sensory studies show higher sensitivity and reliability than individual tests,[349,495] improving diagnostic outcome in some patients[275] and establishing good correlation with clinical outcome after surgical intervention.[372]

Two motor conduction measures compare the terminal latency of the distal segment to the conduction time in the proximal segment adjusted to the same distance (see Chapter 5-4). Of these, the residual latency increases[315] and the terminal latency index decreases below the normal range[546,557] in patients with the CTS. Even with complete denervation of the thenar muscles, the first and second lumbricals may maintain part of their innervation presumably because of a deeper location of their motor funiculi.[168] Thus, studies of lumbricals may help establish the diagnosis, especially in advanced cases with severe loss of axons supplying thenar muscles[357] and in patients with underlying axonal polyneuropathy.[597] Conversely, lumbrical muscles may show a prolonged latency despite an otherwise normal motor study with recording from the thenar eminence.[54,168]

In advanced cases, EMG studies show fibrillation potentials and positive sharp waves in the median innervated intrinsic hand muscles. Needle studies, though not necessary in typical cases of the CTS, may aid in excluding other diagnostic possibilities.[113,209] Some advocate the use of portable nerve conduction testing for screening, but its inability to measure the amplitude and waveforms poses a major limitation.[567] Automated handheld nerve conduction devices may accurately record raw data, but the interpretation lacks the specificity necessary for diagnostic examination.[529] Quantitative magnetic resonance imaging (MRI) of the wrist helps assess severity of the disease.[599] Despite a high sensitivity reaching 96% in an overall impression of abnormality,[259] MRI, as a structural rather than functional test, provides limited information at a high cost.[169] Sonography may serve as an additional investigation in subcategories of CTS patients.[34,277,454]

In one series of 132 untreated patients a 2-year follow-up of clinical and electrophysiologic studies showed deterioration in 23%, no change in 29%, and recovery in 48%. These findings support nonoperative measures, which often suffice as the initial treatment,[49,261] although some recommend early surgery.[641] Conservative therapy consists of patient education, wrist splinting,[191] hand brace,[373] nonsteroidal anti-inflammatory medication, oral or percutaneous administration of steroid, and job change or modification.[90] The results of conduction studies do not necessarily predict the outcome of nonsurgical management.[644]

Local steroid injections may help alleviate symptoms[22,215,246] and confirm the diagnosis. In one series, treatment with a single dose of 40 mg of triamcinolone acetonide resulted in complete remission in 35% of patients and partial relief in 58%.[193] An inadvertent injection into the nerve can result in permanent damage.[354] To avoid this complication, some recommend placing the needle midway between the palmaris longus tendon and the flexor carpi ulnaris tendon at the proximal edge of the transverse carpal ligament[175] and discontinuing injection and redirecting the needle if

the patient experiences paresthesia of any kind. Ultrasound studies may reveal changes of nerve cross-sectional area following therapeutic steroid injection for CTS.[84] Surface application of corticosteroids over the carpal tunnel, though less invasive, does not seem to render therapeutic effect.[14] Others advocate noninvasive laser neurolysis as an alternative therapy,[412] but without further confirmation.[251]

If conservative therapy fails, the standard operative procedure comprises division of the transverse carpal ligament for unilateral and occasionally for bilateral release at one operation. Carpal tunnel decompression usually benefits the patients,[594] including those with advanced thenar atrophy and sensory deficits,[77] and less convincingly those with underlying peripheral neuropathy.[408] In one series,[154] all electrophysiologic measure improved at 18 weeks postoperatively except for distal sensory latency, which changed at 42 weeks, indicating differential affection between motor and sensory fibers in CTS. Although symptoms usually abate after successful surgery,[47,55] a substantial number of patients will have either residual or recurring complaints, especially in the presence of a symptomatic polyneuropathy. In patients with diabetes,[187,451] however, marked median nerve conduction abnormalities across the wrist or signs of polyneuropathy do not necessarily preclude satisfactory recovery after surgical decompression.[591] Elderly patients show less improvement than 20-54 age groups.[403] Endoscopic release may shorten the convalescence time for return to work if the intraoperative safety and outcomes equal those of traditional surgery.[600,601] Postoperative splinting after open carpal tunnel release does not seem to improve functional outcome.[245]

Digital Nerve Entrapment

The interdigital nerves supply the skin of the index and long fingers and half of the ring finger as extensions of the median sensory fibers. Sensory symptoms may result from compression of these small sensory branches against the edge of the deep transverse metacarpal ligament. Entrapment results from trauma, tumor, phalangeal fracture, or inflammation of the metacarpophalangeal joint or tendon. Patients complain of pain in one or two digits exacerbated by lateral hyperextension of the affected digits, and tenderness and dysesthesia over the palmar surfaces between the metacarpals. Local infiltration of the steroid may relieve the symptoms and assist in diagnosis. Abnormal median sensory potentials may result from unsuspected digital nerve lesions.[257]

6. ULNAR NERVE

Tardy Ulnar Palsy and Cubital Tunnel Syndrome

The ulnar nerve enters the flexor carpi ulnaris between the humeral and ulnar heads of the muscle. After an intramuscular course of several centimeters, the nerve exits the flexor carpi ulnaris to lie between this muscle and the flexor digitorum profundus. In one study of 130 cadavers, the humeroulnar arcade lay 3–20 mm distal to the medial epicondyle, the intramuscular course ranged 18–70 mm through the flexor carpi ulnaris, and the nerve exited the tunnel 28–69 mm distal to the medial epicondyle.[72] Ulnar neuropathy commonly results from a focal entrapment in the retroepicondylar groove or at the aponeurotic arcade joining the two heads of the flexor carpi ulnaris.[72,571] Compression neuropathies, although rare, can also occur more proximally at the medial intermuscular septem, called arcade of Struthers,[413] and more distally at the point of exit from the flexor carpi ulnaris.[71] Other uncommon lesions include intraneural hemangiomas, which involve the nerve at multiple levels.[287]

The term *tardy ulnar palsy* originally implied antecedent traumatic joint deformity or recurrent subluxation as the cause of the nerve injury. Many clinicians, however, now use the term for entrapment of the ulnar nerve at the elbow, even without a history of documented injury. Ulnar neuropathy at the elbow results from widely varying causes.[395] These include repeated trauma at the retrocondylar groove, pressure from immobilization of the upper limb during surgery,[625] entrapment by the accessory anconeus epitrochlearis muscle,[380] spontaneous intraneural hemorrhage,[474] and a gouty tophus.[622] Relatively slender individuals have comparatively higher risk for developing

this neuropathy,[331] especially in women.[491] The compressive lesion at this site can affect different fascicles, involving the terminal digital nerves and the fibers to the hand muscles much more frequently than those to the forearm muscles.[569]

Classic clinical symptoms of the tardy ulnar palsy also appear with a more proximal lesion involving the brachial plexus at Erb's point[273,316] or at the level of the upper arm after injections into the middle deltoid.[188] Ulnar nerve palsy at the elbow may also constitute part of diffuse neuropathy, for example, as a possible complication of diabetes mellitus.[3] It may also develop concomitantly with lower cervical spine disease involving C8 and T1 roots or with the thoracic outlet syndrome, raising a speculation that a proximal compression may predispose the distal involvement. In one study of motoneuron disease, however, ulnar sensory fibers showed similar conduction changes as motor nerve fibers across the elbow. This finding casts doubt on the double crush syndrome, which postulates the greater susceptibility of the proximally affected axons to a distal entrapment[101] Syringomyelia, with apparent involvement of a single segmental level unilaterally, may rarely mimic ulnar neuropathy.[527]

Some reports emphasize the cubital tunnel syndrome as the most common discrete entity.[395] With this condition, nerve entrapment accompanies neither a joint deformity nor a history of major trauma.[153] A number of factors give rise to entrapment of the nerve under the aponeurosis connecting the two heads of the flexor carpi ulnaris. Here, the nerve has the largest diameter, may show palpable swelling in the ulnar groove, and appears hyperemic at surgery. Frequent hand use with the elbow in flexed position narrows the cubital tunnel and exacerbates the symptoms. In one study[426] autopsy studies revealed focal pathologic changes at the aponeurosis in 5 of 12 presumably normal nerves. The appearance of ulnar neuropathy bilaterally in a large number of patients suggests a congenital predisposition.[232,395] In some cases of idiopathic ulnar neuropathy the asymptomatic contralateral nerve may show some involvement histologically.

Earliest clinical features include impairment of sensation over the little finger and the medial half of the ring finger. Weakness and wasting predominate in the first dorsal interosseous and other ulnar-innervated intrinsic hand muscles, such as the third and fourth lumbricals, giving rise to the partial claw hands, and the third volar interosseus, causing the Wartenberg sign or inability to adduct the little finger. Needle studies further define the site of involvement by demonstrating the distribution of denervation. Typically, the cubital tunnel syndrome affects the ulnar half of the flexor digitorum profundus, which receives the nerve supply distal to the aponeurosis, sparing the flexor carpi ulnaris innervated by a proximal branch. This commonly held distinction, however, does not necessarily apply universally because the innervation patterns vary greatly.

Nerve conduction and EMG studies help identify the site of major pathology in these patients.[486] Some have localized slowing of motor or sensory conduction velocity across the elbow as compared with the more proximal or distal segments.[547] Tests conducted with the elbow flexed rather than extended generally yield a more reliable result.[312] Maintaining the identical limb position during recording and surface measurement of the nerve length also improves the test accuracy. Waveform changes provide a more sensitive measure than the generally accepted criteria for slowing of conduction exceeding 10 m/s.[439] The segment distal to the presumed compression may show mild slowing associated with a reduction in amplitude of the CMAP elicited by distal stimulation. This finding usually indicates axonal degeneration, although on rare occasion it may result from a quickly reversible change in nerve membrane excitability.[387]

Recording from the flexor carpi ulnaris helps improve the NCS in advanced cases with severe atrophy of the intrinsic hand muscles.[598] A normal or nearly normal response, if elicited in a clinically weak muscle by distal stimulation, usually indicates the presence of conduction block at a proximal lesion site. A drop in motor amplitude across the elbow then localizes the lesion in this segment. The cold elbow may cause selective, spurious slowing of ulnar nerve conduction velocity over the across-elbow segment, which normalizes with adequate local warming.[332] Elbow heating, however, increases the relative drop in across-elbow conduction velocity and the degree of across-elbow conduction block.[514]

A nonlinear change in amplitude or latency or both serves as the most sensitive measure of a focal abnormality (see Chapter 11-7).[297] Stimulating the nerve at multiple sites across the cubital tunnel localizes the lesion more precisely (see Figs. 11-15 and 11-16).[26,73,241,394] Such a focal delay may result from membrane depolarization induced by localized compression and not necessarily by demyelination.[248,318,430] Intraoperative studies pinpoint the site of entrapment for optimal surgical therapy showing a major conduction block at the point of exit from the cubital tunnel in many cases. Some electromyographers advocate near nerve recording for betterlocalization.

A strict nonoperative regimen should constitute the initial management of the cubital tunnel syndrome.[21,448] Surgical treatment consists of transposition, simple decompression, or interfascicular neurolysis. Ultrasonographic studies may demonstrate enlargement of the ulnar nerve and help distinguish between a lesion at the cubital tunnel versus the ulnar groove.[78] In one study,[35] sonographic detection of nerve thickening implied poor outcome, whereas electrodiagnostic signs of demyelination indicated favorable outcome. In one series,[178] 86% of those with conduction block across the elbow and normal distal latency achieved full subjective recovery compared to only 7% of those with distal axonal degeneration. Once a moderate degree of motor deficit has developed, symptoms often persist after surgical intervention. In selected cases, anterior transposition of the nerve results in good clinical and electrophysiologic improvement even as a reoperation for failed decompression. Postoperative position of the ulnar nerve near the medial epicondyle may predispose the nerve to recurrent trauma and frequent traction.[383]

Compression at Guyon's Canal

The ulnar nerve enters the hand through Guyon's canal at the wrist. Nerve injury at this level, though less common than at the elbow, gives rise to clinical features similar to those of tardy ulnar palsy. Sensory deficit, if present, characteristically spares the dorsum of the hand innervated by the dorsal cutaneous branch, which arises proximal to the wrist. In the Guyon's canal syndrome, the responsible lesion may involve both deep and superficial branches of the ulnar nerve (Type I), only the deep branch (Type II) thus sparing the palmaris brevis and sensory fibers[470] or the superficial branch (Type III) with selective paralysis of the palmaris brevis and loss of sensation in the little finger and ulnar half of the ring finger. In Type II, abduction of little finger against resistance may induce excessive cocontraction of palmaris brevis muscle, deep in the palmar cup.[252] This sign, however, may also appear in some normal hands (like mine). Chronic compression of the proximal hypothenar eminence by a computer mouse, for example, may stretch the superficial branch inducing the syndrome of palmaris brevis spasm.[352] An ulnar nerve lesion at the wrist spares the flexor carpi ulnaris and flexor digitorum profundus III and IV. The reverse, however, does not necessarily hold because a proximal lesion can selectively damage the bundle of axons destined for the more distal muscles. In fact, ulnar nerve lesions at any level tend to affect the first dorsal interosseus muscle most consistently.

Entrapment in this region commonly results from a ganglion.[445] Less frequent causes include trauma, rheumatoid arthritis, tortuous arteries,[536] calcium deposits in Guyon's canal in scleroderma,[592] an accessory palmaris muscle that arise from the base of the fifth metacarpal,[487] pisiform-hamate coalition,[41] and, in patients with CTS, as a consequence of high pressure in the carpal tunnel preoperatively[203,204] and from translocation of the carpal tunnel contents postoperatively.[469] Ganglions and fractures usually cause combined motor and sensory deficits or isolated motor weakness, whereas synovitis may cause isolated sensory loss.[323] The presence of a Martin-Gruber anastomosis may confuse the issue with an unusual presentation.[304] Handcuff neuropathy, which usually involves the superficial radial nerve, may also affect the ulnar nerve selectively or concomitantly.[525,535] Ulnar nerve compression in the distal forearm may result from the enlarged, normally tendinous portion of the flexor carpi ulnaris.[70] A segment of the nerve may anomalously penetrate this tendon.[658] Surgical decompression generally improves the symptoms.[271,452] Pathological process leading to

CTS may affect ulnar motor and sensory fibers in the Guyon canal.[651]

In Types I and II, motor conduction studies reveal reduced amplitude and increased distal latency of the abductor digiti quinti and first dorsal interosseus responses showing asymmetry between the affected and normal sides.[445] Other useful techniques include short incremental stimulation across the wrist,[117,452] and comparison between ulnar and median motor latency by lumbrical and volar interosseus recording (see Fig. 11-5 in Chapter 11).[313,548] Eliciting a normal sensory potential from the dorsal ulnar cutaneous nerve, which branches more proximally, helps localize the lesion at the wrist.[258,288] This does not hold universally, as normal subjects may have high frequency of asymmetry and absent potentials.[151] A lesion at the elbow could also possibly spare this branch in partial involvement.[614] A reduced or absent ulnar SNAP of the little and ring fingers indicates involvement of the superficial branch. The mixed nerve action potential between wrist and elbow remains normal. Recording from the ring finger provides a sensitive measure of comparison between median and ulnar nerve sensory amplitude and latency (see Chapter 6-3).

Involvement of the Palmar Branch

Further distally, the deep motor branch may sustain external trauma or compression by a ganglion arising from the carpal articulations[207] or by the arch formed by the adductor pollicis muscle[511] or tumor.[482] Using the heel of the hand against a crutch causes repeated injuries to this branch as does an attempt to shut or raise a window by striking the bottom edge with the palm. Compression of the ulnar nerve at the palm has also followed prolonged bicycle riding.[230] Other entities reported include video-game palsy [177] and pizza cutter's palsy.[508] Damage distal to the origin of the superficial branch gives rise to no sensory abnormality clinically or electrophysiologically. In cyclist's palsy, however, a severe lesion may also affect the sensory fibers supplying the skin of the little and ring fingers.[433]

A palmar lesion usually spares the more proximal motor fibers supplying the hypothenar muscles. Thus, conduction studies reveal no abnormalities between the elbow and wrist and a normal distal latency from the wrist to the abductor digiti minimi. The CMAP recorded from the first dorsal interosseous, however, may show a prolonged latency and reduced amplitude compared with the unaffected side. Palmer stimulation distal to the site of injury can document a conduction block and slowing, which may resolve on sequential studies.[407] Segmental stimulation of the motor branch in the palm can establish precise localization of the lesion along the course of the nerve (see Chapter 6-3). Needle studies show selective abnormalities of the ulnar innervated intrinsic hand muscles except for the abductor digiti minimi.

7. NERVES OF THE PELVIC GIRDLE

Because of the protection afforded by the pelvic bones, traumatic injury rarely affects the lumbar plexus. Individual nerves derived from the plexus may sustain isolated damage by either chronic compression or acute injury.

Ilioinguinal Nerve

Patients with ilioinguinal neuropathy complain of pain in the groin region, especially when standing. The nerve may also suffer traumatic injury, sometimes during surgery. Pressure immediately medial to the anterior-superior iliac spine causes pain radiating into the crural region. Muscle weakness and increased intra-abdominal tension may lead to the formation of a direct inguinal hernia.

Genitofemoral Nerve

Selective damage of the genitofemoral nerve may result from trauma to the groin or surgical adhesions. Clinical features include pain in the inguinal region, sensory deficits over the femoral triangle, and the absence of a cremasteric reflex.

Lateral, Anterior, and Posterior Femoral Cutaneous Nerves

Entrapment of the purely sensory lateral femoral cutaneous nerve causes a condition known as

meralgia paresthetica often associated with obesity, advancing age, and diabetes mellitus.[460] The damage usually occurs at the anterior superior iliac spine where the nerve, sharply angulated over the inguinal ligament, emerges from the lateral border of the psoas major. The precipitating factors include the compression of the nerve by tight belts, corsets, or seatbelts; strenuous exercise;[284] and prolonged postoperative hip flexion for relief of pain after abdominal incision.[255] The symptoms may also develop without an obvious cause at the point where the nerve penetrates the inguinal fascia. Pathologic changes consist of local demyelination and wallerian degeneration, particularly of the large-diameter fibers. Malignant tumors of the psoas and other lesions located above the inguinal ligament can mimic meralgia paresthetica, bearing a more serious prognosis.[15]

Clinical diagnosis depends on the characteristic distribution of paresthesias, pain, and objective sensory loss over the anterolateral surface of the thigh without motor weakness. Patients with an L2 or L3 lesion may also have radiating pain along the lateral aspect of the thigh.[492] The absence of motor deficits clinically as well by EMG, despite objective sensory loss, tends to support the diagnosis. Sensory NCS may reveal a reduced amplitude and an increased latency across the compression site,[544,563] but not universally because of technical difficulty[115] and anatomical variations.[550] The use of dermatomal or cutaneous SEP advocated by some[155,324] provides only limited help because the long conduction pathway assessed by this means tends to dilute a focal delay (see Chapter 11-7). Conservative treatment suffices unless intractable symptoms call for neurolysis with transposition, or in some, sectioning of the nerve.[38]

Anterior femoral cutaneous nerve injury may occur during femoral artery reconstructive surgery.[36] Isolated posterior femoral cutaneous neuropathy may result from a venous malformation surrounding the nerve[108] or misdirected intragluteal injection.[289]

Femoral Nerve

An intrapelvic lesion of the femoral nerve may result from compression by tumors of the vertebrae, psoas abscesses, retroperitoneal lymphadenopathy, hematoma, or synovial cyst of the hip[577] Diabetes and vascular disease also commonly cause femoral neuropathy. Fractures of the femur or cardiac catheterization may render direct nerve damage.[66,281,480,623] The lithotomy position during surgery or gestational deliveries may cause hyperextension injury.[86,381] Excessive hip abduction and external rotation also stretch the nerve, compressed at the inguinal ligament.[7]

With a complete lesion, the patient cannot flex the thigh on the abdomen or extend the leg at the knee, and has a reduced or absent knee stretch reflex and variable sensory loss. Electrophysiologic studies of the femoral nerve show an increased latency and reduced amplitude in addition to denervation in the appropriate muscles. Partial femoral nerve lesions may affect a single head of the quadriceps muscle selectively.[82] In general, two-thirds of patients show some functional improvement in 2 years after femoral nerve injury.[322] In individual cases, an estimated degree of axonal loss based on the size of CMAP serves as a good measure of prognosis.

Localized hypertrophic mononeuropathy, a rare, benign disease, can involve the femoral nerve.[583] Patients with diabetes may develop amyotrophy, which mimics a mononeuropathy of the femoral nerve (see Chapter 24-2). The syndrome begins with pain in the anterior aspect of the thigh followed by weakness and atrophy of the quadriceps. Careful clinical and EMG examinations reveal more widespread involvement in the territory of L2 through L4, suggesting polyradiculopathy. Differential diagnoses should also include traumatic quadriceps tendon rupture[499] and an underlying disease such as renal failure[270] or anabolic steroid abuse.[126]

Saphenous Nerve

The saphenous nerve exits from Hunter's subsartorial canal together with the femoral vessels. Obstructive vascular disease may injure the nerve at this level, causing localized pain over the medial aspect of the knee as the main clinical feature. It often radiates distally to the medial side of the foot and worsens with any exercise such as climbing stairs. Saphenous neuropathy,

usually seen as a spontaneous entrapment syndrome, may also develop with the formation of a neuroma in the dissection site after vascular procedures on the medial area of the knee.[537] Further distally, saphenous nerve lesions caused by bursitis may develop as part of an athletic overuse injury, which may mimic a stress fracture of the tibia.[239] Electrophysiologic studies may reveal a slow saphenous nerve conduction tested either orthodromically[574] or antidromically.[620]

Obturator Nerve

The obturator nerve, though well protected deep in the pelvis, may sustain selective damage during pregnancy or labor by pressure from a gravid uterus. Other causes include pelvic fracture, surgical procedures for obturator hernia, laparoscopic tubal occlusion,[260] pelvic cancer,[496] and lipomatosis of the nerve.[422] The nerve may also sustain damage entrapped in the obturator canal by increased intra-abdominal pressure or stretched at the bony obturator foramen during prolonged urologic surgery.[465] Injury to this nerve weakens the adductors and internal and external rotators of the thigh. Typically, the patient complains of pain in the groin radiating along the medial aspect of the thigh, together with hypesthesia or dysesthesia over the same dermatome. Needle studies show evidence of denervation in the gracilis and adductor muscles. Patients with acute obturator neuropathy, treated conservatively, usually show a good clinical outcome.[561]

Superior and Inferior Gluteal Nerves

The superior and inferior gluteal nerves, situated directly behind the hip joint, suffer damage from various causes, such as fractures of the upper femur, misdirected intramuscular injection,[435] compression from iliac artery aneurysm,[220] and pelvic trauma.[640] Compromise of the inferior gluteal nerve documented electrophysiologically may herald clinical signs of recurrent colorectal carcinoma.[329] Damage to the superior gluteal nerve gives rise to weakness and denervation of gluteus medius and minimus, which abduct and rotate the thigh inward. A lesion of the inferior gluteal nerve involves the gluteus maximus, which extends, abducts, and externally rotates the thigh.

Anterior-superior tendinous fibers of the pyriformis may compress the superior gluteal nerve, causing buttock pain and tenderness to palpation in the area superolateral to the greater sciatic notch.[484] The pyriformis muscle may rarely entrap the inferior gluteal nerve as it exits the pelvis through the greater sciatic notch,[150,306] causing the sometimes disputed pyriformis syndrome.[56,166,573] This uncommon cause of sciatica involves buttock pain referred to the leg but otherwise has few specific validated features. Unlike a more proximal lesion, this syndrome selectively involves the gluteus maximus, sparing the gluteus medius, gluteus minimus, tensor fasciae latae, and paraspinal muscles. The use of botulinum toxin has gained popularity aimed at relieving myofascial pain from a tight piriformis.[306]

The same symptoms may also result as a complication of surgery performed with the patient in the sitting position.[60] Other possible causes include neural compression by pseudoaneurysm of the inferior gluteal artery,[457] B-cell lymphoma with neurolymphomatosis,[650] and arteriovenous malformation of the pyriformis muscle.[124] For such a focal lesion not accessible to segmental stimulation, conventional nerve conduction studies provide little, if any, clinically pertinent information (see Chapter 11-7). Some authors reported a change in the H-reflex latency following forcible contraction of the pyriformis muscle as a provocative test[167] but without further confirmation.

Sciatic Nerve

Sciatic neuropathy[655] may result from direct spread of neoplasm from the genitourinary tract or rectum, neurinoma of the sciatic nerve itself, abscess of the pelvic floor, pressure from a gravid uterus, ischemia resulting from aortic occlusion, fractures of the pelvis, hip or femur,[334] or late effect of radiotherapy.[475] Prolonged squatting compresses the sciatic nerve in the segment between the ischial tuberosity and trochanter major or between the adductor magnus and hamstring muscles. Baker's popliteal cyst, formed by effusion into the semimembranous bursa, can compress

the sciatic, peroneal, tibial, and sural nerve in any combination, especially with the knee extended.[419] Other uncommon compressive lesions include solitary primary lymphoma of the sciatic nerve,[468] popliteal artery aneurysm,[33] segmental neurofibromatosis,[552] unusually prominent lesser trochanter,[119] and acetabular fracture.[161] Sciatic endometriosis may cause cyclic sciatic pain and a sensorimotor mononeuropathy.[522]

Misdirected intragluteal injection may damage the sciatic nerve,[421] inferior gluteal nerve, posterior femoral cutaneous nerve,[254] or pudendal nerve.[435] Other traumatic possibilities include penetrating wound, hip surgery, and insertion of prosthesis. For reasons not entirely clear, trauma affecting the sciatic nerve as a whole tends to involve the peroneal component much more frequently than the tibial portion.[610] Reaction to injuries may depend on funicular size and disposition of the nerves. The peroneal nerve trunk has less connective tissue and fewer but longer nerve bundles than the tibial nerve. The topical distribution may also make the peroneal division, located laterally and posteriorly, more susceptible than the tibial division to an injection in the buttock. Evidence of denervation in the short head of biceps femoris supplied by the peroneal division above the knee helps distinguish a sciatic nerve lesion from a compressive lesion of the peroneal nerve at the knee. Proximal sciatic nerve injury may induce distally projected sensory symptoms, mimicking a distal tibial nerve involvement.[214]

To confirm clinical localization of the lesion, NCS and EMG help delineate the extent and distribution of the abnormality. Studies of the H reflex or F wave or direct needle stimulation of the nerve at the radicular level and sciatic notch[365] may reveal conduction abnormalities.

8. COMMON PERONEAL NERVE

Following the separation into individual nerves in the lower thigh, the common peroneal nerve becomes superficial to reach the lateral aspect of the knee. Habitual crossing of the leg compresses the nerve against the head of the fibula at this vulnerable point. Injury here most frequently affects the deep branch, and less commonly, the whole nerve.[562] The superficial nerve innervates the peroneus longus and brevis, both everter and plantar flexor. Thus, stimulation of the common peroneal nerve after selective injury of the deep branch causes foot eversion and plantar flexion. Rarely, a ganglion in the same location may involve only the superficial branch, which may show a number of anatomical variations.[4]

Most cases of peroneal neuropathy have an identifiable predisposal factor, which shows a good correlation to electrophysiologic findings.[17] Sustained kneeling (considered good manners in Japan) or squatting may compress the peroneal nerve against the biceps tendon, lateral head of the gastrocnemius, or the head of the fibula.[25] Peroneal nerve palsy may also develop during intended weight reduction[122] or following the excessive use of an exercise bicycle.[227] It also occurred as a complication of proximal tibial osteotomy,[305] gestational deliveries in lithotomy position,[112] and liver transplantation.[636] Peroneal neuropathy in a newborn may have a prenatal onset.[264]

Uncommon compressive lesions include thrombosis of crural veins,[37] intraneural synovial cyst,[434] and ganglion[346] sometimes identifiable only after the incision of epineurium[473] and preferentially involving a proximal tibialis anterior branch.[240] In one study of peroneal palsy,[653] patients with a ganglion typically had a large body mass index, local pain, fluctuating weakness with weight bearing, and a high incidence of a palpable mass as compared to those with a compression neuropathy who tended to have a history of weight loss, immobility, and leg crossing.

Injury to the deep branch weakens the toe and foot dorsiflexors with cutaneous sensory changes over the web area between the first and second toes. Lesions of the superficial branch include loss of eversion and plantar flexion with sensory deficits over most of the dorsum of the foot. The tibialis posterior, a foot inverter, receives L4 and L5 innervation via the sciatic and tibial nerve. Thus, a needle study of this muscle helps differentiate between peroneal palsy and L5 radiculopathy. For the same reason, the ability to invert the foot normally in addition to preservation of the ankle reflex usually distinguishes peroneal nerve palsy from a sciatic nerve lesion. Patients with a

footdrop, however, may have a lesion selectively involving the peroneal division at the level of the sciatic nerve. Differentiation here depends on EMG exploration of the hamstring muscles, especially the short head of the biceps femoris innervated by the peroneal division above the knee. The differential diagnoses for footdrop also includes, in addition to central and peripheral nervous system disorders, muscle diseases and exertional compartment syndrome.[351]

The use of electrodiagnosis helps evaluate patients with a suspected peroneal neuropathy.[378] A change in amplitude or, less frequently, slowed conduction across the fibular head localizes the site of the lesion. To diagnose a focal abnormality based on conduction velocity, slowing must exceed 10 m/s compared with the remaining distal segment below the knee. A drop in amplitude from distal to proximal stimulation may indicate a localized lesion at the compression site. In our experience, an inching study across the fibular head serves as the most sensitive measure by revealing a nonlinear change in latency, amplitude, or waveform at the site of focal lesion (see Chapter 11-7). In one series, electrophysiologic studies revealed axonal loss in one-half, conduction block in one-fourth, and a mixed pattern in the remainder.[274] In another study, the extensor digitorum brevis tended to show the signs of axonal degeneration, and anterior lateral compartment muscles, evidence of conduction block.[61] Focal cooling improves neural conduction in peroneal neuropathy at the fibular neck.[513] Sparing of superficial peroneal sensory nerve in common peroneal neuropathy provides evidence for selective vulnerability of different nerve fascicles to injury.[268]

A smaller response elicited by distal as compared with proximal stimulation suggests the presence of an accessory deep peroneal nerve. In these cases, a proximal shock at the knee but not a distal stimulus at the ankle excites the anomalous fibers, giving rise to the amplitude discrepancy (see Chapter 11-4). A fascial band may compress the accessory sensory branch of the superficial peroneal nerve, which traverses the lateral malleolus laterally.[510] Recording from the tibialis anterior, in lieu of the atrophic extensor digitorum brevis, improves the accuracy of conduction assessment across the knee in some cases.[274] Additionally, clinical recovery relates more to the function of the tibialis anterior and other muscles of the anterolateral compartment. Distal stimulation elicits a small and delayed mixed nerve potential above the head of the fibula in mild compression and no responses in advanced stages.

The anterior tarsal tunnel syndrome, rare entrapment of the deep peroneal nerve at the ankle, causes pain on the dorsum of the foot, sensory deficits in the small web area between the first and second toes, and atrophy of the extensor digitorum brevis. An incomplete form affects the motor or sensory fibers selectively after their division under the inferior extensor retinaculum.[317] Nerve conduction studies show an increased distal motor latency with stimulation of the deep peroneal nerve proximal to the retinaculum.[512] Needle studies reveal denervation in the extensor digitorum brevis, although spontaneous discharges in the intrinsic foot muscles may simply reflect chronic nerve damage caused by wearing a tight shoe.[159]

9. TIBIAL NERVE

The tibial nerve, because of its deep location, rarely sustains injury in the posterior compartment of the thigh or leg. The nerve may undergo rare compression in the popliteal fossa by the tendinous arch originating from the soleus muscle. Presence of severe pain and tenderness and a Tinel sign in the popliteal fossa distinguish this condition from S1 radiculopathy and tibial nerve compression distally as it enters the abductor hallucis muscle at the ankle.[382] Some patients improve spontaneously and others, after surgical division of the soleus arch.

Occasional compression by the flexor retinaculum as it passes behind the medial malleolus causes tarsal tunnel syndrome.[565] It may result from trauma, tenosynovitis, and venous stasis of the posterior tibial vein or a ganglion arising from the subtalar joint. In our experience, most, if not all, patients with nontraumatic tarsal tunnel syndrome have an underlying neuropathic condition such as overt or subclinical diabetic polyneuropathy. A patient with a more proximal lesion, for example, a tumor of the tibial nerve,

may show signs and symptoms of the tarsal tunnel syndrome possibly because of venous thrombosis in the calf.[24, 639] The clinical features consist of painful dysesthesia and sensory deficits in the toes and sole and weakness of the intrinsic foot muscles. Needle studies reveal denervation of the intrinsic foot muscles supplied by the tibial nerve. Anterior heel pain syndrome may also result from isolated injury of the inferior calcaneal or Baxter's nerve, a branch of the lateral planter nerve, which innervates, in addition to the periosteum of the calcaneus, the abductor digiti quinti.[32,458,459] In this condition, EMG shows selective denervation of this muscle, located inferior to the lateral malleolus sparing the flexor digiti minimi brevis supplied by lateral plantar nerve proper.[459]

In the tarsal tunnel syndrome,[461] NCS shows increased motor latencies along the medial or lateral plantar nerve with stimulation of the tibial nerve slightly above the medial malleolus. Additional stimulation slightly below the malleolus may document segmental slowing across the compression site.[9] The calculated conduction velocity ranges widely, reflecting the short distance between the two stimuli. Alternatively, serial stimulation in 1 cm increments along the course of the nerve reveals an abrupt change in waveform of the recorded response together with a disproportionate latency increase at the compression site (see Chapter 11-7). Near-nerve sensory conduction of the medial and lateral plantar nerve may elucidate slowed velocities and abnormal temporal dispersion[441] The conduction studies on the clinically unaffected side serve as a control. In one series, both motor and sensory conductions improved after surgical decompression.[440]

The digital nerve proper arises from the medial plantar nerve as a terminal sensory branch. Its selective injury or compression causes a focal neuropathy called Joplin's neuroma.[109] Useful diagnostic techniques include EMG of the intrinsic foot muscles and conduction studies of the medial and lateral plantar nerves[131,223,442] and medial calcaneal nerve.[458,538] Chronic compression of the terminal digital branches under the metatarsal heads, usually in the third and fourth interspaces, gives rise to a syndrome of painful toes or Morton's neuroma. The interdigital nerve syndrome also results from ligamentous mechanical irritation with hyperextension of the toes in high-heeled shoes, hallux valgus deformities, congenital malformation, rheumatoid arthritis, or any form of trauma. Typically, walking precipitates pain in the affected digits, although the patient also suffers from spontaneous nocturnal discomfort.

10. SURAL NERVE

Isolated compression and traumatic neuropathy of the sural nerve, although infrequent, results from a ganglion,[479] Baker's cyst,[419] use of a combat boot,[533] or stretch injury.[221] The sensory innervation differs from one patient to another as the nerve receives various contributions from the tibial and peroneal nerves. In general, sensory changes involve the posterolateral aspects of the lower third of the leg and the lateral aspects of the dorsum of the foot. In addition to the NCS, which helps delineate the lesion[221] its superficial location makes the sural nerve suitable for diagnostic biopsy, if necessary. Some advocate combination of neurophysiologic and ultrasound studies in evaluating sural nerve lesions.[556]

11. PUDENDAL NERVE

The muscles of the pelvic floor, unlike other skeletal muscles, exhibit tonic contraction except during voiding and defecation.[489] Injury to the muscles or nerves of the pelvic floor often results from third- or fourth-degree perineal tears during vaginal delivery, pelvic tumors, or delayed effects of pelvic radiation therapy.[170] Other causes include iatrogenic injury during pelvic surgery, damage to perineal branches during bicycle riding, chronic stretch injury seen with repeated and excessive straining during defecation,[137] and complication of surgical procedures involving traction on the fracture table.[12] Clinical features consist of fecal and urinary incontinence, numbness of the perineal region, impotence, loss of penile erection, and loss of support for the viscera in the pelvic region associated with weakness and atrophy of the pelvic floor muscle.

Currently available electrodiagnostic techniques include NCS (see Chapter 6-6) for both the inferior rectal and the perineal branch to assess terminal motor latencies[40] pudendal SEP for its

sensory pathways, and needle examination of the muscles innervated by this nerve or its branches. Studying the muscle supplied by other sacral roots helps exclude lesions of the cauda equina and sacral root as opposed to the pudendal nerve per se.

12. OTHER MONONEUROPATHIES

Hypertrophic and Idiopathic Mononeuropathies

Localized hypertrophic neuropathy or intraneural perineurinoma causes predominantly motor weakness in the distribution of a single nerve. Biopsy specimen shows the histologic appearance of the onion bulb formation.[554] If this condition of unknown etiology affects the tibial nerve, the patient develops progressive wasting of the leg muscles.[253]

An unusual clinical entity described in young patients shows insidiously progressive, painless weakness in the distribution of a single major lower-limb nerve.[157] Electrophysiologic and histologic findings suggest a chronic axonal mononeuropathy without conduction block or focal slowing. Mononeuropathy as part of multiple nerve compression may result from malignantly transformed hereditary multiple exostoses.[455]

Postherpetic Neuralgia

Herpes zoster and shingles may result from reactivation of the varicella zoster virus lying dormant in the dorsal root ganglion (see Chapter 24-3). One study[404] found no correlation between the degree of postherpetic neuralgia and electrophysiologic abnormalities, with the inference that pain has little to do with the damage to the large-diameter sensory fibers tested in electrodiagnosis. Focal weakness not limited to the involved dermatomes may follow segmental herpes zoster with various neuropathic findings, including multiple mononeuropathies, radiculopathies, and brachial plexopathies.[10] Neurophysiologic investigation has localized the lesion at the root, plexus, or peripheral nerve level.[111,516] In one series,[226] 21 of 40 patients had the evidence of denervation, suggesting widespread subclinical motor involvement.

Occupational Entrapment Neuropathy

SPORTS INJURY

In one study involving 169 athletes,[320] one-third of 190 sports injuries occurred while playing football. The most common injuries included, in addition to burners and stingers representing cervical radiculopathies, median, axillary, ulnar, suprascapular, or peroneal nerve mononeuropathies. Bodybuilders develop rare mononeuropathies of the upper limb most commonly involving thoracodorsal, dorsoscapular, suprascapular, or medial pectoral nerves.[401] Acute focal neuropathies also affect weight lifters who develop usually sudden, painless weakness in a muscle supplied by a terminal motor nerve branch.[45]

MUSICIANS' ENTRAPMENT NEUROPATHY

Many instrumental musicians suffer from entrapment neuropathies, most commonly thoracic outlet syndrome, CTS, and ulnar neuropathy.[342,343,366] The available information regarding ulnar neuropathy suggests that violinists and violists tend to develop symptoms depending on their playing position.[341] Ulnar neuropathy may initiate or sustain a hand dystonia by inducing a central disorder of motor control.[100] Conservative treatment, which provides relief for a substantial percentage of patients,[39] consists of splinting, medication, and modification in playing technique or training time.[340] The specific diagnoses most likely to require surgical decompression include trigger digits, CTS, ulnar nerve entrapment, rheumatoid arthritis, and Dupuytren's contracture.[129] To supplement clinical assessments, NCS and EMG help confirm the diagnosis, establish the extent and type of pathology, detect coexisting peripheral nerve disorders, and determine the efficacy of therapy.[366]

OTHERS

Other professions with a possible predisposition to mononeuropathies include cleaners, industrial workers, and chefs. Reported cases as "la main du cusinier" comprise distal median, ulnar, and posterior interosseous nerve neuropathy, all involving the dominant hand.[319]

Traumatic Mononeuropathy

Common causes of peripheral nerve injuries include motor vehicle accidents, stabbing incidents, gunshots, and stretching and crushing after falls.[494] Nerve injuries have followed wrist tattooing in the proximity to the palmar cutaneous nerve of the median nerve[410] and intramuscular injections, often involving sciatic nerve in the lower limb and radial nerve in the upper limb.[456] Electrophysiologic evaluations play an important role in determining the outcome of mononeuropathies produced by a single episode of limb trauma. In an axonal injury, amplitude loss begins on days 3–5 for CMAP and days 5–7 for SNAP.[102, 443] With complete axonal degeneration, conduction studies alone cannot provide the conclusive evidence for or against neurotmesis, or loss of continuity. In clinically suspected cases of transection, failure to demonstrate evidence of reinnervation in 2–3 months calls for surgical exploration for suture or grafting.[310] In studies of finger amputation and toe-to-digit transplantation, early surgical intervention prevented retrograde degeneration and improved recovery of function.[106,107]

Perioperative Mononeuropathy

Perioperative nerve injuries, as a complication of surgical procedures, account for approximately 16% of all anesthesia-related claims in the United States.[30] In one study, 9 of 520 patients who underwent liver transplantation developed mononeuropathy involving the peroneal nerve, radial nerve, and cutaneous branch of the femoral nerve.[636] In another study,[75] 10% of liver transplant recipients developed focal peripheral nerve lesions, most commonly involving the ulnar nerve. The operative procedures during hip arthroplasty may injure a number of nerves traveling in the vicinity for different reasons such as compression, traction, and ischemia[210,428] These include the peroneal division of the sciatic nerve,[280] femoral nerve,[553] and gluteal nerve.[2,138]

Complex Regional Pain Syndrome

This entity represents a poorly defined symptom complex called *complex regional pain syndrome* (CRPS) Type I, replacing the now obsolete term, *reflex sympathetic dystrophy*, and CRPS Type II, or causalgia with burning pain and local tissue changes associated with a definable nerve injury.[609] The skin manifestations usually involve the entire limb and consist, in most instances, of color and temperature change, edema, and bony atrophy. Changes in peripheral blood flow may result from supersensitivity to sympathetic neurotransmitters, which also contribute to spontaneous pain and allodynia by disrupting sympathetic modulation of sensation. The impairment of high-energy phosphate metabolism suggests reduced oxygen extraction in the affected limb.[238] During sympathetic blocks, which lead to a temporary reduction of symptoms, even vigorous mechanical and cold stimuli fail to rekindle hyperalgesia attributable to central pain-signaling neurons sensitized to mechanoreceptor input.[595]

A normally painless signal from the low-threshold afferents could activate the abnormally hyperexcitable pain-transmitting dorsal horn neurons, which accounts for stimulus-induced hyperalgesia.[359] Normal spontaneous sympathetic input to tactile mechanoreceptors might drive such afferent activity to maintain the vicious circle. Thus, sympathetic efferents excite tactile afferents, which in turn drive chronically hyperexcitable central nociceptors.[74,218] This interaction would not only explain sympathetic dependence of the spontaneous pain but also relief of the symptom by blocking the normal sympathetic efferent.[493] Some[74,483] advocate this feed-forward loop concept, whereas others[437] question it for the reasons described next.

Although CRPS, as a clinical syndrome, has withstood the test of time, the underlying pathophysiology remains obscure. In particular, debates and controversies continue about the possible role of sympathetic input in neuropathic pain.[31,76,140,212,436,462,532] Psychologically mediated symptoms further confound the evaluation of patients with chronic pseudoneuropathic pain.[6145] Abnormal movement commonly seen in CRPS may also signal an underlying psychoneurological disorder.[616] Despite the widely held view implicating sympathetic overactivity as the cause of autonomic disturbances, venous blood collected from the painful side has a lower concentration of

plasma noradrenaline and its intracellular metabolite.[144] Sympathetic underactivity would explain skin redness associated with loss of vasoconstriction, anhidrosis, and, at times, edema but not pain. In contrast, sympathetic overdrive may enhance nerve excitability and ectopic firing, possibly inducing pain, but also should cause pallor and increased perspiration not seen in this syndrome.

An alternative mechanism proposed by some, centers on the role of substance P together with histamine released from mast cells at the injury site, which promote ectopic firing of peptidergic fibers, plasma extravasation, and vasodilatation.[46,336,657] Nociceptive afferent barrage can cause substantial changes in the central nociceptive system, leading to its hyperexcitability. Hyperalgesia would then result as a consequence of exaggerated response of pain-signaling dorsal horn neurons in response to single or repeated stimuli.[19]

The central effects of the nociceptive response occur at N-Methyl-D-aspartic acid (NMDA) receptor sites mediated by excitatory amino acids such as glutamate and aspartate. Thus, NMDA antagonists can reduce central hyperexcitability, inhibiting hyperalgesia and neurogenic pain.[18,646] Altered central opioidergic neurotransmission may also play a role in CRPS.[309] Pinprick hyperalgesia, a characteristic feature of this syndrome, may also result from central sensitization through ongoing Aδ fibers or C-fiber discharges.[308,368] Indeed, patients with this syndrome show attenuated motor cortex reactivity[307] and shrinkage of cortical maps on primary and secondary somatosensory cortex,[471] suggesting a role of central mechanism. If so, stimuli arousing sympathetic activity may act by a central process to exacerbate pain, independent of the peripheral sympathetic nervous system.[43] After careful selection and testing, spinal cord stimulation may result in a long-term pain reduction.[211,279,369]

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PART VIII

Disorders of Neuromuscular Junction, Muscle Disease, and Abnormal Muscle Activity

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26

Myasthenia Gravis, Myasthenic Syndrome, and Related Disorders

Abbreviations: ACh—acetycholine, AChE—acetylcholine esterase, AChR—acetycholine receptor, ALS—amyotrophic lateral sclerosis, ChAT—choline acetyl-transferase, CIDP—chronic inflammatory demyelinative polyneuropathy, CMAP—compound muscle action potential, CMS—congenitale myasthenia syndrome, DAP—diaminopyridine, ECC—excitation contraction coupling, EMG—electromyography, EPP—endplate potential, GBS—Guillain-Barré syndrome, HIV—human immunodeficiency virus, IgG—immunoglobulin G, IVIG—intravenous immunoglobulin, LEMS—Lambert-Eaton myasthenic syndrome, MD—muscular dystrophy, MEPP—miniature endplate potential, MG—myasthenia gravis, MND—motoneuron disease, MS—multiple sclerosis, MUP—motor unit potential, MuSK—muscle-specific tyrosine kinase, NCS—nerve conduction study, NMT—neuromuscular transmission, SFEMG—single-fiber electromyography, SNAP—sensory nerve action potential

1. INTRODUCTION

In disorders of neuromuscular transmission, morphologic abnormalities correlate with physiologic alterations in the kinetics of acetylcholine (ACh) release, which in turn diminishes twitch strength[218] (see Figs. 17-1 and 17-2 in Chapter 17). Accumulated evidence clearly implicates the postsynaptic acetycholine receptors (AChRs) as the site of pathology in myasthenia gravis (MG). In contrast, presynaptic defects of ACh release characterize the Lambert-Eaton myasthenic syndrome (LEMS) and botulism. Although such a dichotomy helps simplify the

classification of pathogenesis, the exact physiologic or morphologic basis of various myasthenic syndromes remains unknown. These additional diseases affect the complex process of chemical transmission at different steps, as exemplified by the original case of a congenital defect of acetylcholin esterase (AChE).[93]

Physicians must always consider potentially treatable defects of neuromuscular transmission in any patient with unexplained weakness. Diagnostic possibilities include not only primary diseases of the neuromuscular junction but also abnormalities of the nerve terminals seen in motoneuron diseases (MNDs) and certain types of neuropathy. Electrodiagnostic studies help confirm and categorize the abnormalities. Autoantibody testing also plays an important role in diagnosing disorders of neuromuscular junction.[147]

2. MYASTHENIA GRAVIS

In the United States, MG has an incidence of approximately 1 per 20,000,[242] primarily affecting young women in the third decade and middle-aged men in the fifth or sixth decades,[9] although the age-specific incidence shows a bimodal distribution for both genders.[316] Female predominance changes with the disease onset, increasing from prepubertal to postpubertal stages, suggesting a modulating role of sex hormones.[11] Despite the unequal prevalence ratio, MG affects men and women equally.[263] Children account for 11% of all patients with MG,[248] and the older population has a higher incidence than young adults.[10,16] The sharp fall after 80 years of age may indicate substantial underdiagnosis of this entity in this population.[348] The disease occurs sporadically, although about 5% have a familial incidence. The late-onset anti-AChR antibody–seropositive MG may constitute a distinct entity provoked by environmental factors.[315] Universally accepted classifications help promote clinical management of patients with MG.[142]

Etiologic Considerations

Findings in support of an autoimmune hypothesis include the development of potentially malignant thymoma[104] in 10% and thymic hyperplasia in 70% of patients with MG.[312] Patients may also have other potentially immunologic diseases such as thyroiditis, hyperthyroidism, hypothyroidism, myositis, systemic lupus erythematosus, dermatomyositis,[342] Hodgkin's disease,[333] neuromyelitis optica,[194] transverse myelitis,[172] multiple sclerosis,[313] stiff-person's syndrome,[217] sarcoidosis,[74] chronic inflammatory demyelinating polyneuropathy (CIDP),[256] generalized myokymia,[298] human immunodeficiency virus (HIV)-1 infection,[19,70,345] rheumatoid arthritis,[318] cramp-fasciculation syndrome, acquired rippling muscle syndrome (see Chapter 28-3),[120,346] and autoimmune autonomic ganglionopathy.[259]

About 80%–90% of patients with MG have antireceptor antibodies.[15,54,174] Approximately 40%–50% of the remaining patients with generalized MG have antibodies to the muscle-specific tyrosine kinase (MuSK). Analyses in a large series[54] yielded a seronegative rate of 8.2%, defining it as nonimmunosuppressed patients with generalized MG who lack muscle AChR-binding, AChR-modulating, and MuSK antibodies at presentation and at follow-up of at least 12 months. Occasional patients suffer from subsequent or concurrent occurrence of both anti-AChR and anti-MuSK antibodies.[14] Familial history, though extremely rare, has documented different antibody specificity for affected members, for example, a mother with autoimmune seropositive and a daughter with anti-MuSK MG.[168] Seronegative patients also show a favorable response to thymectomy or plasmapheresis, indicating the presence of nondetectable antibodies.[262,347] False-positive antibody assays, though rare, may occur in penicillamine-treated or thymoma patients without MG, and in patients with amyotrophic lateral sclerosis (ALS), bone marrow transplants, Down's syndrome, tardive dyskinesia, and primary biliary cirrhosis as well as those having thyroid or mitochondrial antibodies.[314] A patient with HIV-1 may show an improvement of neuromuscular transmission (NMT) as the infection progresses, with a decline in cellular immune responses, reducing ACh receptor antibody titers.[19,285] Similarly, proteinuria may cause remission followed by exacerbation after treatment of the nephrotic syndrome.[8,143]

Histometric studies of motor endplate ultrastructure[95] reveal a reduced size of the nerve terminal area and a simplified postsynaptic membrane with poorly developed folds and clefts. In contrast, mean synaptic vesicle diameter and mean synaptic vesicle count per unit nerve terminal area remain unaltered. Microphysiologic findings indicate reduced sensitivity of the postsynaptic membrane to iontophoretic application of ACh. Studies using alpha bungarotoxin demonstrated a decreased number of functional AChR.[105,141] Myasthenic muscles contain immunoglobulin G (IgG) and complement bound to the postsynaptic membranes. These observations clearly implicate the ACh receptor in the pathogenesis of MG.[173]

Clinical Signs and Symptoms

The main clinical features consist of weakness and excessive fatigability of striated muscles. Although usually of insidious onset, the disease may become clinically manifest after acute infection or following various surgical procedures, including a thymectomy.[152,217] Symptoms initially appear toward the end of the day or after strenuous exercise. These patients usually have weakness confined to restricted groups of muscles. Involvement of the ocular muscles causes diplopia in about half of the patients, sometimes mimicking internuclear ophthalmoplegia or its variant, one-and-a-half syndrome, with additional ipsilateral horizontal gaze palsy. Less frequently, isolated bulbar or respiratory muscle weakness constitutes the presenting symptom.[184] Paralysis of palatal and pharyngeal muscles, seen in about one-third of the patients, results in nasal speech, difficulty in chewing and swallowing, and occasional aspiration.[153] Patients rarely complain of generalized weakness of the trunk and limbs, or urinary and fecal incontinence as the initial symptom.[32,326] The mildest form of the disease comprises weakness limited to the muscles of the eye. This entity, designated as ocular myasthenia, usually has a benign course. If signs outside the eye have not appeared within 1 year, 90% of such patients will develop no further progression of symptoms.[247,260] In one series, senior-onset ocular MG patients who received immunotherapy developed generalized MG less frequently than those not so treated.[7]

The clinical courses vary, often showing remissions and exacerbations, although the most severe level of weakness and high mortality occur during the first 2 years.[121] Approximately one-third of the patients improve spontaneously, some nearly completely, requiring no further medication.[241] In one series,[186] gender showed no association with remission, unlikeage at onset less than 40 years and time of diagnosis less than 1 year from onset, which predicted a better outcome. Symptoms often fluctuate without apparent cause, but several circumstances tend to exacerbate the symptoms. These include infection, exposure to heat, emotional stress, thyroid disease, and, perhaps most important, overmedication. Though unpredictable, the disease commonly worsens early and improves later during pregnancy, which does not worsen the long-term outcome.[27]

Semiquantitative assessments, useful in clinical evaluation, include serial measurements of sustained upward gaze, grip dynamometry, arm abduction, vital capacity, and maximal voluntary ventilation, which evaluate respiratory function through a dynamic exercise.[136] Investigators have developed quantitative MG scoring systems for use in clinical trial,[30,47,48,106,204] and MG-QOL15 for following the health-related quality of life of patients with MG.[49]

Paralysis worsens with elevation of body temperature[38,123] or following administration of certain drugs such as magnesium,[25] chloroquine,[275] β-blocker,[144] calcium channel blocker,[359] imiperanem,[244] cocaine,[71] statin,[76,229] and interferon-α.[26] Conversely, local cold application produces a clinical and electrophysiologic improvement.[224] The complement component C3 level correlates with clinical severity of generalized MG.[175]

If the patient exercises the limb with a pneumatic cuff inflated around the upper arm, myasthenic signs worsen in the rest of the body upon release of the cuff.[352] Early workers erroneously interpreted this phenomenon to indicate the presence of a circulating toxic substance. The spreading weakness probably results from reduction in serum calcium that binds with the lactate produced during ischemic exercise.[255] Similarly,

citrate used for anticoagulation during plasmapheresis reduces serum ionized calcium levels, thus aggravating myasthenic weakness at the end of exchange sessions.[358] Myasthenic muscles have characteristic hypersensitivity to curare, as seen in any disorders with defective NMT, such as MND, ocular myopathy, and antibiotic toxicity. A human study of the biopsied intercostal muscles revealed transmission failure but also reduction in excitation-contraction coupling and contractility as the cause of myasthenic weakness.[252] An electrophysiologic study of the human masseter muscle also revealed an impaired ECC.[139]

An intravenous administration of edrophonium (Tensilon), currently unavailable in the United States, almost uniformly improves the strength of involved muscles. The usual clinical diagnostic procedure consists of injecting a 2 mg test dose initially, followed by an 8 mg booster dose, if the patient shows neither improvement nor adverse reaction. The effect of edrophonium begins within 1 minute and ceases in 5 to 10 minutes. For objective assessment, an injection of normal saline in a double-blind fashion serves as a control. Some patients, especially those with ocular myasthenia, have an equivocal or a false-negative result with a brief effect of edrophonium. In these cases, the administration of longer acting neostigmine (Prostigmin) may improve the strength more appreciably. The administration of edrophonium may improve the clinical signs in some cases of the LEMS, botulism, congenital myasthenic syndrome (CMS), drug-induced myasthenia, Guillain-Barré syndrome (GBS), and ALS.[227]

Differential diagnoses comprise all diseases characterized by weakness of ocular, bulbar, or limb muscles.[146] These include muscular dystrophy (MD), MND, progressive bulbar palsy, multiple sclerosis (MS), ophthalmoplegia, pseudobulbar palsy, and psychoneurosis. Patients with MG typically complain of excessive fatigability after exercise. In mild cases, symptoms may appear only after exertion, not uncommonly leading to a mistaken diagnosis of hysteria. A hot bath may worsen symptoms by lowering the margin of safety in NMT. Here, distinction from MS may prove difficult, especially if the patient has pseudo internuclear ophthalmoplegia.[179] Routine muscle biopsy has a limited diagnostic value. Type II fiber atrophy, though commonly seen in MG, can also result from disuse or corticosteroid treatment.

In addition to anticholinesterase medication such as mestinon,[267] effective therapeutic regimens include thymectomy,[269,283] steroids,[29,43,274] immunosuppressive drugs,[150,272,282] intravenous immunoglobulin (IVIG),[3] plasma exchange,[268] and calcineurin inhibitors.[209]

Although not universally upheld, thymectomy probably has its place as the treatment of choice for symptomatic anti-ACh antibody–seropositive patients in the middle age or older group.[155,278] Some advocate thoracoscopic thymectomy,[286,324] a view not accepted universally. Administration of prednisone, sometimes used to stabilize the condition before thymectomy, may cause acute inhibition of neuromuscular function. Patients then have a prominent decremental response to repetitive nerve stimulation, reduced twitch tension, and lowered force of maximum voluntary contraction. For an invasive thymoma, treatment consists of total excision, if possible, and high doses of corticosteroids and combination chemotherapy for the remaining tumor.[351] In one series, the incidence of stable remission peaked in 2 years when treated with thymectomy alone and 5 years with additional immunosuppressive therapy.[86]

Patients sometimes improve after the initial administration of IVIG,[110] which may rarely cause complication of aseptic meningitis.[88] Those who fail with this regimen may respond to intensive plasma exchange.[66,145] In one series,[185] delaying plasmapheresis for MG by more than two days after admission led to higher mortality and complication rates. These two regimens play a greater therapeutic role in juvenile MG to avoid a long-term consequence of using steroids.[59] Intranasal neostigmine also produces acute clinical and electrophysiologic improvement.[270] As an alternative therapy, 3,4 diaminopyridine (DAP) enhances ACh release by blocking the potassium channels located along the nerve terminal, thereby enhancing nerve action potentials (see Chapter 28-6). This, in turn, improves congenital or hereditary myasthenia (see Chapter 26-4), which comprises a heterogeneous group of disorders without immune abnormalities.[253]

MuSK Antibody–Positive Myasthenia

MuSK antibody–positive MG, mainly found in women aged 18 to 60 years, shows varying ethnic incidences—higher in African American,[321] lower in Chinese[366] and Polish population,[156] and none reported in Norway. This entity has a wide spectrum, ranging from infantile[205] to ocular forms[51] with variable clinical features.[239] Some show symptoms indistinguishable from MuSK antibody–negative MG, while others have weakness limited to one or more anatomic regions, commonly the face and oropharynx muscles,[128,167,212,293] associated with marked muscle atrophy from the myopathic process.[107] These characteristics account for the common bulbar involvement, respiratory symptoms, and neck extension weakness.[79] Repetitive nerve stimulation and jitter studies also tend to show greater abnormality in the face than in the limbs, although testing any symptomatic muscles improves diagnostic yields.

Benefit from thymectomy remains unknown, but most respond favorably to immunotherapy. In one series[254] 53% of patients improved on corticosteroids, 51% with plasma exchange, and 20% on IVIG. Treatment with IV rituximab improved clinical signs of MG in an HIV-positive MuSK MG patient.[159] Anti-MuSK antibody levels, reduced by immunosuppression but not after thymectomy, show a positive correlation with disease severity.[24] An AChE inhibitor may worsen weakness in some and produce profuse fasciculations in others, and nerve stimulation at low frequency may display extra discharges after each CMAP.[265] Although anti-MuSK antibodies disrupt the neuromuscular junction in mice,[62] neither AChR loss nor complement deposition or morphological changes occured in human studies.[193,307] In vitro electrophysiologic and histologic studies revealed low levels of presynaptic ACh release and a small miniature EPP. These findings suggest that anti-MuSK antibodies reduce the stability of muscle-nerve contact.[220] Careful selection of muscles based on electrophysiologic abnormalities helps improve the yields in detecting molecular, morphologic, and microphysiologic abnormalities.

Myasthenic and Cholinergic Crisis

Patients with MG having an acute exacerbation of weakness may have myasthenic or cholinergic crisis. A careful therapeutic management does not necessarily avoid the occurrence of myasthenic crisis (see Fig. 18-6 in Chapter 18), a potentially life-threatening complication that requires aggressive therapy.[28,149] In most such cases, neuromuscular functions improve in correlation with plasma drug levels of pyridostigmine.[41] Conversely, anticholinesterase overdose causes cholinergic crisis characterized by a compound muscle action potential (CMAP) with extra discharges (see Fig. 18-10 in Chapter 18) in response to a single stimulation[266] reminiscent of organophosphate poisoning (see Chapter 26-6). The edrophonium test, recommended as a means of distinguishing the two opposing types of abnormalities, should improve a myasthenic crisis but worsen a cholinergic crisis, which reverses rapidly as the short-acting effect of the drug wanes.

On occasions, these studies may give an equivocal result, without clearly establishing the diagnosis. In such a situation, we discontinue all medication under assisted respirations in the intensive care unit with intubation or tracheostomy, if necessary, for removal of saliva that pools in the nasopharynx. After this "drying out" period for 4 to 10 days, reinstatement of anticholinesterase therapy in small doses very often shows a dramatic improvement as the patient may have increased sensitivity to cholinergic medication. Some patients undergo cycles of these crises, requiring increasing amount of anticholinesterase medicines to control the disease.

Any patient seen in myasthenic crisis may have predisposing conditions such as intercurrent infection and administration of certain drugs with an adverse effect on NMT. These include quinine, quinidine, procainamide,[154] other β-adrenergic blockers,[137] and diphenylhydantoin antibiotics such as neomycin and streptomycin.

Electrophysiologic Tests

Electrophysiologic studies play an important role in establishing the diagnosis of MG.[1,2,368] The incidence of decremental response to repetitive

nerve stimulation varies widely from 30%[176] and 41%[294] to 95% [250] depending on the muscle examined, disease severity, racial differences,[235] and types of MG under consideration.[67] In general, 65% to 85% of patients show a positive result, after a comprehensive survey from multiple recording sites.[230] Despite the technical difficulty with movement artifacts, an adequate set of studies must include recordings from proximal muscles (see Chapter 18-3). Studies of the easily immobilizable distal muscles, though less sensitive, provide more consistent results. The commonly tested include intrinsic hand muscles; deltoid, trapezius, other shoulder girdle muscles and nasalis;[219] and, to a lesser degree, masseter[257] serratus anterior,[177] and diaphragm.[369] Warming the muscle improves the yield (see Fig. 18-2 in Chapter 18).

A single supramaximal stimulus elicits a CMAP of normal or only slightly reduced amplitude. The muscle action potentials show a decremental tendency to repetitive stimulation at 2–3 Hz and to a lesser extent at higher rates (see Figs. 18-4 and 18-5). The amplitude drops maximally between the first and second response of a train with less change for the next few peaks and partial recovery, or repair, thereafter based on early mobilization of ACh from secondary stores and intra-axial accumulation of calcium. According to the generally accepted criteria, at least two muscles should show a reproducible reduction of more than 10% between the first response and the smallest of the first five of a train. In my experience, any reproducible decrement should raise suspicion, provided the study reveals a clean tracing free of technical problems. If repetitive stimulation at 2–3 Hz demonstrates a decrement, a brief voluntary exercise for 15–30 seconds repairs a bona fide tendency for decrement during subsequent trains, a phenomenon called posttetanic potentiation. In contrast, amplitude diminution within a train exceeds the pre-exercise value 2–4 minutes later during posttetanic exhaustion. Again, an additional 5 seconds of exercise will partially correct the change. Failure to repair by this means may suggest a movement artifact rather than defective neuromuscular transmission. Thus, a brief voluntary exercise helps differentiate an abnormal response from technical problems (see Fig. 18-4 in Chapter 18). The degree of decrement appears to relate to disease severity and muscle weakness, but not to objective measures of fatigue.[328]

Needle studies show varying amplitude and configurations of recurring motor unit potentials (MUPs). Although unpredictable, the initial few discharges tend to decrease progressively in size and duration. Fibrillation potentials and positive sharp waves, seen in up to 20% of cases, indicate either the loss of innervation in severely affected muscles or presence of inflammatory myopathy seen in some patients of MG. Single-fiber electromyography (SFEMG) serves as one of the most sensitive measures of neuromuscular transmission abnormalities.[292,319,320,361] Clinically strong muscles that show no decrement to repetitive nerve stimulation may show increased jitter.[112] An occasional bimodal distribution of response latencies seen in SFEMG using axonal microstimulation implies the presence of dual neuromuscular junctions in some affected myasthenic muscles.[335] The degree of disturbed neuromuscular transmission in a proximal limb muscle reflects the patient's subjective experience.[280] Studying SFEMG of the extraocular muscles[273] and, to a lesser extent, the orbicularis oculi[226] and frontalis muscles[281] also serves as a good measure for ocular myasthenia. Normal study in the limb muscles tends to refute future development of generalized MG in these patients.[356] Other measures of interest include the ECC time determined as the difference in onset latencies between the masseter CMAP and mandibular movement recorded using an acceleration converter after electrical stimulation of the trigeminal nerve.[140,337] In an anti-ryanodine-receptor-positive, AChR-negative MG patient, ECC time decreased from 4.8 ms to 2.9 ms after prednisolone treatment.[139]

Occasional patients with MG show the electrophysiologic features more typically associated with LEMS, suggesting the existence of an intermediate disorder characterized by defective ACh release as well as diminished numbers of ACh receptors. Although immunologic evidence implies the coexistence of the two entities in a few reported patients (see Chapter 26-3)[214,236] microelectrode studies have generally provided no convincing evidence to support such a contention.

Even in healthy subjects, ACh release progressively declines with low rates of stimulation and enhances with high rates of stimulation (see Chapter 17-6). These physiologic phenomena result in clinical and electrophysiologic abnormalities only if a defective neuromuscular transmission diminishes the margin of safety (see Fig. 17-8 in Chapter 17). In the same patient, some muscles may demonstrate an abnormal pattern typical of MG, whereas others may show changes reminiscent of the myasthenic syndrome.[208] In this instance, the size of the first CMAP often dictates the response pattern to repetitive stimulation. An initially subnormal response tends to show an increment during a train of rapid stimulation. In contrast, if the first shock elicits a full response, subsequent stimuli have no room to show an increment (see Figs. 18-7 and 18-8 in Chapter 18).

3. MYASTHENIC SYNDROME

Although reported cases included children aged 4 and 9 years, the LEMS[87] usually have onset after age 40 years, affecting men twice as commonly as women. A clear association with malignancy is essential for elucidating the manner by which a tumor leads to defective release of ACh. The pathogenesis centers on the presence of autoantibodies to the voltage-gated calcium channels and related structures demonstrated in the patient's tumor. In fact, accumulated evidence indicates the presence of autoantibodies that block ACh release by interfering with the voltage-gated calcium influx at the nerve terminal.[63,213]

Etiologic Considerations

More than 50% of affected patients have small cell carcinoma of the bronchus, the most common tumor seen in this syndrome.[323] Careful search reveals a malignant neoplasm in about 75% of men and 25% of women, but not necessarily at the time of initial neuromuscular symptoms. One series estimated a 62% initial risk of an underlying small cell lung cancer, which declined sharply after 2 years becoming very low at 4–5 years.[240] Thus, the malignancy may escape detection for many months or, occasionally, for many years after the onset of the LEMS. With adequate follow-up, however, only 30% of the patients remain free of cancer.[164] The tumors include large-cell neuroendocrine carcinoma of the lung,[122] reticulum cell sarcoma,[279] rectal carcinoma,[50] renal carcinoma,[52] basal cell carcinoma of the skin,[329] leukemia,[304] malignant thymoma,[166] and lymphoproliferative disorders.[17] Systemic disorders associated with the syndrome include thyrotoxicosis,[222] Sjogren's syndrome,[45] rheumatoid arthritis,[329] systemic lupus erythematosus,[42] paraneoplastic cerebellar degeneration,[118] and other autoimmune entities.[125] Some of these disorders show transient myasthenic syndromes associated with antibodies against calcium channels.

Histometric studies of motor endplate ultrastructure[101] have revealed overdevelopment and an increased area of the postsynaptic membrane (see Fig. 17-2 in Chapter 17). The nerve terminal retains a normal mean synaptic vesicle diameter and density. Routine muscle biopsy material shows only nonspecific findings with some Type II fiber atrophy and mild inflammatory reactions. Microelectrode studies of excised intercostal muscles revealed an abnormally low discharge frequency of the miniature endplate potential (MEPP), which remained normal in amplitude.[89] The mean quantum content of the endplate potential (EPP), defined as the number of ACh vesicles released per volley of nerve impulse, though initially low, increases with repetitive nerve impulses.[162] These findings suggest either an abnormality in the calcium-dependent release of ACh from the motor nerve terminals or a decreased store of available ACh. Ultrastructural studies show a normal synaptic vesicle number per unit nerve terminal, which tends to discount the possibility of defective storage. Thus, weakness in the LEMS must result from presynaptic abnormalities that lead to a reduced number of ACh quanta released by nerve impulse. In an experimental setting, high magnesium or low calcium ion concentrations block neuromuscular transmission. A similar syndrome may also occur as an adverse effect of the calcium antagonist, diltiazem.[341]

Showing a good correlation with physiologic indices of clinical grade, IgG obtained from patients inhibits voltage-gated calcium flux in tumor cells.[165,261] The same IgG autoantibodies

also inhibit calcium channels at the motor terminals, diminishing transmitter release.[46,119,163,264] In one series of 36 patients,[171] 44% had a significant level of antibody. Pharmacologic experiments using antibody from patients revealed a close link between P/Q-type voltage-gated calcium channels and the genesis of the parasympathetic response.[349,354] Antibody titers showed no correlation with disease severity across individuals, but longitudinal studies found a clear positive relationship to the severity of the patient's symptoms. Seronegative patients have the same clinical characteristic as the seropositive group except for a lower incidence of small cell lung carcinoma. The result of passive transfer experiments suggests the presence of autoantibodies even in seronegative LEMS.[210]

Findings vary among atypical cases. In one patient who had a small decremental response and increased jitter and blocking, for example, histologic studies showed alteration in the number and affinity of junctional ACh receptors and prominent tubular aggregations in muscle fibers. Two patients had immunologic evidence for the coexistence of the LEMS and MG.[214] In these cases, radioimmunoassays detected serum antibodies to the voltage-gated calcium channels that constitute the antigenic target in the LEMS, as well as antibodies to the ACh receptors affected in MG.

Clinical Signs and Symptoms

In striking contrast to the fatigue phenomena in MG, weakness in the LEMS peaks during rest, thus unknown to the patient. Immediately upon awakening in the morning, strength quickly improves with brief exercise, although it fails to sustain during a prolonged effort. Weakness and fatigability primarily affect the lower limbs, particularly the pelvic girdle and thigh muscles.[240] Thus, patients have difficulty in climbing stairs and, to a lesser degree, arising from a chair. The abnormality also involves the shoulders and upper limbs, usually but not always, sparing the neck, bulbar, and extraocular musculature.[148] Neck weakness, though rare, may give rise to a dropped head syndrome.[340] The usual distribution of weakness counters the typical patterns seen in patients with MG, who show conspicuous bulbar symptoms such as ptosis, diplopia, dysphagia, and dysarthria. Patients often complain of dryness of the mouth and, less frequently, impotence, paresthesias, and dysautonomia. These symptoms suggest a defect of ACh release affecting not only the skeletal muscle but also the autonomic nervous system, predominantly causing parasympathetic dysfunction.[60,249]

Neurologic evaluation reveals marked weakness of the proximal muscles in the lower limbs that appreciably improves after exercise. With each successive effort, the resistance needed to overcome the patient's strength increases, giving the examiner a sensation of drawing up water from a well with a hand pump.[44] Ptosis, if seen in LEMS, may show paradoxical improvement in lid elevation with sustained upgaze[40] in contrast to the exercise-induced worsening in MG. Similarly, reduced muscle stretch reflexes may improve after brief exercise.[225] Peripheral neuropathy and subacute cerebellar degeneration may develop probably as manifestations of a paraneoplastic syndrome.[118] Calcium-channel blockers, administered for a cardiac condition, have precipitated respiratory failure.[336]

Guanidine partially corrects defective calcium-dependent ACh release and results in dramatic improvement in strength, although hematologic and renal complications usually precludes a long-term use in high dosage.[232] The neuromuscular defect also improves partially after the administration of calcium, aminophylline, or caffeine, which increases the cyclic adenosine monophosphate essential in calcium mobilization in cells.[295] Treatment with 4-aminopyridine or 3,4-diaminopyridine (3,4-DAP) blocks voltage-sensitive potassium channels, prolonging the action potential duration, which in turn increases calcium influx and enhances transmitter release.[228,297] Contraction-induced CMAP augmentation decays faster after treatment with 3,4-DAP, indicating that the rate of calcium efflux also accelerates.[181] Adverse side effects limit the use of 4-aminopyridine and related drugs.[207]

Plasma exchange and immunosuppressive drug may temporarily alleviate the symptoms.[215] Clinical and electrophysiologic studies of muscle strength show an improvement after long-term therapy with prednisone,[322] azathioprine,[291] or

high-dose IVIG.[21,203,271] Patients with lung cancer tend to have a more progressive course.[360] Conversely, patients without lung cancer generally have a favorable outcome, although they often need immunosuppressive treatment to remain clinically stable.[180]

Electrophysiologic Tests

As the electrical hallmark of the syndrome, nerve stimulation typically elicits a very small CMAP (see Fig. 17-8 in Chapter 17, and Figs. 18-7 and 18-8 in Chapter 18) and, in striking contrast, entirely normal sensory nerve action potentials (SNAPs).[240] Paired stimulation with interstimulus intervals of 5–10 ms causes the second response to increase, as in a patient with botulism, rather than decrease as expected in normal muscles (see Fig. 18-3 in Chapter 18). Repetitive stimulation at low rates further diminishes CMAP amplitudes similar to the decrement seen in MG. Stimulation at high rates causes substantial increments, usually exceeding 50%–200% of the baseline value in amplitude and area (see Fig. 17-8 in Chapter 17).[234,331] Very brief voluntary contractions for up to 10 seconds, depending on the severity of illness, facilitates the subsequent responses elicited by nerve stimulation. A slower rate of stimulation also facilitates the response if combined with voluntary contraction.[178] In contrast to MG with variable electrical changes usually confined to clinically symptomatic muscles, the patients with LEMS show widely distributed abnormalities. Thus, all muscles show a mild decrement at low rates and prominent increment at high rates of stimulation. Nonetheless, abductor digiti minimi, abductor pollicis brevis, and anconeus serve best to detect the characteristic electrophysiologic findings.[182]

Nerve stimulation may reveal marked abnormalities even in patients with mild clinical symptoms, who complain little of motor dysfunction because posttetanic facilitation during voluntary contraction produces nearly normal strength. Unknown to them, however, resting muscles have an unequivocal defect of neuromuscular transmission. This type of facilitation, which decays exponentially within 20 seconds, lasts longer after cooling, which reduces the rate of calcium removal from the nerve terminal.[183] A prolongation of this effect in part underlies the patient's symptomatic improvement in cold weather. During posttetanic exhaustion that peaks in 2–4 minutes, the muscle potential falls below the resting level (see Figs. 18-14 and 18-15 in Chapter 18).

Electrophysiologic abnormalities may show various patterns, reflecting different degrees of blocking[233] and availability of releasable ACh from the terminal axon.[126] Seronegative patients with LEMS may have less postexercise facilitation compared to the seropositive group.[231] In one reported case,[160] electrophysiologic studies revealed a unique combination of marked depression to single-nerve stimulation and facilitation at all rates from 1–200/s. This case may represent a separate entity or a variation of the myasthenic syndrome.

Needle studies show varying MUP amplitudes in successive discharges with an incrementing tendency (see Chapter 14-5). As expected, jitter and blocking abnormalities seen in single-fiber studies improve with high rates of stimulation and worsen following rest.[299] Treatment with 3,4-DAP may correct this abnormality.[288]

4. MYASTHENIA IN INFANCY

Transient Neonatal Myasthenia

The nicotinic AChR comprises five subunits: α x 2, β, γ, and δ in the fetus and α x 2, β, ε, and δ in the adult, as ε replaces γ around 33 weeks gestation (see Chapter 17-2).[246] Most infants of a myasthenic mother remain asymptomatic despite intrauterine exposure to AChR antibodies. A higher fetal-to-adult AChR antibody ratio can lead to a transient neonatal MG. Thus, as an experiment of nature, approximately 15% to 20% of infants born to myasthenic mothers have a neonatal MG.[202] This condition presumably results from transplacental transfer or transient synthesis of anti-AChR antibodies, which serve as one of the best indicators. This type of assay, however, may not adequately discriminate maternal transfer from a prepubertal-onset juvenile MG with high frequency of seronegativity.[11,365] The onset of clinical weakness on the second or third day coincides with the release of antibodies from hemoglobins,

which combine them at birth. Some patients with MG have autoantibodies to MuSK instead of AChR. Similar to anti-AChR antibodies, anti-MuSK antibodies transferred across the placenta can cause a self-limiting neonatal MG.[221,223]

Clinical features during the first few days after birth consist of diffuse hypotonia with difficulty in breathing and sucking, although some infants have selective weakness of the diaphragm.[135] The neonates usually respond to AChE medication. These symptoms, which generally abate in a few weeks when the infants develop their own immune system,[211] may occasionally persist beyond 2 months of age.[39] Electrophysiologic studies show characteristic abnormalities in distal muscles as late as 30 days after clinical recovery.[78] An elevated antibody titer against AChR returns to normal over a 3-month period.

Other Forms of Infantile Myasthenia

In the absence of maternal passive transfer, infantile MG may result from acquired autoimmune pathogenesis or nonautoimmune hereditary diseases. The term *congenital myasthenic syndrome* (CMS) or familial infantile myasthenia implies the absence of anti-AChR or MuSK antibodies in the serum. These patients, other than a family history of similar disease, resemble the autoimmune type without readily distinguishable clinical features. The congenital type accounts for about 1% of all cases of MG. The disease begins in infancy but, unlike transient neonatal myasthenia, continues into childhood and adulthood. In many cases, the family history reveals affected siblings, although the mother has no disease. Initially mild symptoms slowly progress despite therapy. The infants may have respiratory depression at birth, and episodic weakness and apnea during the first 2 years. They may[276] or may not[334] improve with anticholinesterase medication. This entity encompasses a variety of specific genetic defects at the neuromuscular junction, with no evidence of immunologic abnormalities. Thus, antibody determinations help differentiate autoimmune and hereditary myasthenia in infancy. Genetic defects of AChR seen in CMS, however, may play a role in the etiology of some patients with autoimmune MG.[69]

Detailed physiologic, chemical, and histologic studies have elucidated a number of types with specific presynaptic, synaptic, or postsynaptic abnormalities (Table 26-1). These disorders have divergent features, such as absence of AChE from the neuromuscular junction,[138] failure of ACh synthesis or packaging,[92,93] an abnormality in the regulation of AChR density,[90,169,339] kinetic dysfunction of AChR[62,96,243] with or without AChR deficiency, and familial limb-girdle myasthenia with tubular aggregates.[109] These genetic defects either impair NMT directly or result in secondary derangements that eventually compromise its safety margin by one or more specific mechanisms.[31,97,116,146,308] For example, a kinetic abnormality of AChR results from missense mutation in the α, β, or ε subunits. Various types of CMS stem from defects in presynaptic, synaptic basal lamina, and postsynaptic proteins.[99,100]

Presynaptic etiologies, or defects that curtail the evoked release of ACh quanta or ACh resynthesis include choline acetyl-transferase (ChAT) mutation,[157] paucity of presynaptic vesicles, and deficiency in action potential–dependent quantal release.[191] In one such case, a deficient synthesis of ACh resulted in intermittent ptosis, feeding difficulties, dyspnea, and vomiting in an infant.[133] Weakness worsened with febrile illness or by exercise, showing a gradual improvement with age. Progressive weakness developed during prolonged nerve stimulation at 10 Hz. Brief repetitive nerve stimulation produced no CMAP decrement. In another term infant with similar clinical features, electrodiagnostic studies demonstrated defective NMT characterized by borderline low CMAP amplitudes, profound decremental responses at all stimulus rates, and 50%–74% facilitation 15 seconds after 50 Hz stimulation for 5 seconds.[5] Although not proven, these findings suggest an abnormality in ACh resynthesis, mobilization, or storage rather than defective receptors.[92] Indeed, prolonged nerve stimulation induced a temporal decline in EPP and MEPP amplitudes in normal muscles after ACh synthesis was blocked with hemicholinium.[77] Despite abnormally small synaptic vesicles found in some patients with CMS, vesicle size showed no reliable correlation with the MEPP amplitude.[201]

Table 26-1 Characteristics That Differentiate Neuromuscular Transmission Defects in Myasthenic Syndromes

MYASTHENIC SYNDROME	ACHR ANTIBODIES	REPETITIVE MUSCLE AP TO SINGLE NERVE STIMULUS	MEPP DURATION	MEPP DURATION INCREASED BY ESTERASE INHIBITION	MEPP AMPLITUDE	MARKED DECREMENT OF EPP AND MEPP DURING 10 HZ STIMULATION	QUANTUM CONTENT
MG	+	–	–	+	↓	–	–
LEMS	–	–	–	+	–	+	↓
Congenital							
A	–	+	↑	–	↓	–	↓
B	–	+	↑	+	↓	–	–
C	–	–	–	+	–	+	–
D	–	–	–	+	↓	–	–
Dog	–	–	–	+	↓	–	–

AChR, acetycholine receptor; AP, action potential; EPP, endplate potential; MEPP, miniature endplate potential; MG, myasthenia gravis ; LEMS, Lambert-Eaton myasthenic syndrome; A, myasthenic syndrome with endplate acetylcholinesterase deficiency, small nerve terminals, and reduced acetylcholine release (Engel, Lambert and Gomez[93]); B, familial, congenital myasthenic syndrome possibly from an abnormal acetylcholine receptor with prolonged open time (Engel, Lambert, Mulda, et al[94]); C, familial, congenital myasthenic syndrome possibly from deficient synthesis of acetylcholine (Hart, Sahashi, Lambert, et al[133]); D, familial, congenital myasthenic syndrome with a possible abnormality of acetylcholine receptor synthesis or incorporation in the postsynaptic membrane (Lambert[161]);. Dog, congenital myasthenia in dogs.

Synaptic basal lamina abnormality results from mutations in the collagenic tail subunit of the AChE.[238] In the first type, originally described in a 15-year-old boy who had intermittent ptosis, delayed motor development, and generalized weakness, detailed analyses showed three main features: AChE deficiency, small nerve terminals, and reduced ACh release.[91,93,138] The patient had a negative edrophonium test, no serum antibodies to muscle AChR, and absent AChE at the endplates. Nerve terminals averaged one-third to one-fourth of the normal size. In vitro microelectrode studies revealed a number of unusual features: normal amplitude but low discharge frequency of MEPP, a marked reduction in number of ACh quanta released per nerve stimulation, and prolonged duration of MEPP and endplate potential (EPP). A single shock to the nerve elicited repetitive discharges, whereas a train of stimuli at 2 and 40 Hz gave rise to a decremental response (Fig. 18-10 in Chapter 18).[343] Needle studies showed temporal variability of MUP configuration.

Postsynaptic defects from mutations in subunits of the AChR alter the kinetic properties of gating, giving rise to slow and fast channel syndromes. Mutations underlying the slow channel syndrome cause a "gain of function" with dominant inheritance, whereas mutations responsible for the fast channel syndrome cause a "loss of function" with recessive inheritance, usually involving the ε-subunit gene.[237] A certain mutation, however, results in a dominantly inherited fast channel syndrome, severely compromising receptor function.[355] Differential diagnosis includes an immune-mediated disorder called acquired slow channel syndrome with the formation of an antibody specific to the adult form of ACh receptors, which results in alteration of the channel properties, reducing the total current and slowing the channel closure.[300,357] Various mutations in AChR subunits also result in different types of AChR deficiencies.

In the slow channel syndrome with missense mutations in the genes encoding subunits of the endplate AChR,[98,115] a prolonged EPP results from abnormal transmitters resistant to muscle AChE or an abnormal ACh receptor with a prolonged open time, or slow channel.[94,243] The affected infants have ophthalmoparesis and weakness of neck muscles. The patient develops easy fatigability and weakness of shoulder girdle and forearm muscles later in the teens or adulthood. Single stimuli to motor nerves elicit repetitive muscle action potentials in proximal and distal muscles.[343] Quinidine sulfate shortens the opening episodes of the mutant ACh receptors, thus improving clinical strength and the amplitude of muscle potentials elicited by rapid rates of stimulation.[130] Fluoxetine, which shortens the prolonged opening bursts, may also serve as a therapeutic agent in patients with a slow channel syndrome.[132]

In the fast channel syndrome, a kinetic abnormality of the ACh channel stems from a point mutation in a receptor subunit.[102] Mutations causing severe endplate AChR deficiency usually reside in the ε subunit, partially compensated for by the residual low-level expression of the fetal γ subunit, which rescues the phenotype.[306,309] In the original report, propositus had poor suck and cry after birth and intermittent ocular symptoms and abnormal fatigues later. A younger sister had elements of the same disease. Physiologic studies revealed a normal quantal content of the EPP, but an abnormally large MEPP and short decay time constant, considered characteristic of high conductance, seen in the fast channel syndrome.[96] Repetitive nerve stimulation showed no decrement in limb muscles, but SFEMG of the facial muscles uncovered findings consistent with a neuromuscular transmission defect. In two CMS patients with ε-subunit mutations, treatment with the B2-adrenergic agonist, albuterol, produced dramatic improvement in strength and in daily activities.[289]

Endplate AChR deficiency may also result from mutation of its subunits, rapsyn, a molecule that plays a critical role in the formation of the postsynaptic membrane[188] or mutations in MuSK gene.[197] With early diagnosis and therapy, rapsyn deficiency has a benign cause in most patients. In one series of 39 patients with endplate AChR deficiency,[198] all but one patient had onset of disease early in life and most responded to cholinergic agonists. A patient with a possible abnormality of AChR synthesis had clinical features consisting of ptosis, limb weakness, and

easy fatigability since birth.[161] He had a similarly affected brother. Intracellular microelectrode studies revealed low-amplitude but otherwise normal MEPP in duration and frequency, a normal number of ACh quanta released by nerve stimulation, a normal store of readily releasable quanta in the nerve terminal, and an abnormally low content of AChR. In the absence of autoimmunity, the abnormality probably resulted from a defect of the AChR molecule or its synthesis.

In still another type of AChR deficiency characterized by paucity of secondary synaptic clefts, clinical features included weak fetal movements during pregnancy, muscle weakness at birth, multiple contractures of the lower limbs and myasthenic crisis during febrile illness.[339,364] Neurophysiologic studies demonstrated a 55% decrement to stimulation at 3 Hz and a reversal of this abnormality by administration of edrophonium. These and other congenital syndromes probably represent separate pathologic, electrophysiologic, and clinical entities.[114,287,334]

In one series,[131] results of clinical neurophysiologic tests showed fair correlation to clinical manifestation and findings on ultrastructural, microelectrode, and molecular genetic studies. Patients with AChE deficiency and congential slow channel syndrome develop extra discharges after the initial CMAP in response to single stimuli (see Fig. 18-10 in Chapter 18). Patients with mutations affecting kinetic properties of the AChR often show a rate-dependent decrement. Needle EMG studies, though nonspecific, reveal abnormalities, which support the diagnosis of CMS. Thus, clinical analyses and neurophysiologic studies often enable the clinician to make an accurate diagnosis in most such cases.[127,129]

5. BOTULISM

Botulinum Toxin

The exotoxin of Clostridium botulinum has a generalized effect on the neuromuscular junction involving both striated and smooth muscles.[85] Of the six immunologic types of Bacillus botulinus,[61] Types A, B, and E account for the majority of human cases. The most common infantile form develops after the consumption of food containing spores that germinate in the gut and produce toxin. In adults, poisoning by this heat-sensitive toxin usually follows the ingestion of the preformed toxin in contaminated raw or inadequately cooked or canned vegetables, meat, or fish.[134,200,332] An infected wound may occasionally harbor the toxins. Bulbar weakness with visual symptoms in patients with subcutaneous heroin abuse strongly suggests the possibility of wound botulism.[187,189] Types A and B usually originate in contaminated canned vegetables and Type E in fish products. Types A and E have higher mortality rates than Type B.

The incidence of botulism increases at high altitudes probably because water boils at lower temperatures.[57] Botulism bears a great resemblance to the LEMS with marked impairment of ACh release from the nerve terminal. In vitro studies of the MEPP show extremely low rates of discharge but normal or only slightly reduced amplitudes. A small quantum content per volley of nerve impulse results in a markedly decreased EPP. In-vitro microelectrode study in a 6-week-old infant revealed substantial reduction of the EPP quantal content and marked latency variability.[189] This combination indicates a severe presynaptic failure of transmission resulting from impaired vesicle release following the influx of calcium into the nerve terminals. Ultrastructural study of the motor endplate revealed the postsynaptic regions denuded of their nerve terminals.[338]

Clinical Signs and Symptoms

Botulism should be considered first when several members of a family develop similar symptoms after sharing the same meal. Isolated cases pose a greater diagnostic challenge. The mouse toxin neutralization test and culture of the suspected food confirm the diagnosis. Ingestion of a large amount of toxin may rapidly result in fatal cardiac or respiratory failure. Some cases of the sudden infant death syndrome may result from botulism, now recognized with increasing frequency in this age group. In less severe cases, mild symptoms abate and, as the rule, complete recovery ensues. Botulism in infants may relapse after apparent clinical resolution.[113]

Symptoms appear within 1–2 days after consumption of contaminated food, and in 1–2 weeks after wound inoculation, which requires time for elaboration of the toxin. Gastrointestinal dysfunctions such as diarrhea, nausea, and vomiting precede the onset of cranial weakness, initially characterized by external ophthalmoplegia and ptosis. Patients may also have failure of convergence, fixed and dilated pupils, dysarthria, dysphagia, and difficulty in mastication. The involvement of the intestine and bladder causes constipation and urinary retention.

The disease affects the muscles of the limbs and later of the trunk. By then, examination reveals a flaccid and areflexic patient with widespread paralysis. Exercise causes fatigue but not as prominently as in MG. Unlike the weakness seen in the LEMS, muscle strength does not improve with repeated efforts. Identification of the toxin in the patient's serum confirms the diagnosis. Its early recognition by electrodiagnosis can lead to immediate therapy with antitoxin, which increases the rate of survival.[55,305] Severely affected patients should receive supportive therapy. Administration of guanidine or 3,4-DAP showed no effect in facilitating recovery from botulism.[73]

Electrophysiologic Tests

Nerve conduction studies show a normal SNAP in amplitude and latency. A small CMAP elicited by a single shock further declines with repetitive stimulation at a slow rate. Paired stimuli at interstimulus intervals of less than 10 ms characteristically potentiate the second response by summation of the first and second EPP (see Fig. 18-3 in Chapter 18). This finding, also seen in LEMS, counters the normal pattern consisting of a full response followed by a smaller response during the refractory period induced by the first of the paired stimuli. In botulism, as in the LEMS, the first supramaximal stimulation characteristically elicits a small CMAP, activating only a small number of muscle fibers, which will become refractory to the second stimulus. The remaining muscle fibers, subliminally excited by the first shock, tend to fire in response to the second shock, making the second response greater than the first. Very brief voluntary contraction also facilitates the subsequent responses elicited by single stimuli with a usual percentage increment of 25%, showing an inverse relationship to the initial CMAP amplitude.[362]

A fast train of stimuli causes a posttetanic potentiation, progressively facilitating the muscle response though usually not to the same degree as in the LEMS.[22,187] This does not hold, however, in severe cases with a complete block of neuromuscular junction, which precludes any augmentation.[305] In infantile botulism, repetitive stimulation at 20–50 Hz shows an incremental response in over 90% of patients (see Fig. 18-13 in Chapter 18).[65] Prolongation of posttetanic facilitation, at times for up to 4 min, also constitutes a unique feature of botulism.[124] The presence of fibrillation potentials may indicate functional denervation caused by limited release of ACh, which also explains an increased jitter and blocking and some reduction in fiber density.[56,251,330]

Therapeutic Application

Botulinum toxin Type A plays its therapeutic role by blocking the presynaptic release of ACh. Formation of antibodies occurs in some patients.[83] Injection under EMG guidance helps improve the efficacy and safety of the low-dose regimen.[277] Serial SFEMG studies of orbicularis oculi muscle treated with botulinum toxin injections revealed formation of new neuromuscular junctions and functional maturation.[37] Local injection of botulinum toxin for blepharospasm causes abnormal jitters in the arm muscles, indicating a remote spread of toxin from the site of injection,[13,20,296] although fiber density remains unchanged in noninjected muscles.[108] Botulinum A toxin injected intradermally to treat palmar hyperhidrosis also spreads to the underlying muscles as evidenced by SFEMG.[325] Intragastric botulism toxin injection for obesity treatment, however, induced no subclinical sign of distant effect.[245] Focal cosmetic injection of unapproved botulinum toxin Type A caused severe botulism characterized by dilated pupil, flaccid quadriplegia, and a lengthy recovery.[317]

Local botulinum toxin injections unmasked the symptoms of a subclinical LEMS[103] and caused generalized weakness in a patient with

ALS.[196] Acute, generalized neuromuscular failure also occurred after a long-term botulinum toxin therapy in a patient with no underlying disorder other than posttraumatic lower-limb spasticity.[199] In one study,[363] local botulinum toxin application caused remote F-wave changes suggestive of decreased α-motoneuron excitability, possibly through reduction of muscle spindle activity. Occasional patients develop an exaggerated muscle weakness remote from the injected site.[36,75] Recording surface EMG helps quantitate the paralyzing effect of botulinum toxin.[82,84]

6. OTHER DISORDERS

A variety of natural toxins of animal, plant, and bacterial origin can cause disorders of NMT.[303] Animal toxins include those from venomous snakes,[64,310,353] arthropods, certain marine creatures, dart-poison frogs, poisonous fish, shellfish, and crabs. These toxins act at single or multiple sites of the neuromuscular apparatus, interfering with voltage-gated ion channels, ACh release, depolarization of postsynaptic membrane, or generation and spread of muscle action potentials.

Tick Paralysis

Available data suggest that this neurotoxin affects either the nerve terminal or the neuromuscular junction. The paralytic condition, reported worldwide, results from infestation by the gravid female tick Dermacentor andersoni (wood tick) or Dermacentor paridulis (dog tick) in the United States and Ixodes holocyclus (scrub tick) in Australia. Most cases involve young children, especially girls with long hair in spring or summer when ticks strike. The symptoms and signs begin 5–7 days after the tick has embedded. During this latent period, the organism, attached near the hairline, may remain unnoticed. The toxin probably prevents depolarization in the terminal axons by altering the ionic conductance that mediates action potentials in the nerve. Like other potent biotoxins such as tetrodotoxin and saxitoxin, tick toxin blocks the inward flux of sodium ions at sensory and motor nerve terminals and at internodes. Tick toxin may also interfere with release of ACh at the nerve terminal but not with its synthesis or storage.[206] Intracellular studies of hamsters paralyzed by tick toxin, however, have shown normal size and frequency of MEPP and normal quantal content of EPP.[195]

Illness begins with general symptoms such as irritability and diarrhea. Weakness initially affects the lower limbs and, within a day, spreads to the upper limbs. Paralyses of the bulbar and respiratory musculature, although now rare, pose a major threat until the removal of the embedded tick. Other features include dysarthria, dysphagia, blurred vision, facial weakness, and reduced muscle stretch reflexes. Occasional patients complain of numbness and tingling of the limbs. Removal of the tick usually leads to rapid improvement. Application of heat or petroleum jelly causes the tick to withdraw from the skin, allowing its gentle separation in one piece with a forceps.

Electrophysiologic studies in a few confirmed cases have consistently shown reduced CMAP amplitude.[58,258,327] In one series of six patients,[344] clinical and electrodiagnostic findings failed to adequately distinguish tick paralysis from GBS. In another study,[327] muscle action potentials changed little on repetitive stimulation at 50 Hz. Mildly increased distal motor and sensory latency during the paralytic phase returned to normal after clinical recovery. Persistent weakness and the presence of fibrillation potentials in some cases after the removal of the tick suggest a structural lesion of distal motor axons.[81]

Effects of Drug or Chemicals

The administration of some drugs, notably kanamycin and neomycin and all other polypeptide aminoglycoside antibiotics, may cause abnormalities of NMT.[18,151] At low rates of repetitive nerve stimulation, the muscle action potentials show a decremental response, although facilitation after exercise typically exceeds that seen in MG. In rats, a small MEPP amplitude and an abnormally low EPP mean quantum content suggest combined pre- and postsynaptic effects.[72] Another type of abnormality is produced experimentally with hemicholinium, which impairs ACh synthesis.[77] Myasthenia-like weakness may also develop during procainamide therapy.[216] Extended use of nondepolarizing neuromuscular blocking agents

such as vecuronium, pancuronium, and atracurium can produce prolonged neuromuscular paralysis, imitating a myasthenic syndrome.[23,301] Hypermagnesemia may cause a spectrum of symptoms and signs, including quadriparesis, probably by presynaptic defect as suggested by repetitive stimulation studies.[53] Tandutinib, an orally active tyrosine kinase inhibitor used in the treatment of leukemia, induces reversible muscle weakness and electrophysiologic changes consistent with NMT abnormalities.[170] Numerous drugs affect NMT, producing only subclinical effects concealed by a high margin of safety. Abnormalities may become clinically evident in cases of drug overdoses as reported in children with carbamazepine intoxication.[367]

The use of penicillamine may herald the clinical onset of myasthenia in rheumatoid arthritis[80] and, less commonly, in Wilson's disease.[12] The clinical and electrophysiologic characteristics, although indistinguishable from those of idiopathic MG, improve after discontinuation of the drug.[6] The degree of jitter shows positive correlation with the duration of administration but not with the dosage of penicillamine.[4] This disorder and idiopathic autoimmune MG probably share a similar pathophysiology, including reversible elevation of antireceptor antibodies, which results in quantitative reduction in available junctional ACh receptors.[158] These data suggest that penicillamine produces an MG by initiating a new autoimmune response rather than by enhancing existing abnormalities.

Exposure to an organophosphate insecticide, which inhibits AChE, causes flaccid paralysis. Organophosphate poisoning can also produce a subacute postsynaptic neuromuscular syndrome without marked symptoms of acute toxicity.[117] In vitro microelectrode studies in rats showed an increase in their half-decay times, but no reduction in MEPP amplitude or EPP quantal content. Trains of stimuli induced sustained endplate depolarization via summation of a prolonged EPP, a phenomenon enhanced by edrophonium and abolished by D-tubocurarine. Sustained endplate depolarization probably accounts for a CMAP decrement to repetitive nerve stimulation and weakness seen in acute organophosphate intoxication.[192] Electrophysiologic studies demonstrate extra discharges following the initial CMAP in response to a single nerve stimulus.[284,343] Other findings include decrement-increment response at higher rates of stimulation, a tendency accentuated by administration of edrophonium (see Fig. 18-11 in Chapter 18) and normal nerve conduction studies (NCSs) during acute stages.[190,302,350] In one series of acute organophosphate poisoning,[311] reduced diaphragmatic CMAP amplitude after phrenic nerve stimulation correlated with the need for mechanical ventilation. Intravenous pancuronium partially abolishes the abnormalities to repetitive stimulation, probably by blocking the AChR located at the motor endplates.[33,34] Electrophysiologic studies can rapidly determine the efficacy of oximes in reactivating AChE.[35]

Lower Motoneuron Disorders

Defects of NMT also accompany MND and peripheral neuropathies. Experimental studies suggest the diminution of the immediately available store of ACh as the cause of transmission failure during nerve regeneration. Alternatively, a defect may lie in the propagation of impulses along the terminal portion of the nerve, showing abnormally prolonged refractory periods. In these cases, repetitive stimulation results in a progressive CMAP decrement, minimal at low rates and progressively more prominent at faster rates in contrast to the changes seen in MG.[111] Posttetanic potentiation and exhaustion may also occur.

Muscle Diseases

In myotonia and periodic paralysis, a decremental response on repetitive stimulation results from increasing muscle membrane refractoriness associated with recurring discharges (see Chapters 18-8 and 28-2). Unlike the pattern seen in MG, the decrement occurs regardless of the rate of stimulation, showing a steadily progressive reduction in amplitude with no tendency for repair at the fifth or sixth stimulus. Immediately after exercise, CMAP amplitudes diminish in proportion to the number of refractory muscle fibers. The amplitude returns to resting values in 15 to 30

seconds. Thus, the exercise first suppresses muscle excitability followed by recovery, as opposed to the initial posttetanic potentiation and subsequent exhaustion seen in MG. The decremental response in myotonia may erroneously suggest defective neuromuscular transmission. Improper interpretation of such findings may account for alleged coexistence of myotonic dystrophy and MG in a few reported cases.

In a small series, a patient with proximal myotonic myopathy (DMII) showed no postexercise depression[290] despite the clinical resemblance to myotonic dystrophy (DMI) (see Chapters 18-8 and 28-2). In McArdle's syndrome and other muscle glycogenoses, weakness increases with exertion, which induces electrically silent muscle contractures (see Fig. 12-3 in Chapter 12). Thus, CMAP amplitudes progressively decline as contractures develop in response to rapid repetitive stimulation.

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27

Myopathies

Abbreviations: AChR—acetylcholine receptor antibody, ACTH—adrenocorticotropic hormone, ALS—amyotrophic lateral sclerosis, ATP—adenosine triphosphate, CK—creatine kinase, CMAP—compound muscle action potential, CMD—congential muscular dystrophy, CMTI—Charcot-Marie-Tooth Type I, CMTX—Charcot-Marie-Tooth X-linked, CPEO—chronic progressive external ophthalmoplegia, CPT—carnitine palmitoyltransferase, CRD—complex repetitive discharge, CSF—cerebrospinal fluid, CT—computed tomography, DAG—dystrophic-associated glycoproteins, DM—Duchenne muscular dystrophy, DMI—myotonic dystrophy Type I, DMII—myotonic dystrophy Type II, DMRV—distal myopathy with rimmed vacuole, EMG—electromyography,

FSH—facioscapulohumeral, GNE—UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene, GOT—glutamic-oxaloacetic transaminase, GPT—glutamic pyruvictransaminase, HAM/TSP— HTLV-I associated myelopathy or tropical spastic paraparesis, HIBM—hereditary inclusion body myositis, HIV—human immunodeficiency virus, HMG-COA—3-hyroxy-3-methylgutaryl coenzyme, HTLV—human T cell lymphotrophic virus, HypoPP—hypokalemic periodic paralysis, IBM—inclusion body myositis, IVIG—intravenous immunoglobin, LDH—lactate dehydrogenase, LG—limb girdle, MELAS—mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke, MERRF—myoclonic epilepsy with ragged-red fibers, MG—myasthenia gravis, MND—motor neuron disease, MRI—magnetic resonance imaging, MUNE—motor unit number estimate, MUP—motor unit potential, NCS—nerve conduction study, NEM—nemaline myopathy, NMT—neuromuscular transmission, PCR—polymerase chain reaction, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy

1. INTRODUCTION

Myopathies, defined as any disorders with primary pathology involving the muscle tissue, include genetically determined disorders and those of a toxic or inflammatory nature. Of these, muscular dystrophies have a clearly delineated mode of genetic transmission and a progressive clinical course, whereas congenital myopathies have a less well-defined pattern of inheritance and a relatively benign clinical course. Some myopathies also result from an inborn error of metabolism as part of a hereditary systemic disorder. In addition, a wide variety of inflammatory processes such as dermatomyositis and inclusion body myositis (IBM) affect the muscle. Dysmaturation myopathy without specific histochemical or cytoarchitectural characteristics accounts for many cases of hypotonia in infancy. Although patients with a myogenic disorder develop such weakness as one of the essential features, not all floppy infants have a primary muscle disease (see Chapter 29-10). Overall, disorders of muscle constitute less than 10% of the identifiable causes of weakness during infancy. A disease of the central nervous system commonly produces so-called cerebral hypotonia. Other nonmyogenic etiologies include spinal muscular atrophy (SMA), poliomyelitis, inflammatory polyneuropathy, myasthenia gravis (MG), and botulism. Central sleep apnea may accompany a variety of neuromuscular syndromes, causing excessive daytime sleepiness. Myalgia may herald the illness as a presenting symptom in some patients with a wide variety of myogenic disorders.

Differential diagnosis depends on the pattern of inheritance, the distribution of muscle weakness, and the time course of progression. Recessively inherited disorders most often show loss of function: homozygous or hemizygous patients have only copies of the defective gene, producing little or no functional protein. In contrast, dominantly inherited disorders most often show change of function: heterozygous patients have both normal and mutant copies of the gene, which produces an abnormal protein that causes dysfunction of the cell. Categorization of inherited disorders simply by their inheritance pattern thus affords some prediction concerning the underlying biochemical defect.

Useful screening tests include determination of creatine kinase (CK) level[198] and, in selected cases, muscle biopsy.[377] Patients with idiopathic increase in serum CK level, or hyper-CK-emia, have a benign prognosis showing no muscle damage with exercise.[337] Electromyographic (EMG) studies and analysis of force help delineate the physiologic mechanism of weakness and fatigue. Muscle biopsy specimens provide histologic and histochemical confirmation. Some advocate needle biopsies over the traditional surgical techniques.[222] Additional studies of interest include computed tomography (CT) and magnetic resonance imaging (MRI).

Despite the advent of gene analysis, the diagnostic use of electrophysiologic technique still has its place as a screening test. Needle studies contribute not only in differentiating myogenic from neurogenic paresis but also in delineating

the distribution of abnormalities and categorizing dystrophies and myopathies.[144,190] The patterns classically associated with myopathy may occasionally result from neurogenic involvement. This confusing feature develops in late stages following complex changes of denervation and reinnervation. Nerve conduction studies (NCSs) also mimic a neuropathic process of the motor axons with a reduction in amplitude of compound muscle action potentials (CMAPs) and preservation of sensory nerve potentials. Neuromuscular transmission (NMT) studies show no abnormality in primary disorders of muscles. This chapter describes a simplified overview of the major disorders commonly encountered in an electrophysiologic laboratory with emphasis on clinical and physiologic features rather than the molecular mechanism, which currently dominates the field.

2. MUSCULAR DYSTROPHY

Muscular dystrophy comprises a group of inherited muscle diseases with a progressive clinical course from birth or after a variable period of apparently normal infancy. Most types result from a primary myogenic lesion in the form of muscle fiber degeneration. The disease process apparently spares the muscle spindle preserving normal proprioceptive function.[341] A currently accepted classification based on the mode of inheritance and distribution of muscle degeneration has four main categories of muscular dystrophy, which encompass most patients: Duchenne, Becker, fascioscapulohumeral (FSH), and limb-girdle (LG) varieties. Other categories include oculopharyngeal dystrophy, hereditary distal myopathies, scapuloperoneal syndrome of Emery-Dreifuss type, congenital muscular dystrophy, and myotonic dystrophy Type I (DMI) and Type II (DMII). Differential diagnosis depends on the clinical features, genetic mode of inheritance, electrophysiologic patterns, and histologic characteristics.

The discovery of the protein product named dystrophin has transformed clinical concepts of muscular dystrophy.[242] Dystrophin forms a part of a large oligomeric complex of sarcolemmal glycoproteins, which includes dystroglycan. A myopathy results from mutation at Xp21, a specific locus on the short arm of the X chromosome. Any mutation at the same locus should affect the dystrophin, causing a variant of dystrophinopathy. Carriers with a myopathy and normal karyotype may have a dystrophin deficiency as evidenced by immunohistochemical studies showing a mosaic of fibers with and without dystrophin. The proportion of dystrophin-deficient fibers, however, does not correlate directly with the degree of clinical weakness in manifesting carriers.

The dystrophin gene has more than 70 exons containing 2.4 million bases, nearly 1% of the haploid genome. The 400 KD proteins contain 24 repeats of a spectrin-like motif that forms alpha helices. The amino-terminal and carboxy-terminal ends have homology to the actin-binding and calcium-binding domains of alpha-actinin. The protein, located under the muscle membrane, plays an essential role in maintaining membrane integrity during contraction.

Dystrophin acts as a functional link between cytoskeletal proteins and the extracellular matrix via transmembrane dystrophin-associated glycoproteins (DAGs). Components of DAG so far identified include dystroglycans, sarcoglycans, sarcospan, syntrophins, and dystrobrevins. Duchenne and Becker dystrophies collectively belong to the entity termed *dystrophinopathy*, whereas LG dystrophies show mutations in the genes for sarcoglycan.[265] The clinical spectrum of the dystrophinopathies ranges from a severe form presenting at birth to an asymptomatic elevation of CK. Females may present as a manifesting carrier or severe phenotype with expression of the abnormal gene as an X-autosome translocation or monosomy X. Another rare type of Duchenne-like muscular dystrophy, named severe childhood autosomal recessive muscular dystrophy,[314] results from a defect of any one of four genes encoding for the sarcoglycan complex. Pathogenic mutations in each gene determine a group of disorders now called sarcoglycanopathies.[80]

Duchenne Muscular Dystrophy

Duchenne dystrophy, also known as the pseudohypertrophic variety, has X-linked recessive inheritance.[114] All mothers of affected sons carry the diseased gene. These phenotypically normal

females transmit the disease to 50% of their sons. In Klinefelter syndrome, with the karyotype 47, XXY, the presence of the two active X-chromosomes accounts for the milder symptoms seen in an affected child.[362] This most common muscular dystrophy has an incidence of approximately 1 in 3500 male births. Female carriers, although generally unaffected, may suffer from a very mild dysfunction with hypertrophic calves, as predicted by the Lyon hypothesis based on disproportional X-inactivation.[177] Symptomatic young girls, if not carriers, have childhood muscular dystrophy of autosomal recessive inheritance. Molecular biologic techniques identified the primary biochemical defect based solely on the chromosomal location.[174]

In Duchene dystrophy, mutations of the dystrophin gene cause an early termination or deletion of the carboxy-terminal or amino-terminal ends, resulting in a nonfunctional protein. A large oligomeric sarcolemmal complex associated with dystrophin includes the laminin-binding glycoprotein called dystroglycan, which provides a linkage to the extracellular matrix. The absence of dystrophin leads to a drastic reduction in all of the dystrophin-associated proteins. Severe childhood autosomal recessive muscular dystrophy shows a similar phenotype with a specific deficiency of the 50 KD dystrophin-associated glycoprotein called sarcoglycan. This causes the disruption of the linkage between the subsarcolemmal cytoskeleton and the extracellular matrix, rendering muscle cells susceptible to necrosis.[15] The main pathologic sequence of events in the early stages consists of inflammation[71] and repeated episodes of muscle fiber necrosis and regeneration. Incomplete regeneration reduces the number of muscle cells, rendering some fibers hypertrophic and others atrophic. Progressive accumulation of collagen finally replaces the muscle cells. Preservation of extraocular muscle function suggests protective properties of fast-twitch fibers against degeneration.

Proximal weakness of the leg begins during early childhood, although histologic evidence indicates that abnormalities already exist at birth. The child normally attains the initial developmental milestones such as raising the head or sitting upright. Early difficulty in standing or walking may give an erroneous impression of clumsiness. Weakness becomes apparent by age 3–4 years with inability to run or to climb stairs. Patients tend to walk on their toes with their feet externally rotated and, on standing up from the floor, show Gower's sign or "climbing up legs to stand." Weakness usually begins in the proximal and only occasionally in the distal musculature, involving primarily the hip and knee extensors, followed by the muscles of the shoulder girdle. The disease progresses slowly and may even remit as natural growth temporarily compensates for the weakness. Neurologic findings depend on the stage of illness. Muscles harden with rubbery consistency, which leads to reduced or absent stretch reflexes. The quadriceps degenerate most, but the muscles of the shoulder girdle also show prominent abnormalities. Later, weakness becomes diffuse, sparing only the extraocular muscles. Other features include macroglossia, mild nonprogressive mental retardation seen at birth in 30%–50% of children with IQs ranging from 50 to 90 and poor cognitive processing.[173]

In advanced stages, the patient develops severe kyphoscoliosis, cardiomyopathy, and respiratory distress as the result of intercostal and diaphragm involvement. Cardiomyopathy may result from abnormal baseline myocardial blood flow.[150,390] Severe spine deformities may cause upper motoneuron abnormalities, which in turn lead to urinary dysfunction.[65] The calf muscle, although initially strong, develops pseudohypertrophy as do the deltoid, quadriceps, and gluteal muscles. With a steady downhill course, frequent falls force 90% of children into a wheelchair before age 12 years. Contractures of the joints prevent limb movement and the patients eventually die usually by age 20. An unusual combination of this dystrophy with Charcot-Marie-Tooth disease Type I (CMTI) resulted in devastating myogenic and neurogenic deficits.[444]

The 6-minute walk test may serve as an outcome measure for natural history and therapeutic trails.[259,261] A quality-of-life questionnaire, which captures physical limitations rather than generic health, serves better for patients with neuromuscular disorders.[361] Some advocate the use of a pediatric quality-of-life inventory neuromuscular module as an outcome measure in clinical trials.[94]

Prenatal studies of amniotic fluid usually show normal levels of CK. The newborn may have abnormal values, which imply definite probability, although normal values do not necessarily rule out the diagnosis. A markedly elevated serum CK during the first year often heralds the clinical onset of illness. The values then fall gradually as the disease advances but do not return to normal. No other neuromuscular disease has such an extremely high CK value. Other enzymes that show nonspecific elevation include pyruvate kinase, aldolase, lactate dehydrogenase (LDH), glutamic-oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT). Cardiac involvement results in typical electrocardiographic changes that consist of a tall, right precordial R wave and a deep limb and precordial Q wave together with characteristic abnormalities seen by cardiac echo and positron emission tomography. Muscle biopsy material usually reveals variations in muscle fiber size, necrotic fibers, phagocytosis, regenerating basophilic fibers, and vesicular nuclei. Other features include swollen, rounded fibers with homogenic eosinophilic material, mildly increased internal nuclei, degeneration of intrafusal muscle fibers without regeneration and a nonspecific increase in satellite cells detected with electron microscopy.

Diagnosis depends on clinical presentation: a 100- to 700-fold elevation in CK, appearance of fatty degeneration in muscle biopsy tissue, direct measure of dystrophin protein by immunohistochemistry or Western protein blotting, and antibody detection in muscle biopsy specimens. In many cases, DNA-based diagnosis and short tandem repeat analysis also serve as prenatal screening for Duchenne/Becker muscular dystrophy.[148] About 65% of dystrophin mutations result from deletions. Southern analysis and polymerase chain reaction (PCR) detect nearly 98% of these deletions. Either RNA analysis or fetal protein analysis suffices in assessing point mutations. Laboratory diagnosis also exploits DNA analysis of the dystrophin gene and immunoassay of muscle with antibodies directed against different regions of the protein product.[270]

Corticosteroids, though limited in therapeutic scope, represent the best treatment option currently available.[13,126] Prednisone produces a rapid increase in muscle strength with maximal effect at a dosage of 0.75 mg/kg or less.[271] Alternate-day prednisone therapy effectively increases strength but does not sustain the improvement to the same extent as daily therapy or mitigate the side effects. Many patients do well on long-term ventilation, but some choose to discontinue this method of life prolongation.[21,172] Advancing ages at death, more for white males than black males, reflect improvements on the treatment of muscular dystrophy.[200] Umbilical cord–derived hematopoietic stem cell transplantation has proven not efficacious.[196]

Different stages of illness give rise to characteristic EMG abnormalities with features of myopathy. Insertion of the needle elicits normal or prolonged activity initially but very little potential in the advanced stage, when fibrosis has replaced muscle tissues. Fibrillation potentials and positive sharp waves appear early (see Fig. 14-8E in Chapter 14) but to a much lesser extent than in myositis or motoneuron disease (MND). Low-amplitude, short-duration motor unit potentials (MUPs) result from random loss of muscle fibers. When recruited in abundance (see Figs. 14-16 and 14-19B right in Chapter 14), these potentials produce a characteristic sound resembling a shower of fibrillation potentials. In mildly affected muscles, the abnormalities, limited in degree and distribution, could escape detection without careful exploration. Needle studies generally offer little help in detecting carrier status. In one series, patients had significantly slower muscle fiber conduction velocities in the biceps brachii (2.4 ± 0.9 m/s) than matched control children (3.2 ± 0.5 m/s), possibly reflecting an increased diameter variation, which also causes a complex and long-duration MUP.[81]

Becker Type Muscular Dystrophy

The Becker type of muscular dystrophy, a benign, X-linked recessive dystrophy, also results from mutation in the dystrophin gene, leading to relatively mild clinical features. Compared with Duchenne dystrophy, the Becker type has a later onset and considerably longer and milder clinical course with survival into middle adulthood.[39] Dystrophin mutations give rise to the milder phenotype that results from an abnormal protein still

maintaining intact amino- and carboxy-terminal ends. An internal deletion that maintains the reading frame, for example, may merely reduce the number of repeats. Some patients may remain asymptomatic possibly because of the overexpression of the dystrophin-related protein in regenerating muscle fibers.

The initial symptoms at ages 5 to 20 years consist of weakness of the pelvic girdle and legs and muscle cramps after exercise. Physical examination shows hypertrophied calves, shortening of the Achilles tendon, flexion contractures, and depressed stretch reflexes. The patient develops difficulty in climbing stairs and rising from the floor but usually walks 25 to 30 years after onset, some with contractures and skeletal deformities. Myocardial disease and myalgia may constitute early primary features, unrelated to the severity of skeletal muscle damage.[297] These patients, albeit with the risk of cardiac failure as a late complication, usually live into the sixth or seventh decade. Other abnormalities include cryptorchidism, hypogenitalia, testicular atrophy, mental retardation, electrocardiographic changes, cardiac dysfunction, and elevated CK values, especially at a young age. An unfortunate coexistence of this dystrophy with X-linked Charcot-Marie-Tooth disease (CMTX) caused a unique phenotype with severe, diffuse wasting and rapid progression.[42]

Needle studies show nearly symmetric abnormalities in the proximal muscles. Fibrillation potentials and complex repetitive discharges (CRDs) abound in the paraspinal muscles. A small, polyphasic MUP shows an early recruitment. Muscle biopsy specimens in an early stage look like those of Duchennes dystrophy with necrotic, basophilic, and large hyaline fibers. In one series of 20 patients, histologic studies revealed conspicuous fiber necrosis and regeneration in younger patients and chronic myopathic changes such as moth-eaten fibers, fiber splitting, and hypertrophic fibers in older patients. Muscle biopsy material revealed fiber atrophy and hypertrophy with many split and angulated fibers and clumps of pyknotic nuclei.

Facioscapulohumeral Dystrophy

Inherited as an autosomal dominant trait, FSH dystrophy affects both genders equally with an incidence of approximately 1 per 100,000. The disorder, with the responsible gene localized to the telomeric region of chromosome 4q35, shows a complete penetrance and variable expression.[411] The vast majority of cases, termed *FSHD I*, result from a heterozygous partial deletion of a critical number of repetitive elements D4Z4, which induces a chromatin change and loss of control over gene expression.[411] Some 5% of patients, termed *FSHD II*, have no D4Z4 repeat contractions but show loss of DNA methylation and heterochromatin markers similar to those seen in FSHD I.[95] Neurotrophins, which guide muscle development and regeneration, may play a role in the pathogenesis.[17] Some authors prefer the term *FSH syndrome* with subdivisions into neurogenic, myopathic, and rare myositic entities. After some months to years, initial myositic features may lead to clinical patterns indistinguishable from the myopathic type. Some patients have congenital absence of the pectoralis, biceps, or brachioradialis muscles.

The disease typically begins toward the end of the first decade, although the symptoms may appear within the first 2 years of life. Early signs, often missed by patients and physicians, include variable degree of mimetic muscle weakness accounting for myopathic faces. Characteristic features include protruded lips, transverse smile, weak eye closure, and inability to wrinkle forehead. Some patients also develop tongue atrophy[460] or mild dysphagia[455] but no major respiratory impairment.[395] The loss of arm function, a common initially recognized symptom, results from weakness of the pectoralis major, latissimus dorsi, biceps brachii, triceps brachii, and brachioradialis muscles. Attempted arm abduction elevates the weak trapezius, giving rise to the typical appearance called trapezius hump. The disease affects the lower limbs later than the upper limbs. Beevor's sign, or the elevation of umbilicus on attempted sit-up from supine position, serves as a prelude to functional weakness of abdominal wall muscles. The patient has bilateral myogenic foot drop (see Chapter 25-8) as the presenting sign in a variety known as scapuloperoneal dystrophy.[414] Here, despite weakness of the tibialis anterior, peroneal nerve motor conduction study remains normal with the distal sparing of extensor

digitorum brevis. Atypical phenotypes abound[429] and include facial-sparing scapular myopathy, LG muscular dystrophy, distal myopathy, and asymmetric brachial weakness.[134] Conversely, clinically typical FSH families may show no linkage to chromosome 4.[415]

The very slowly progressive deficit causes only minor disability and little alteration in life expectancy. Many patients, however, suffer from pain and have reduced quality of life.[316] In one series, right-handed patients had greater preservation of strength on the left, suggesting a role of mechanical factors in the progression of muscle weakness.[319] Some patients develop isolated axial myopathy and bent spine syndrome.[209] In advanced stages, patients develop lordosis and pelvic girdle muscle weakness but no cardiac myopathies. The infantile variant seen in the first 2 years of life has a rapid progression and poor prognosis. The devastating combination of this entity with CMT resulted in severe generalized weakness and early death.[58] Some advocate the use of the FSHD clinical score to standardize clinical evaluation in longitudinal studies.[224]

Unlike in Duchenne or Becker dystrophy, CK levels tend to remain normal, but elevated pyruvate kinase serves as a sensitive test. Biopsy material reveals variably sized fibers of both types, groups of small angular fibers reminiscent of denervation atrophy, and inflammatory responses. In the initial stages, EMG studies show only a limited abnormality, which may escape detection even in clinically weak muscles. The use of quantitative EMG with multi-MUP analysis may help improve the diagnostic sensitivity.[330] The jitter studied by single-fiber electromyography (SFEMG) also remains within normal limits in the facial muscles.[423] Well-advanced cases show a low-amplitude, short-duration, polyphasic MUP with early recruitment for the degree of muscle force. The presence of spontaneous discharges suggests the neuropathic form of this syndrome.

The differential diagnosis consists of all neuromuscular disorders with weakness over a facioscapulohumeral distribution. These include myositis, spinal muscular atrophy (SMA), MG, and congential myopathies like myotubular myopathy, central core disease, and nemaline myopathy. Studies of NMT and paraspinal EMG help exclude MG and myositis with weakness in the facioscapulohumeral distribution. Reported therapeutic regimens such as strength training and administration of albuterol may improve muscle function.[430]

Limb-Girdle Dystrophy

The designation LG dystrophy includes a heterogenous group of hereditary disorders involving multiple different genetic loci. Progressive weakness mainly affects the proximal muscles of the shoulders, pelvic girdle, and upper and lower limbs. Symptoms and signs vary, usually leading to severe disability by midlife. It affects men and women equally with an autosomal dominant or recessive pattern of inheritance. Both sporadic and familial cases present similar clinical and histologic features. The current classification of LG dystrophy, redefined in 1995 as face-sparing, proximally predominant, progressive muscular dystrophies with elevated CK levels and dystrophic features on muscle biopsy, include several autosomal dominant (LGMDI) and autosomal recessive (LGMDII) disorders.[452] Superimposed lettering system denotes the chronologic order of chromosomal linkage for both dominant and recessive categories (Table 27-1).

The dystrophin-glycoprotein complex links the extracellular matrix to the subsarcolemmal cytoskelton proteins. The sarcoglycan subcomplex comprises four transmembrane glycoproteins: α-, β-, γ-, and δ-sarcoglycan, whose gene mutations cause LGMD2D, 2E, 2C, and 2F.[14] Mutated CAPN3 gene located on chromosome 15q15.1-q21.1 cause deficiency in muscle-specific, calcium-activated, neutral protease (calpain-3) responsible for a large disease spectrum called calpainopathy. Mutations in the caveolin-3 gene, first identified in patients with LGMD1C, can also lead to various clinical phenotypes, including LGMD2A, the most common type of LGMD in Western countries, distal myopathy,[245] hyper-CK-emia, rippling muscle disease, and unilateral calf atrophy.[154] Mutations in the dysferlin gene[275] may give rise to LGD2B, Miyoshi myopathy, or, less commonly, distal anterior compartment myopathy, or asymptomatic hyper-CK-emia. The expanding dysferlinopathy phenotype includes

Table 27-1 Limb-Girdle Dystrophies

INHERITANCE TYPE	GENE OR CHROMOSOME	ONSET DECADE	CK ELEVATION	REGIONS AFFECTED
Autosomal Dominant				
LGMD 1A	Myotilin	3rd–4th	2x	Distal greater than proximal weakness, vocal cords, allelic with myofibrillar myopathy
LGMD 1B	Lamin A/C	1st–2nd	3–5x	Resemble Emery-Dreifuss Proximal muscles and heart, joint contractures
LGMD 1C	Caveolin-3	1st	4–25x	Proximal muscles
LGMD 1D	6p	3rd–5th	2–4x	Proximal muscles, cardiomyopathy
LGMD 1E	7q	1st	Nl	Proximal muscles
Autosomal Recessive				
LGMD 2A	Calpain-e	1st–2nd	3–15x	Proximal and distal muscles
LGMD 2B	Dysferlin	2nd–3rd	10–50x	Proximal and distal muscles Allelic to Miyoshi
LGMD 2C-F	α, β,γ,δ-sarcoglycans	1st–3rd	5–40x	Phenotype of Becker dystrophy
LGMD 2G	Telethonin	2nd	3–17x	Proximal greater than distal muscles
LGMD 2H	TRIM32	1st–3rd	2–25x	Proximal greater than distal muscles
LGMD 2I	Fukutin-related protein (FKRP)	1st–3rd	10–30x	Proximal greater than distal muscles FKRP defects also cause CMD
LGMD 2J	Titin	1st–3rd	2x	Proximal and sometimes distal muscles
LGMD 2M	POMGNT1*	Birth		Mutations also associated with muscle-eye brain diseases

CK, creatine kinase; CMD, childhood muscular dystrophy; LGMD, limb-girdle muscle dystrophy; NL, normal. (Modified from Ropper and Samuels.[345])

facial weakness and dysphagia.[447] The complicating scheme of classifying this entity into more than 20 subgroups reflects recent advances of genetic analyses. For the purpose of this discussion, a brief description suffices to highlight typical clinical features (Table 27-1).

The illness often begins during the second or third decade of life with involvement of the pelvis and high elevation of serum CK level. Weakness soon spreads to the shoulder girdle, typically but not always sparing the facial muscles.[317] Symptoms, restricted to these areas for many years, show only mild progression.[396] Rarely, diaphragmatic weakness heralds the onset of a LG sydrome as the presenting symptom. Cardiac involvement may exceed skeletal muscle weakness.[247] Some patients have weakness of only one limb without developing other characteristic features or only one muscle as in quadriceps myopathy. The disease process usually runs a more rapid course in the tibialis anterior than in the gastrocnemius. The calves and deltoid may show pseudohypertrophy. Despite eventual confinement to a wheelchair, the patient usually has a normal life span. Some cases of LGMD 2I may develop muscle pain and myoglobinuria.[256]

The name LG syndrome appropriately denotes the heterogeneity of this entity with the subdivision into myogenic and neurogenic types based on clinical, histologic, and electrophysiologic findings. In addition, a clinical syndrome of progressive proximal LG distribution may characterize other well-defined conditions. These include chronic myositis, MG, and various metabolic and congenital myopathies, such as late-onset acid maltase deficiency and carnitine deficiency. Additionally, SMA also has a similar distribution of weakness, making clinical differentiation difficult. In one series of 18 patients with proximal weakness in the LG distribution,[79] histologic evaluation established a firm diagnosis only in four cases: two with spinal muscular atrophy and two others with muscular dystrophy. Needle studies revealed myopathic changes in 11, denervation in 3, and inconclusive results in 4. In another series of 20 patients, SFEMG confirmed the original diagnosis of myopathic LG syndrome in 11 and chronic SMA in 5, and helped differentiate the other four cases into myopathic and neuropathic varieties.[372]

Oculopharyngeal Muscular Dystrophy

Oculopharyngeal dystrophy, a rare form of progressive ophthalmoplegia, affects French-Canadian families in an autosomal dominant fashion with the responsible gene localized to chromosome 14q11.2-q13. A large number of families have short expansions of GCG repeat encoding a polyalanine tract.[284] Progressive ptosis and dysphagia develop late in life with or without extraocular muscle weakness, although a childhood myopathy occasionally affects the same muscle group. Ptosis has a negative effect on swallowing, which improves if the patient assumes a slightly flexed head position.[98] Differentiation from MG poses a major problem clinically. Patients with oculopharyngeal dystrophy have absent titers for acetylcholine receptor antibody (AChR) and a negative edrophonium test. Muscle biopsy specimens show variation in fiber size, occasional internal nuclei, small angulated fibers, and a moth-eaten appearance of the intermyofibrillar network when stained with oxidative enzyme. A clinical and electrophysiologic review showed no evidence for clear association with peripheral neuropathy.[137,191]

Progressive external ophthalmoplegia can also develop in a number of congenital myopathies such as centronuclear and myotubular myopathy and multicore disease.[192] This general category, classified as ocular myopathy, has either recessive or dominant inheritance and includes autosomal recessive oculopharyngodistal myopathy.[433] Slowly progressive ptosis starts at any age. Head tilts and wrinkling of the forehead compensate for levator muscle weakness. Later, the disease may involve extraocular and facial muscles but not the pupils. Patients may have elevated CK values and an abnormal sensitivity to d-tubocurare. Needle studies usually reveal no spontaneous activity. Brief, low-amplitude, polyphasic MUP shows an early recruitment in proximal muscles of the upper limbs. A neurogenic pattern with a large MUP may accompany the myopathic features. Conduction studies reveal a low-amplitude CMAP in the weak muscles. Repetitive nerve stimulation shows no decrement of muscle response.

Late-Onset Distal Myopathy

Primary muscle disease with a definite distal predilection includes a large series of adult-onset hereditary myopathy in Sweden and rare sporadic distal myopathy with early adult onset. The differential diagnoses include myotonic dystrophy and IBM, both of which characteristically cause atrophy of distal rather than proximal musculatures. Late-onset distal myopathy, first described by Welander,[450] has onset in adulthood, showing an autosomal dominant trait linked to chromosome 2p13.[3] Unlike most other forms of dystrophies, it predominantly affects the distal muscles of the upper and lower limbs. Weakness typically begins in the intrinsic hand muscles and, less commonly, in the intrinsic foot muscles. As the disease slowly progresses, the dorsiflexors of the wrist and foot become weak usually with nearly complete sparing of proximal musculature. Widespread weakness and wasting may occur, especially if the disease appears at an earlier age and worsens rapidly.

Quantitative sensory testings usually uncover a distal sensory disturbance most prominent for temperature. The neurogenic lesion affecting the peripheral sensory fibers may even precede the myopathic changes. Most patients have slightly elevated levels of serum CK. Muscle biopsy specimens show vacuolar changes and increased staining for spectrin and desmin as seen in denervated muscle fibers. These findings may support a neurogenic component in this dystrophy fulfilling the criteria for hereditary IBM (HIBM).[2] Needle studies demonstrate an abundance of low-amplitude, short-duration MUP during mild voluntary contraction.

Dysferlin-Deficient Dystrophy

A muscle gene "dysferlin" on chromosome 2p13 has an essential role in membrane repair. Mutation in this gene causes muscle fiber degeneration in dysferlin-deficient dystrophy.[32,320] Modifying factors may determine the clinical manifestations of the primary dysferlin mutation.[257] These include LGMD-2B, Miyoshi myopathy, or distal posterior compartment muscular dystrophy, and distal anterior compartment myopathy.[32,199,346]

Of these, Miyoshi myopathy has an autosomal recessive inheritance.[282] The disease affects young adults with the initial impairment in walking on the tiptoes, followed by difficulty in climbing stairs and standing. Muscle atrophy as detected clinically and with CT and MRI scans first involves distal muscles in the posterior compartment of the legs and forearms, sparing the intrinsic hand muscles. Asymptomatic subjects may have an elevated serum CK value as a prelude of the disease. Needle EMG reveals abnormalities consistent with myopathy. Muscle biopsy specimens show severe segmental necrosis and regeneration of myofibers with little inflammatory responses.

Other Distal Myopathies

Other hereditary distal myopathies include familial adult-onset muscular dystrophy with leukoencephalopathy,[434] late adult-onset tibial muscular dystrophy,[425] autosomal dominant myopathy caused by mutations within the slow skeletal muscle fiber myosin heavy chain gene, MYH7,[223] Nonaka myopathy, or autosomal recessive, quadriceps sparing, distal anterior compartment myopathy with rimmed vacuole formation,[398] which links to chromosome 9p1-q1, and oculopharyngodistal myopathy.[116]

Hereditary IBM (see Chapter 27-6) constitutes a heterogeneous group of neuromuscular disorders characterized by adult-onset, slowly progressive, usually distal but at times proximal weakness.[99] Most authors in Japan now equate hereditary IBM with Nonaka distal myopathy with rimmed vacuole (DMRV). Some of these patients may also develop cardiomyopathy.[66] Loss of function mutation in the UDP-N-acetylglucosamine 2-epimerase/N-acetylmamosamine kinase (GNE) appears to cause distal myopathy with rimmed vacuoles and hereditary IBM.[299,344,416] Some cases of hereditary rimmed vacuole myopathy show interstitial amyloid deposition in muscle tissue.[205]

Emery-Dreifuss Scapuloperoneal Syndrome

In a rare type of muscular dystrophy, the scapuloperoneal syndrome of Emery-Dreifuss type, patients

develop a triad of slowly progressive humeroperoneal weakness, early contracture, and cardiopathy with conduction defects.[120] Other names used to describe this entity include scapuloperoneal muscular dystrophy, scapulohumerodistal muscular atrophy, and humeroperoneal neuromuscular disease. Some families have a wide phenotypic spectrum. Most pedigrees show an X-linked inheritance but rare kindreds have autosomal dominant or recessive transmission.[52,135] Mutation of the responsible LMNA gene, which encodes the lamin A and C proteins, results in loss or reduction of emerin that serves as membrane anchor.[202]

Scapuloperoneal syndrome has both myopathic and neurogenic abnormalities, with weakness and wasting confined to the muscles of the shoulder girdle and the anterior compartment muscles of the lower limb. Clinical manifestations begin in the second decade, primarily involving deltoids, pectorals, and extensors of the hands, fingers, and feet and occasionally muscles of the face, relatively sparing the muscles of the pelvic girdle. Other features include early contractures with marked restriction of neck and elbow flexion. The patients also develop cardiopathy with atrioventricular block, atrial fibrillation, decreased ventricular rate, and exertional dyspnea, often dying suddenly as the result of cardiac arrest. Electrophysiologic studies usually reveal a short, polyphasic and relatively high-amplitude MUP, which recruits early and normal nerve conduction. Histologic studies of muscle show mixed patterns of neurogenic and myogenic changes with internal nuclei, necrotic fibers, round cell infiltrates, and occasionally Type l fiber predominance as well as rimmed vacuoles.[321]

A variant of this syndrome has onset at ages 3–11 years, with initial symptoms and signs of shortening of the Achilles tendon, flexion contractures of the elbows, weak shoulder girdle muscles, normal CK, and eventually death by cardiac arrest. Other possibly related entities include scapuloperoneal myopathy inherited as an autosomal dominant or X-linked recessive disease and scapulo-peroneal spinal muscular atrophy, a disorder of the anterior horn cells with autosomal dominant or X-linked recessive inheritance. Scapuloperoneal atrophy may primarily involve the peripheral nerve occurring sporadically without sensory abnormalities or as an autosomal dominant or autosomal recessive disorder with sensory loss. Rigid spine syndrome has similar clinical features except for cardiac conduction defects and mode of inheritance.[127,336]

Congenital Muscular Dystrophies

Congenital muscular dystrophies (CMDs) comprise a heterogeneous group of autosomal recessive disorders of a slow evolution with multiple contractures and generalized weakness.[269] The entity consists of two subgroups, one with a fairly homogeneous merosin-negative[117,292] and the other with heterogeneous merosin-positive cases with striking central nervous system abnormalities.[18,131,298] The merosin-negative CMDs usually show severe hypotonia, multiple contractures, delayed milestones, and normal mentation accompanied by a variable degree of central hypomyelination seen on neuroimaging. The merosin-positive CMDs include Fukuyama CMD linked to chromosome 9q encoding the protein Fukutin; muscle-eye-brain disease mapped to chromosome 1P32-P34; rigid spine syndrome with axial muscle weakness, early rigidity of the spine, and nocturnal respiratory insufficiency[139]; Ullrich disease characterized by proximal contracture combined with distal joint laxity; and Walker-Warburg syndrome.[269] Of these, Fukuyama CMD, represents an autosomal recessive disorder with mental retardation, epilepsy, and visual impairment.[168,359] Neuromuscular diseases associated with LMNA mutations include autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD1); dilated cardiomyopathy with conduction defect (DCM-CD); LGMD1B; CMT2BI; and LMNA-related CMD, which presents with infantile-onset myopathy and dropped head syndrome.[69] In all types of CMD, EMG shows typical changes of myopathy. Most patients with merosin-negative CMD have associated neuropathy characterized by uniformly slow motor NCS without signs of denervation.[334]

Other Dystrophies

Other dystrophies include benign hereditary myopathy, an autosomal dominant disorder, with

an extremely slow progression and a normal life expectancy, and autosomal recessive quadriceps myopathies,[246] which may represent a generalized myopathy despite selective quadriceps muscle atrophy and absent knee jerks. A dominantly inherited multisystem disorder, called proximal myotonic dystrophy or myotonic dystrophy Type II (DMII), has CCTG repeat expansion rather than CTG repeat seen in DMI despite phenotypical similarities between the two types (see Chapter 28-2).

3. CONGENITAL MYOPATHY

A number of congenital conditions have nonprogressive or only slightly progressive muscular weakness.[122,130] Some of these entities have morphologically distinctive structural alterations in muscle biopsy material. These conditions include central core disease, nemaline myopathy (NEM), myotubular or centronuclear myopathy, congenital fiber type disproportion, cytoplasmic body myopathy, fingerprint body myopathy, zebra body myopathy, and congenital hypotonia with Type I fiber predominance. Clinical features common to this group consist of generalized hypotonia after birth with several modes of hereditary transmission; congenital skeletal abnormalities such as high arched palate, long face, hip dislocation, and pes cavus; delayed motor milestones with no ability to run or jump; proximal weakness, thinned muscle bulk, and absent or decreased stretch reflexes; and slow or no progression. Concurrent structural cardiomyopathy may result in cardiac conduction abnormalities or contractile insufficiency.

Electrophysiologic features include a short-duration, small-amplitude polyphasic MUP and normal conduction studies. The diagnosis of these rare conditions primarily depends on histologic examination of the muscle, identifying distinctive pathologic features that may or may not represent the fundamental manifestations. In rare cases, two or more structural changes coexist in the same patient or in one family, possibly indicating abnormalities of Z-bands.[413] Muscle biopsy abnormalities include Type I fiber predominance or Type II fiber paucity and characteristic histopathologic and electromicroscopic changes, which virtually name the individual disorder.

Central Core Disease

Central core disease, a heterogeneous myopathy, shows typical core features in nearly all fibers as the common finding, irrespective of the mode of genetic transmission. Its pathogenesis, although unknown, probably relates to an abnormality of neural influence, which affects embryonic differentiation of muscle fibers. Infants occasionally have congenital hip dislocations, hypotonia shortly after birth, and delayed developmental milestones. Older children may have proximal weakness but no distinct muscular atrophy. Neither the patient nor the family recognizes the disease before the onset of skeletal deformities such as lordosis, kyphoscoliosis, and abnormalities of the foot. Malignant hyperthermia may complicate operative interventions in children with central core disease. For high-risk patients who require surgery for musculoskeletal defects, preoperative evaluation should include in vitro tests for this devastating phenomenon described later (see Chapter 27-4).

Muscle biopsy material shows a marked Type I fiber predominance. The central region of the muscle fiber contains compact myofibrils devoid of oxidative and phosphorylase enzymes reflecting the virtual absence of mitochondria.[113] These central areas, referred to as cores, show no histochemical reactivity with the oxidative enzyme. They commonly appear in Type I and to a lesser extent in Type II fibers. The resemblance of the cores to target fibers, which usually indicate denervation and reinnervation, supports the disputed neurogenic pathogenesis. Electrophysiologic findings vary but tend to show mixed myopathic-neuropathic features. Needle studies usually detect normal insertional activity, no spontaneous discharges at rest, and a small MUP with early recruitment. Electrophysiologic studies also show reduced amplitudes of muscle potentials with either normal or mildly slowed conduction velocity.

Nemaline Myopathy

This condition, called nemaline myopathy (NEM), either sporadic or inherited as an autosomal dominant trait, causes nonprogressive hypotonia that usually begins at a very early age. Mutations identified to date include α-actin

(ACTA1), α and β-tropomyosin (TRM3 and TRM2), tropin T (TNNT1), nebulin (NEB), and cofilin2 (CFL2). A unique subtype, NEM6, maps to chromosome 15q21-q23.[308] Although considered benign in older children and adults, it may cause early death in neonates and young infants mostly from respiratory insufficiency.[358] In the severe infantile form, increased axonal sprouting of the intramuscular nerve suggests maturational arrest of developing muscle or nerve fibers.[301] In addition to diffuse weakness, children show dysmorphism with reduced muscle bulk and slender musculature. The clinical features include elongated faces, high-arched palate, high-arched feet, kyphoscoliosis, dropped head,[239] and an occasional isolated respiratory failures.[451] Many have a slightly elevated level of serum CK. As a variant, a late-onset rod disease manifests initially as proximal muscle weakness at ages 37–60 years followed by a progressive course, leading to severe disability and death. Patients with sporadic late-onset NEM may respond favorably to intravenous immunoglobulin (IVIG) and immunotherapy[277] or stem cell transplantation.[41]

Patients and carriers both have a predominance of small Type I fibers in muscle biopsy specimens. Gomori trichrome stain shows the characteristic rod-shaped bodies, not apparent with other methods. These contain material identical to the Z-bands of muscle fibers, involving either Type I or Type II fibers, or both. The myopathy derives its name from the presence of these rod-like or thread-like (*nemaline* in Greek) structures seen in both fiber types lying under the sarcolemma. Rods, devoid of enzyme activity, stain bright red with trichrome and have periodic lines showing structural continuity with actin filaments. The number of rods, seen not only in NEM but also in other neuromuscular disorders and occasionally in normal muscles, shows no correlation with the severity of disease.[357] A repeated biopsy may find a dramatically decreased number of rods, implying a reversible anomaly of Z-discs.

Myotubular or Centronuclear Myopathy

In myotubular myopathy[388] or centronuclear myopathy,[368] fetal myotubes persist into adult life. This rare heterogeneous condition has central nuclei as the common feature but otherwise shows diverse clinical and genetic characteristics. Three subgroups, based on severity, mode of presentation, and genetic pattern, comprise (1) a severe neonatal X-linked recessive type,[385] (2) a less severe infantile-juvenile autosomal recessive type, and (3) a milder autosomal dominant type.[169] The autosomal dominant type progresses more slowly than the generally severe X-linked form, which may lead to death from respiratory insufficiency. Female heterozygous carriers, though usually asymptomatic, may develop progressive limb girdle and facial weakness.[400] The milder autosomal dominant type may show clinical features simulating FSH syndrome.[133] The affected infants have early difficulty in lifting their head after a normal labor and delivery. They can have hypotonia, ptosis, facial weakness, and extraocular palsy at birth. Patients can walk but cannot run. Some patients die in infancy from cardiorespiratory failure, but others live until adulthood with little progression and only mildly elevated serum CK. Those who survive suffer from generalized weakness with facial and extraocular muscle involvement.

Biopsy specimens show internal nuclei, absent subsarcolemmal nuclei and aggregates of mitochondria near the central nuclei. Myotubes resemble those seen in fetal muscle, thus the name, *myotubular myopathy*. The fetus-like dystrophin expression further suggests maturational arrest,[182] although sequential muscle biopsy findings indicate a progressive nature of disease in some cases.[89] The central part of the fiber, devoid of myofibrils and myofibrillar adenosine triphosphate (ATP), stains poorly with the ATPase reaction. Oxidative enzymes may show increased or decreased activity in the central region.

Electrophysiologic abnormalities include an excessive number of polyphasic, low-amplitude MUP, fibrillation potentials, positive sharp waves and CRD,[33,169] and normal motor and sensory NCS. These findings distinguish this entity as the only congenital myopathy consistently associated with spontaneous activities.[118] Occasional myotonic discharges may lead to an erroneous diagnosis of myotonic dystrophy, especially in a patient with distal weakness and ptosis. Two sisters with

otherwise typical centronuclear myopathy had clinical myotonia.[147]

Congenital Fiber Type Disproportion

In normal muscles, Type II fibers comprise more than 60% of the fibers and Type I, 30%–40%. A reversed relationship characterizes the histologic findings in some children with congenital hypotonia. Infants may have generalized weakness with dysmorphic features at birth. Additional signs include contractures as the major source of functional limitation, congenital dislocation of the hip joint secondary to intrauterine hypotonia, and other skeletal abnormalities such as deformities of the feet and kyphoscoliosis. The disease progresses for the first several years and then either stabilizes or improves slightly. Some patients have profound weakness of respiratory muscles, needing assisted ventilation from early infancy.[418] The patient has a short stature and fails to develop expected motor skills despite a normal or above normal mental capacity. A family history, if present, shows a variable pattern of inheritance.

The patient may have elevated CK values but not as a consistent finding. Muscle biopsy specimens show, in addition to fiber type disproportion, small Type I fibers, hypertrophic Type II fibers, and scattered internal nuclei. Needle EMG usually demonstrates a low-amplitude, short-duration MUP with early recruitment.

Other Congenital Myopathies

Advent of molecular techniques has commenced to alter the nosology of congential myopathies caused by unequivocal mutation.[151] Ultrastructural studies implicate the Z-disk as the site of the initial pathologic change with mutations in several Z-disk-related proteins, such as desmin, myotilin, αB-crystallin, filamin, and Bag3. Desmin myopathy, often familial and marked by accumulation of desmine, reveals a wide spectrum of clinical phenotypes and muscle pathology.[235] Its alternate term, *myofibrillar myopathy*, denotes the common pathologic feature, focal dissolution of myofibrils and accumulation of multiple proteins besides desmin.[397] Mutation in myotilin[366] and filamin,[207] both key Z-disk components, also causes myofibrillar myopathy in the spectrum of myotilinopathy.

In cytoplasmic body myopathy, weakness characteristically involves the face, neck, and proximal limbs as well as respiratory, spinal, and cardiac muscles. Patients may have scoliosis and cardiorespiratory failure especially after lung infection. They have elevated serum CK values and abnormal electrocardiograms. Muscle biopsy material reveals centrally placed nuclei, necrosis, fibrosis, and cytoplasmic bodies. Electrophysiologic studies show normal NCS and abnormal EMG consistent with myopathy sometimes showing myotonic discharges.[290] Cytoplasmic body myopathy characterized by proteinaceous inclusions in muscle tissue may cause diagnostic confusion with disorders such as IBM, myotonic dystrophy, and MND.[214]

Other entities include multicore myopathy with multifocal degeneration of muscle fibers,[123,464] fingerprint body myopathy with typical electromicroscopic features showing inclusions of complex lamellae arranged in fingerprint patterns, zebra body myopathy with distinct ultrastructual image of zebra bodies,[339] reducing body myopathy characterized by purple-gray periodic acid Schiff-negative sarcoplasmic masses, appearing as "empty" spaces with both ATPase and nicotinamide adenine dinucleotide-tetrazolium reductase,[300] actin myopathy with intranuclear rods,[152] myosin myopathy with embryonic heavy-chain mutations,[404] Ullrich disease with collagen VI deficiency,[183] autosomal dominant hyaline body myopathy characterized by the presence of subsarcolemmal, eosinophilic hyaline body,[51] myopathy with I-Z-I-like complexes[340] and Danon disease, or X-linked cardiac and skeletal myopathy caused by a deficiency of lysosome-associated membranae protein-2 (LAMP-2).[392]

4. METABOLIC MYOPATHY

A variety of myopathies result from inborn errors of metabolism. These include certain types of glycogen storage disease and disorders of lipid metabolism. Of the 11 glycogen storage diseases identified to date[105] prominent muscle

involvement occurs only in Types II (Pompe disease), III (Cori-Forbes), V (McArdle), and VII (Tarui) glycogenosis. Two other metabolic myopathies, mitochondrial diseases and malignant hyperpyrexia or hyperthermia, deserve a brief mention.

Acid Maltase Deficiency (Type II Glycogenosis)

In acid maltase deficiency, inherited as an autosomal recessive disease with a defect of lysosomal enzyme acid α-glucosidase gene located on chromosome 17q25, the deficiency leads to accumulation of glycogen in tissue lysosomes, causing a vacuolar myopathy.[440] In the infantile type, Pompe's disease, children develop severe hypotonia shortly after birth and die within the first year from cardiac or respiratory failure. Anterior horn cells contain deposits of glycogen particles as do other affected organs such as the heart, tongue, and liver. An enlarged tongue and cardiac abnormalities differentiate this condition from Werdnig-Hoffmann disease. The diagnosis depends on a blood-based enzyme activity deficiency, confirmed by a second test; either an enzyme activity assay in another tissue or gene sequencing.[10] Intravenous administration of recombinant human α-glucosidase from rabbit milk can improve muscle morphology [454] and halt progression even in late-onset Pompe disease.[208]

In the more benign childhood and adult types, which show a high genetic heterogeneity,[29,221] the symptoms limited to skeletal muscle mimic those of LG syndromes or polymyositis. Patients with the onset of symptoms in childhood have proximal limb and trunk muscle weakness with variable progression. They may die of respiratory failure before the end of their second decade. Acid maltase deficiency may have heterogeneous presentations within a family and an adult-onset case can present as a scapuloperoneal neuromuscular syndrome.[38] The pathogenesis may relate to increased net muscle protein catabolism because the condition improves with a high protein diet.[382] In the adult variant, symptoms begin with insidious LG weakness during the second or third decade and respiratory difficulty some years later, necessitating a tracheostomy. In a 12-month follow-up[456] symptom duration ranked the best as the predictor of the extent of skeletal and respiratory muscle weakness. Compliance with nutrition and exercise therapy slows the deterioration of muscle function and improves the natural history of adult-onset acid maltase deficiency.[381]

Both types have elevated serum enzymes. Muscle biopsy specimens reveal a vacuolar myopathy affecting Type I more than Type II fibers.[75] Glycogen commonly deposits in the central nervous system, particularly in the infantile form. Tissue cultures have reproduced the enzymatic defect. In EMG studies, the infantile form shows increased insertional activity, fibrillation potentials, positive sharp waves, and CRD as expected from anterior horn cell involvement. Severely affected muscles typically lack insertional activity. As one of the few exceptions to the rule (see Chapter 14-3), myotonic discharges may occur in the absence of clinical myotonia. Mild voluntary contraction recruits many motor units showing a polyphasic, low-amplitude, short-duration MUP in abundance. In contrast to the widespread abnormalities in the infantile type, the adult or late-onset childhood type has changes restricted to the gluteal, paraspinal, and other proximal muscles. Most of these patients have myopathic features without fibrillation potentials. Motor and sensory NCSs and studies of NMT reveal no abnormalities, except for a reduced CMAP amplitude.

Debrancher Deficiency (Type III Glycogenosis)

In Debrancher deficiency, inherited as an autosomal recessive trait, the absence of the debrancher enzyme prevents breakdown of glycogen beyond the outer straight glucosyl chains. Consequently, glycogen with short-branched outer chains, called phosphorylase-limit-dextrin, accumulates in the liver and striated and cardiac muscles causing heterogenous neuromuscular manifestations.[201] Despite the generalized enzymatic defect, the skeletal muscles do not necessarily show weakness on clinical examination.

Affected children with hypotonia and proximal weakness fail to thrive. Accumulation of glycogen in the liver causes hepatomegaly, episodes

of hypoglycemia, and markedly elevated serum CK. Clinical features of myopathy may develop after hepatic symptoms have abated. Patients may improve in adolescence despite the enzymatic defect. Distal weakness and wasting sometimes resemble those in patients with MND.[107] Needle EMG studies reveal profuse fibrillation potentials, CRD, and a small, short-duration MUP. Muscle biopsy specimens show subsarcolemmal periodic acid-Schiff positive vacuoles in Type II fibers without histochemical signs of denervation.

Muscle Phosphorylase Deficiency (Type V Glycogenosis)

McArdle[260] first described muscle phosphorylase deficiency as a rare autosomal recessive condition and others have subsequently reported families with an autosomal dominant pattern. It affects men more frequently than women by a ratio of 4 to 1.[106] Myophosphorylase deficiency blocks the conversion of muscle glycogen to glucose during heavy exercise under ischemic conditions. Although the exercise intolerance mainly results from impaired ATP generation from anaerobic glycogenolysis, defects of oxidative metabolism may also play a role.[30,97] The myophosphorylase gene, sequenced and assigned to chromosome 11q13, though heterogeneous, shows thymine substitutes for cytosine at codon 49 as the most common mutation.[248,424] In about 90% of cases, analysis of the patient's leukocytes identifies the responsible mutations confirming the diagnosis.[424]

The disease has a wide clinical spectrum.[250] In infants, generalized hypotonia may lead to respiratory insufficiency and early death. Patients developing symptoms later in life have more variable clinical presentations as late-onset or childhood myopathies. The abnormality, confined to skeletal muscles, initially causes only nonspecific complaints of mild weakness and fatigue.[457] Sometime during adolescence, patients begin to notice exercise intolerance.[309] Despite the onset of symptoms in childhood or adolescence, muscle cramps rarely develop before late adulthood. The differential diagnoses include muscle phosphofructokinase deficiency characterized by recurrent myoglobinuria and persistent weakness[43] phosphoglycerate mutase deficiency,[419] lactase dehydrogenase-A deficiency,[281] and Brody's disease, or a deficiency of calcium-adenosine triphosphatase in sarcoplasmic reticulum.[197]

Neurologic examination between bouts of muscle cramps initially reveals only mild proximal weakness without apparent muscular wasting. Patients may develop permanent limb girdle weakness later in life.[286] A heavy muscle contraction or repetitive stimulation of the nerve produces painful cramps that may last for several hours. In advanced stages, even mild exercise precipitates the attack, severely limiting the patient's activities. Associated breakdown of muscle leads to myoglobinuria causing the urine to become wine colored. Bouts of renal failure may develop following relatively mild exertional event such as an occult seizure if it causes myoglobinuria.[446]

Muscle pain and fatigue may improve during continued exercise if the patient sustains nonstrenuous activity such as cycling at a moderate workload.[439] This second wind phenomenon, which may serve as a diagnostic test, presumably results from increased mobilization of serum-free fatty acids as an alternative source of energy. Glucose infusion after a spontaneous second wind results in further increase in oxidative capacity.[165] Exposure to cold during exercise may also delay the development of contracture. A patient with an unusual combination of McArdle's disease and MG regained the ability to live independently after carefully prescribed exercise training.[243]

The ischemic exercise test can confirm the diagnosis in suspected cases. The test consists of contracting the forearm muscles under ischemic conditions induced by an inflated pneumatic cuff placed around the arm. The inability to convert glycogen to glucose for anaerobic glycolysis promptly precipitates a muscle cramp. Normally, lactate levels in venous blood should rise with the breakdown of glycogen under ischemic conditions. Patients with McArdle's disease show no rise in the lactate level in blood drawn from the exercised arm.[407] Early on during moderate exercise, a small number of muscle fibers reach metabolic depletion, indicated by a reduction in the adenine nucleotide pool. An increasing number of motor units recruited to compensate for muscle fatigue may contribute to the pathophysiology

of exercise intolerance.[463] The ischemic exercise test can identify patients with absence of myophosphorylase but fails to detect partial expression of McArdle's disease. Lactic acidosis during exercise, another characteristic feature of this disorder, does not account for exercise intolerance in mitochondrial myopathy.[438] Nonischemic forearm exercise test may serve as a safe screening without inducing cramps, myoglobinuria, or rhabdomyolysis.[175]

The pathogenesis of the contracture remains undetermined. The depletion of high-energy phosphates in the absence of glycogen metabolism might prevent the energy-dependent reuptake of calcium by the sarcoplasmic reticulum, but no studies have confirmed such an abnormality. Membrane excitability also appears unimpaired during ischemic exercise as tested by muscle fiber conduction velocity and surface analysis of the frequency spectrum.[238] Muscle fatigue may result from failure of energy-dependent excitation-contraction coupling, but MRI studies have shown no depletion of ATP.[19] Contractures probably develop following the disruption of the complex interplay among the contractile proteins, calcium release, and the calcium sequestration mechanism.[351] Additionally, a decreased density of sodium-potassium pumps will reduce muscle fiber membrane excitability,[164] lowering the exercise capacity.[352] In a single blind study of 12 patients, the ingestion of sucrose, rapidly metabolized to glucose and fructose, led to a marked improvement of exercise tolerance.[8,439]

Between attacks, EMG studies may find no abnormalities or may reveal fibrillation potentials and a polyphasic MUP with myopathic features reminiscent of inflammatory muscle disease. Early EMG may also show high-amplitude units possibly resulting from compensatory fiber hypertrophy.[401] Myotonic discharges and CRD may appear predominantly in paraspinal muscles.[326] In one study, quantitative MUP analysis in the biceps showed a mean duration of 7.1 ms compared with 9.4 ms in the controls, suggesting myopathic changes.[53] Needle studies of the contracted muscle (see Chapter 28-3) reveal no electrical activity (see Fig. 12-3) unlike the ordinary muscle spasm that shows abundant discharges. During regional ischemia, a prolonged low rate of repetitive nerve stimulation causes a progressive decrease in CMAP amplitude.[240] In one patient, the posttetanic contracture reached only 17% of the peak tetanic tension, and twitch force superimposed on the contracture fell by one-half, as did CMAP amplitude.[53]

Muscle Phosphofructokinase Deficiency (Type VII Glycogenosis)

This disorder, first described by Tarui and associates,[410] results from a defect in muscle phosphofructokinase, which precludes the conversion of fructose-6-phosphate to fructose 1–6 diphosphate.[409] The clinical features include painful muscle contracture and myoglobinuria much like those of McArdle's disease.[1] An infant with this syndrome may have, in addition to limb weakness, seizures, cortical blindness, and corneal opacifications. Distinguishing this entity from McArdle's disease depends on biochemical or histochemical determination of phosphofructokinase activity in the muscle biopsy specimens. Studies have shown reduced phosphofructokinase activity not only in the muscle but also in the heart and liver.[11] Electrophysiologic studies show no electrical activities during muscle contracture as in McArdle's disease with no abnormalities between attacks.

Disorders of Lipid Metabolism

Whereas glycogen serves as the major source of energy for rapid strenuous effort, circulating lipid in the form of free fatty acids maintains the energy supply at rest and during prolonged low-intensity exercise. Carnitine palmityltransferase II (CPT II) catalyzes the reversible binding of carnitine to plasma fatty acids; once bound, carnitine can transport fatty acids across the mitochondrial membrane for oxidation. Disorders of lipid metabolism include primary carnitine deficiency, multiple acryl-coenzymes A dehydrogenation deficiency, neutral lipid storage disease with myopathy and ichthyosis,[109,304] and other rare conditions such as lipid myoneuropathy with normal carnitine.[26]

Of these, CPT II deficiency, a rare disorder inherited as an autosomal recessive trait, results

from a missense mutation replacing a leucine for a serine residue at amino acid position 113 of the CPT II protein.[249,262] The patient develops painful muscle cramps and, on prolonged exercise or fasting, recurrent episodes of myoglobinuria.[31] Long chain fatty acids, not coupled to carnitine, cannot shuttle across the inner mitochondrial membrane, which impairs oxidation of lipid substrates. The first attack of myoglobinuria appears in adolescence, although muscle pain may develop in early childhood. Muscle remains strong between attacks, but exercise during fasting results in painful cramps. The disorder has diverse clinical features, which include episodic exertional dyspnea, exercise intolerance, and myoglobinuria without cramps or myalgias. Exercise tolerance, assessed by exercise duration and perceived exertion, improves on a carbohydrate-rich diet.[310] Muscle biopsy specimens may show no abnormalities or only slight excess of intrafiber lipid droplets next to the mitochondria in Type I fibers. Electrophysiologic findings, reported only in a few patients, include normal EMG and motor and sensory NCS.[31,124]

Carnitine deficiency, the first biochemical defect identified in muscle lipid metabolism,[16] has two forms, both inherited as an autosomal recessive disorder. The restricted type affecting the muscle predominantly or exclusively causes a lipid storage myopathy, so called before recognition of the specific biochemical defect. Reduced muscle carnitine possibly results from a deficit in carnitine uptake in the muscle despite normal serum carnitine levels in most patients. In contrast, the systemic type shows insufficient synthesis of the carnitine, lowering its level in the serum, liver, and muscle. Carnitine deficiency causes congenital and slowly progressive myopathy of the limb-girdle type and episodic hepatic insufficiency. Severe defects from bulbar and respiratory involvement may lead to death at an early age. Some patients show features of both systemic and muscle carnitine deficiency.

Muscle biopsy specimens reveal an excess of lipid droplets mostly in Type I fibers, which depend on oxidation of long-chain fatty acids to a greater extent than Type II fibers. In EMG studies, mild voluntary contractions induce a small-amplitude, short-duration, polyphasic MUP in abundance. Slightly over half of the patients have fibrillation potentials and other forms of spontaneous activity such as CRD. A neuropathy may develop in some, but the motor and sensory NCS and tests of NMT usually reveal no abnormalities.

Lipid utilization takes place in the mitochondria. This link may explain some overlap between lipid storage and mitochondrial myopathies. Most infants with a lipid metabolism disorder benefit from long-term therapy with L-carnitine.[370] In one series, 21 of 48 patients with mitochondrial myopathy had plasma carnitine deficiency, and most responded favorably to L-carnitine therapy.[62] Treatment with riboflavin and carnitine had a favorable effect on pure myopathy associated with complex 1 deficiency.[44]

Mitochondrial Disease

Many proteins in the mitochondria receive coding not only from the nuclear DNA of the cell but also from their own DNA. Mitochondrial DNA codes for 2 ribosomal RNA, and 22 transfer RNA and 13 proteins that constitute subunits of the respiratory chain complexes. Thus, deletions and point mutations of the mitochondrial DNA induce defects in aerobic oxidation. Most pathology associated with these mutations involves multiple systems to a variable degree, depending on the ratio of normal to mutant mitochondria in any given tissue.[108] Mitochondria, with their own genome predominantly inherited from cytoplasm of the oocyte, follow maternal transmission rather thanmendelian genetics, making the risk assessment for genetic counseling difficult. This type of inheritance should affect all offspring equally regardless of gender.

A large number of normal and abnormally shaped mitochondria, often densely packing the cristae, characterize mitochondrial myopathies. On light microscopy, granular material stains red with trichrome, thus the name "ragged red fiber." Abnormal fibers, often restricted to Type I, show high activity when stained for oxidative enzyme. Heat shock proteins, localized in ragged-red fibers with the use of monoclonal antibodies, may act as a protein repair enzyme catalyzing the refolding of misfolded proteins in the matrix of mitochondria.[386] Ragged red fibers,

as a nonspecific abnormality, also appear in myositis, hypothyroiditis, thyrotoxic myopathy, and SMA. Conversely, the expression of a mitochondrial defect can vary so much that the absence of ragged red fibers does not necessarily rule out the diagnosis of mitochondrial myopathy. Patients with mitochondrial cytopathy have abnormalities of muscle energy metabolism, which alters venous lactate response to subanaerobic exercise.[166,170,251] Markedly lower oxygen desaturation in venous blood after a forearm exercise may serve as a screening test for mitochondrial myopathy.[188]

Structural changes of the mitochondria cause progressive muscle weakness as part of complex neurologic manifestations.[293,347] These entities comprise three subgroups; chronic progressive external ophthalmoplegia (CPEO) including Kearns-Sayre syndrome, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF) or Ramsey Hunt syndrome. Mitochondrial gene studies in general show large-scale deletions in CPEO and point mutations in the transfer RNA genes of leucine in MELAS and of lysine in MERRF.[72,176,315] Some reports indicate phenotypic heterogeneity,[376,426] for example, absence of ophthalmoplegia in CPEO,[405] presence of external ophthalmoplegia,[128] or familial thiamine deficiency[363] in otherwise typical MELAS syndrome; combination of MERRF and Ekbom's syndrome characterized by lipomas, ataxia, and neuropathy[59] and MERRF/MELAS[63]; and MERF/Kearns-Sayre overlap syndrome.[121]

In Kearns-Sayre syndrome, a deletion of the mitochondrial DNA leads to progressive external ophthalmoplegia, retinitis pigmentosa, heart block, and cerebellar syndrome. Ocular abnormalities occur sporadically with the clinical signs of ptosis and extraocular palsy appearing during childhood or adolescence. As indicated by its alternative name, ophthalmoplegia plus, patients may develop a wide variety of neurologic deficits such as progressive weakness and fatigue, sensorineural deafness, cerebellar degeneration, endocrine abnormalities, sensorimotor neuropathy, demyelinating radiculopathy, and myasthenic symptoms.[140,266] Characteristic features include ragged red fibers in muscle biopsy material, indicating a mitochondrial abnormality. Laboratory studies reveal a moderate increase in cerebrospinal fluid (CSF) protein level and a mild elevation of serum CK.

In the beginning, EMG shows normal or mildly abnormal results with early recruitment of a low-amplitude, short-duration MUP and, in some cases, myotonic discharges.[179] Clinically asymptomatic members of the family may also have subtle changes consistent with subclinical myopathy as detected by conventional EMG or SFEMG.[132] In the more advanced stages, electrophysiologic studies may uncover an axonal type of neuropathic changes but no abnormalities of NMT.[417] Other features include absent or reduced ankle jerk, impaired distal vibration sense, and reduced sural nerve potential.[267] In one series, 10 of 20 patients had NCS abnormalities, although only 5 had clinical signs of a mild sensorimotor neuropathy. In these patients, sural nerve biopsy material revealed a reduced density of myelinated fibers and axonal degeneration affecting myelinated and unmyelinated fibers.[462]

In another study,[100] brief periods of low-intensity exercise produced a decrease in twitch tension with only a very slight change in CMAP amplitude. Progressive dissociation between the electrical and mechanical responses suggests a failure of contraction rather than a disorder of NMT. Multimodal evoked potentials revealed subclinical impairment of central sensory and motor pathways.[104,437] Blink reflex studies showed increased latencies and decreased amplitudes of R1 and R2 and greater habituation, perhaps indicating reduced excitability of brainstem interneurons.[210]

The syndrome of MELAS results from multiple sites of point mutations that may give rise to the same or similar clinical features.[408] Conversely, the same point mutation may lead to a diversity of clinical syndromes determined by the proportion of mutant genomes in combination with other still unidentified tissue-specific modulating factors.[283] Some families with mitochondrial myopathy have deficiency of complex I, or nicotinamide adenine dinucleotide-lubiquinone oxidoreductase,[158] whereas others show decreased activity of not only complex I but also complex IV, or cytochrome c oxidase, resulting in a fatal infantile

mitochondrial disease.[288] Still others suffer from a marked deficit in the activity of complex IV.[323] A deficiency of the mitochondrial enzyme, lipoamide dehydrogenase, may give rise to recurrent myoglobinuria and lactic acidemia.[119]

Ramsay Hunt syndrome, or MERRF, results from a point mutation in a mitochondrial gene coding for a transfer RNA at various loci.[70,186] Clinical manifestations include myoclonus, rare generalized seizures, mitochondrial myopathy, cerebellar ataxia, dementia, short stature, and sensorineural hearing loss. The syndrome may accompany celiac disease with or without overt gluten intolerance[46,73] or multiple symmetric lipomatosis.[285]

Malignant Hyperthermia or Hyperpyrexia

Malignant hyperthermia or hyperpyrexia denotes a rare, potentially lethal heterogeneous pharmacogenic myopathy with autosomal dominant inheritance.[162,255] Affected individuals may show an unusual sensitivity to anesthetics, although the role of succinylcholine as a malignant hyperthermia trigger remains questionable.[273] Fluoroquinolones influence the intracellular calcium handling in individuals susceptible to malignant hyperthermia.[274]

Without knowing a patient's family history, clinicians rarely suspect malignant hyperthermia. Susceptible individuals have no symptoms unless subjected to anesthesia. Common physical characteristics include proximal hypertrophy and distal atrophy of the thigh muscles and lumbar lordosis. Some patients have mild weakness of the proximal muscles, diminution of the muscle stretch reflexes, and elevated serum CK level. After the induction of general anesthesia, these patients develop fasciculations and increased muscle tone. An explosive rise in temperature coincides with the development of muscular rigidity and necrosis. If untreated, they die of metabolic acidosis and recurrent convulsions. Homozygosity for this trait seldom occurs, with only a few cases documented on the basis of pedigree information. These cases show more severe clinical symptoms in the absence of triggering agents and have marked muscular weakness and elevated serum CK levels between attacks.[101] As mentioned before, malignant hyperthermia may develop in association with central core disease.

The remarkable hyperpyrexia, metabolic in nature, may result from abnormal depolarization of skeletal muscle by halothane. The abnormal muscle shows hypersensitivity to caffeine, which normally causes muscle contracture by increasing the concentration of calcium in the sarcoplasm.[412] Patients with malignant hyperthermia typically show reduced reuptake of calcium by the sarcoplasmic reticulum. In an in vitro screening test for suspected cases, concentrations of halothane and caffeine too low to affect normal muscles produce contracture in specimens obtained from the patients. Screening for mutations in the gene encoding the skeletal muscle ryanodine receptor-1 and the dihydropyridine receptor usually substantiate the diagnosis,[195] although the caffeine-halothane-contracture test still remains the gold standard.[136]

Toxic Myopathies

Toxins may produce necrotizing, lysosomal, hypokalemic, or protein synthesis–related muscle damage.[375] Some toxic myopathies have distinct clinical, morphologic, biochemical, or molecular characteristics. Possible causes include ingestion of a toxic substance and the side effects of drugs. Eosinophilia-myalgia syndrome characterized by generalized muscle pain and eosinophilia presumably results from administration of contaminated L-tryptophan. Most studies emphasize neuropathy, but pure or combined myopathy may also develop,[57] as evidenced by electrophysiologic studies.[406] Pentazocine abuse may induce a myopathy characterized by proximal weakness and EMG findings of a low-amplitude, short-duration polyphasic MUP.[76] Chronic alcoholism may also cause myopathy, not associated with a deficiency in mitochondrial energy supply.[64] Acute myopathy and myoglobinuria with a markedly elevated CK level may develop after gasoline sniffing, presumably as the result of lead toxicity.[211] Alcohol misusers frequently develop not only the symptoms of neuropathy such as cramps and local pain but also the signs of myopathy like selective atrophy of Type II fibers and reduced muscle mass.[331] Other infrequent causes of toxic myopathy include mushroom poisoning from

consumption of Amanita phalloides, which also causes fulminant hepatic failure[155] and delayed rhabdomyolysis.[40]

Many pharmaceutical agents can induce muscle and nerve dysfunction[360] Table 27-2 lists common drugs that may cause myopathy and the clinical spectrum of drug-induced myopathies.[252] Introduction of highly active antiretroviral therapy has dramatically modified the natural history of HIV. Lengthening survival of HIV-infected individuals has increased the prevalence of iatrogenic condition.[27] Zidovudine induces a mitochondrial myopathy with ragged-red fibers associated with partial cytochrome c oxidase deficiency as a marker of this condition.[68] The symptoms ameliorate with discontinuation of the drug or administration of prednisone or nonsteroidal anti-inflammatory drugs. Selenium-deficient myopathy[312] may complicate HIV infection.[67] Colchicine, given in customary doses, may produce a neuromuscular disorder. Myopathic features predominate with proximal weakness and elevated serum CK values that remit after discontinuation of the drug.[355] Although rare, 3-hydroxy-3-methylgutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins[159,264,459] may induce necrotizing myopathy possibly by immune-mediated mechanism. It

Table 27-2 Drug-Induced Myopathies

A. TYPE OF DRUGS	B. THE CLINICAL SPECTRUM
1. Lipid-Lowering Agents	Asymptomatic hyper-CK-emia
Statins	Myalgia and muscle cramps
Fibrates	Myotonia
Nicotinic acid	Acute rhabdomyolysis
Ezetimibe	Acute quadriceps myopathy
2. Glucocorticoids	Chronic proximal myopathy
Prednisone and prednisolone	Mitchondrial myopathy
Methylprednisolone	Inflammatory myopathy
Dexamethasone	Dyskalemic myopathy
Inhaled steroids	Focal myopathies
3. Anti-Rheumatic Drugs	
Colchicine	
Chloroquine	
Hydroxychloroquine	
4. Cardiovascular Drugs	
Amiodarone	
Perhexiline	
5. Other Drugs	
Emetine-aminocaproic acid	
Etretinate	
Zidovudine	
Interferon-α	
D-penicillamine	
Streptokinase	

(Modified from Mastaglia.[252])

may also unmask hyaline inclusion myopathy (see Chapter 27-3)[399] or cause rhabdomyolysis triggered by grapefruit consumption.[110] Therapeutic administration of chloroquine may cause a vacuolar myopathy.[369] Osteomalacic myopathy results from an overuse of vitamin D.[354]

Other drugs known to induce myopathy include amiodarone, an antiarrhythmic agent that also causes neuropathy[333]; bezafibrate[441]; ipecac[111]; finasteride used for prostatic hyperplasia[163]; and azidothymidine (AZT). Focal myopathy with fibrosis also results from chronic intramuscular administration of an analgesic such as heroin,[241] pentazocine,[96] pethidine,[232] and piritramide.[427]

5. ENDOCRINE MYOPATHY

Endocrine myopathies develop in hyperthyroidism, hypothyroidism, parathyroid disease, and adrenal or pituitary dysfunction. Cushing's syndrome secondary to systemic administration of corticosteroids or adrenocorticotropic hormone (ACTH) also causes myopathy.

Thyroid Myopathy

Disorders of thyroid function may lead to a variety of neuromuscular problems, although fulminating systemic features may obscure muscular symptoms. Thyrotoxic myopathy probably ranks first in incidence with most patients having some proximal weakness and electrophysiologic abnormalities. Myopathy affects men more frequently than women, who have a higher incidence of thyrotoxicosis. Typically, weakness involves the muscles of the shoulder girdle more than those of the pelvic girdle. Patients usually have normal or at times even hyperactive muscle stretch reflexes. Spontaneous muscle twitching and generalized myokymia may develop but not commonly. Muscle biopsy specimens show increased axonal branching and degenerative changes of preterminal axons. Other neuromuscular conditions commonly associated with thyrotoxicosis include exophthalmic ophthalmoplegia, MG, and hypokalemic periodic paralysis (HypoPP) (see Chapter 28-2).

Hypothyroidism causes proximal muscle weakness, painful muscle spasm, and muscle hypertrophy, especially in children. Characteristic features of myxedema include Hoffmann's sign or delayed relaxation of contracted muscle. The ankle stretch reflex best demonstrates this change in contractibility, showing a brisk reflex movement of the foot with a slow return to the resting position. A sharp tap to the muscle with a reflex hammer causes a local ridge of muscle to contract. This phenomenon, called myoedema or mounding of hypothyroidism, accompanies no electrical activities (see Chapter 28-3). In some cases, EMG studies show increased insertional positive waves with transient myotonic discharges without evidence of clinical myotonia (see Fig. 14-6 in Chapter 14). Elevations of serum CK levels commonly, but not necessarily, imply the presence of myopathy.[365]

Parathyroid Disease

The influx of calcium into axon terminals facilitates the release of ACh at the neuromuscular junction, leading to excitation contraction coupling (see Chapter 17-3 and 17-4). Calcium apparently plays an opposite role at the central junction of axons: a reduction in calcium here results in increased conductance for sodium and potassium, causing instability and hyperexcitability of the cell membrane. Thus, in hypoparathyroidism, chronic hypocalcemia gives rise to tetany, the most dramatic neuromuscular complication (see Chapter 28-9). Less frequently, neuromuscular symptoms in hypercalcemia may also result from osteolytic metastases, multiple myeloma, or chronic renal disease. Characteristic EMG findings in tetany include doublets and triplets in addition to a low-amplitude, short-duration MUP, which recruits early, but no spontaneous activities. Motor and sensory NCS reveals a reduced amplitude but normal velocities. Varying degrees of proximal muscle weakness develop in patients with hyperparathyroidism usually affecting the pelvic girdle more than the shoulder girdle. Brisk stretch reflexes and occasional extensor plantar responses, combined with axial muscle wasting, may raise the diagnostic possibility of MND.

Adrenal and Pituitary Disease

Diseases of the adrenal and pituitary glands may give rise to nonspecific muscle weakness as in the

Cushing's syndrome, acromegaly, or Addison's disease. Similar weakness also appears after systemic administration of corticosteroids or ACTH. Steroids reduce the intracellular concentration of potassium, but their relationship to myopathy remains elusive. Dysfunction of the reticulum or mitochondria may also contribute to the pathogenesis. With preferential weakness of the pelvic girdle and thigh muscles, patients have difficulty rising from a chair or climbing stairs. The neuromuscular symptoms usually improve if the underlying abnormality abates or upon discontinuation of the steroids. Laboratory studies show normal serum enzymes but increased urinary creatine excretion. Muscle biopsy material reveals Type II fiber atrophy but neither necrosis nor inflammatory changes, despite muscle wasting observed clinically.

Motor NCS shows areduced CMAP amplitude especially in proximal muscles. Endocrine or steroid myopathy with Type II fiber atrophy usually reveals no specific abnormalities in EMG, which tends to assess only the initially recruited Type I fibers. Patients with an inflammatory myopathy may develop progressive weakness after prolonged steroid therapy. In this situation, a normal insertional activity and the absence of fibrillation potentials suggest steroid myopathy rather than exacerbation of the disease. In some cases, needle studies show an early recruitment of a low-amplitude, short-duration MUP, but such mild changes generally reverse after withdrawal of steroids. Patients with endogenous Cushing's syndrome may have abnormalities in keeping with an inflammatory myopathy.[306]

6. MYOSITIS

Inflammatory processes of the muscle include a variety of myositis, which often occurs concomitantly with a muscular dystrophy or a connective tissue disease.[56,432] Although macrophages play an important role in mediating muscle fiber injury,[112] no studies have shown a persistent enterovirus as the cause of inflammatory myopathies.[230] Patients with dermatomyositis have skin rash associated with the signs and symptoms of muscle involvement. Despite the usually typical features of myositis, its protean clinical presentation poses a considerable diagnostic challenge in some cases, requiring muscle biopsy to confirm the diagnosis.[253] Congential inflammatory myopathy usually, but not always, accompanies congenital muscular dystrophy.[263] Complicated schemes of classifying inflammatory myositis reflect the uncertainty whether different clinical forms represent separate entities or a spectrum of the same illness. Diagnostic insight reflects the molecular profiles of muscle tissue with a large number of differentially expressed genes.[161] For the purpose of this discussion, a brief description suffices to highlight certain clinical features considered characteristic of dermatomyositis and polymyositis as a broad and general category.[82,86] Additionally, IBM deserves a special mention because of its resistance to the usual therapy with steroid or high-dose intravenous immunoglobin (IVIG).

Dermatomyositis and Polymyositis

The combination of skin rash and muscular weakness suggests the diagnosis of dermatomyositis. The symptoms begin at any age but rarely in adolescence or early adulthood. Thus, the incidence histogram shows a bimodal distribution with peaks in childhood and in the fifth and sixth decades. Dermatomyositis in childhood often accompanies the systemic symptoms of collagen vascular diseases but not malignancy. Other common associations include Raynaud's phenomenon, lupus erythematosus, polyarteritis nodosa, Sjogren's syndrome, and pneumonitis. Some patients also have obstructive sleep apnea, which may play a role in persistent fatigue.[367] Accumulating evidence indicates that a complement-mediated microvasculopathy may play a pathogenic role. In one study of 39 dermatomyositis biopsy specimens[204] fascicular comparison showed a significant correlation between focal myofibrillar loss considered ischemic in origin and capillary deposits of membrane attack complex. A perifascicular distribution of muscle fiber atrophy presumably implies the interruption of blood supply to the peripherally located fibers. Chronic immune vascular damage may cause ischemic myofiber atrophy and capillary insufficiency in "watershed" regions near the avascular perimysium.[325]

The initial presentation comprise such nonspecific symptoms as malaise, fever, anorexia, weight loss, features of respiratory infection, and rarely acute abdominal pain as a result of spontaneous hemorrhage.[311] Despite the traditional emphasis, pain and tenderness of affected muscles, if present, constitute neither a presenting nor a primary symptom in most cases. Some patients have demonstrable tenderness restricted to the muscles of the shoulder. The skin lesions that may precede or follow the onset of weakness consist of a heliotrope or lilac-colored rash often resembling the shape of a butterfly over the cheeks and eyelids, a V sign over the neck and upper shoulder, and a shawl over the shoulder and upper arms. Particularly prominent discoloration along the upper eyelids usually accompanies periorbital edema. An erythematous rash may also appear in exposed body parts such as upper chest, knees, and hands. The affected skin thickens with a reddish hue, especially over the interphalangeal joints. Telangiectasia may develop over the chest and the back of the hands in advanced stages. In extreme cases, the inflammation renders the skin over the entire body atrophic, edematous, and reddish in color. Intravenous administration of high-dose immunoglobulins had a favorable effect in some patients.[431]

Polymyositis remains a challenge in definition as an acquired subacute inflammatory myopathy without family history or exposure to myotoxic drugs or toxins. Except for the absence of skin lesions, the signs and symptoms of polymyositis closely resemble those of dermatomyositis. Initial systemic manifestations also bear close resemblance in the two varieties. As a diagnosis of exclusion, studies must first rule out an acquired muscle disease secondary to endocrine, metabolic, and neurogenic causes.[83] Cases of IBM and dystrophies account for most patients with the erroneous diagnosis of polymyositis. Muscle weakness in these conditions develops slowly, over months or years, rather than subacutely. Children usually develop dermatomyositis with skin rashes and only rarely polymyositis as a paraneoplastic phenomenon.[371] Thus, polymyositis primarily affects adults with possible underlying conditions such as collagen vascular disease or malignancy. Men have a higher incidence of neoplasms that involve bowel, stomach, lung, or breast. Muscle-specific autoantibodies may play a role in the pathogenesis of this condition.[138] Early-activated macrophages in subacute polymyositis stand in contrast to late-activated macrophages of acute dermatomyositis.[349] Polymyositis has also accompanied biliary cirrhosis,[461] essential cryoglobulinemia,[442] pregnancy,[272] and mixed connective tissue disease.[160]

In human immunodeficiency virus (HIV)-associated myositis, patients may develop subacute structural myopathy characterized by selective loss of thick filaments and widespread formation of rod bodies.[156] Typical features consist of progressive proximal weakness, elevated serum CK level, and EMG changes consistent with inflammatory myopathy.[379] The development of a single muscle mass or enlargement of several muscles may accompany the generalized muscle weakness in this condition.[343] Some patients with AIDS develop myopathies with unusual segmental vesicular changes of myofibers while receiving zidovudine for therapy. Thus, both infection with HIV and ingestion of zidovudine cause myopathy, although HIV rather than the drug seems to play a more prominent role.[380] The muscle fibers or the cultured myotubes contain neither HIV sequences nor transcriptional products.[230] Therefore, HIV-associated myositis does not seem to result from a persistent viral infection of muscle fiber.

Human T-cell lymphotrophic virus (HTLV)-Type I infection mostly known as HTLV-I associated myelopathy or tropical spastic paraparesis (HAM/TSP)[313] may also cause myositis.[22] The myopathies associated with this condition have clinical and pathologic features similar to those of a dystrophy with a predominantly proximal lower-limb weakness. Thus, retrovirus can trigger myositis not only in HIV-infected patients but also HTLV-1-infected patients, even in the absence of detectable viral genome within the muscle fibers. Patients with cryptogenic adult myopathies, therefore, should have serological screening.

Weakness, as the usual presenting symptom of myositis, ordinarily progresses slowly over a matter of weeks. The disease, however, may take a fulminating course with the patient crippled

during the first week of onset. Weakness of pelvic girdle muscles, involved initially, causes difficulty in climbing stairs or rising from a chair. Subsequent paresis of the shoulder girdle renders patients incapable of lifting objects or combing the hair. In most patients, weakness soon spreads to involve the distal limb muscles and occasionally paraspinal muscles, causing camptocormia, or bent spine syndrome.[216] The disease may begin as a focal process that mimics a localized inflammatory reaction with wasting of only one limb or restricted paralysis of both gastrocnemii asymmetrically.[268] Weakness of the neck musculature shows predilection for the anterior rather than posterior compartment. The disease may cause dysphagia but spares the extraocular and other bulbar muscles. An extremely focal inflammatory process may involve the diaphragm and intercostal muscles. The patient has normal muscle stretch reflexes until very late in the course of the disease. Atrophy, if apparent in the orbicularis oculi or other superficial muscles, may escape detection in the deep muscles of the pelvic or shoulder girdle. Conversely, focal lipoatrophy caused by loss of subcutaneous tissue may mimic focal muscle atrophy seen in myositis.[185] Bulbar-onset myositis may mimic MND, particularly in the absence of inflammatory markers or elevated muscle enzyme levels.[356]

The serum CK level, if elevated, supports the diagnosis and helps monitor the clinical course of myositis. Approximately 10% of patients with a proven diagnosis have no elevation even during the acute stages. A normal enzymatic level despite active myositis may suggest extensive muscle atrophy in long-standing disease. Other inconsistent laboratory findings include elevated erythrocyte sedimentation rate and gamma globulin. In the active stage, MRI shows high intensity on T2-weighted and normal intensity on T1-weighted images[145,338] This abnormality, which probably represents edema and inflammation, usually reverts to normal after corticosteroid therapy.

A triad of EMG abnormalities nearly always appears in untreated myositis, especially in the clinically weak muscles. They consist of (1) fibrillation potentials and positive sharp waves (see Fig. 14-8D in Chapter 14); (2) CRD; and (3) a polyphasic low-amplitude, short-duration MUP with early recruitment (see Chapter 14-6 and Fig. 14–19A in Chapter 14). Certain muscles, however, may remain electrically normal, even in moderately advanced stage. For adequate assessment, therefore, examination should include a number of proximal and distal muscles with emphasis on those exhibiting moderate weakness clinically. A retrospective study of 153 patients with dermatomyositis or polymyositis revealed the following abnormalities[50]: (1) small-amplitude, short-duration, polyphasic MUP (90%); (2) fibrillation potentials, positive sharp waves, and insertional irritability (74%); (3) CRD (38%); (4) a completely normal study with otherwise classic disease (10%); and (5) electrical abnormalities confined to the paraspinal muscle with widespread muscle weakness (1.6%). In another large series of 98 patients[102] findings consisted of the following: (1) fibrillation potentials, positive sharp waves, and a polyphasic, low-amplitude short-duration MUP with early recruitment (45%); (2) the above MUP changes without spontaneous activities (44%); and (3) no abnormalities (11%). No correlation emerged between the grade of clinical impairment at the onset of illness and the EMG findings.

Contrary to the common description of low-amplitude potentials based on manual analysis, a quantitative study[420] revealed no amplitude differences between affected and normal subjects. The patients had three to four times more short-duration and polyphasic potentials than the controls. Another quantitative study also revealed a minimal increase in macro MUP amplitude and fiber density.[35] Thus, reinnervation does not seem to play an important role in the initial motor unit remodeling. In the chronic stage, however, EMG usually reveals increased MUP duration and amplitude with satellite potentials.[402] Repetitive stimulation of the nerve may show a decremental or, less frequently, an incremental CMAP responses.[178,181,436] Such electrophysiologic abnormalities often accompany clinical features of MG. These patients probably represent an overlap of these two entities. Indeed, the electrophysiologic and histologic features characteristic of myositis commonly occurs in patients with severe MG.

Muscle biopsies reveal degeneration and regeneration of both Type I and Type II fibers, with necrosis, phagocytosis, atrophy, internal nuclei, vacuolization, random variation of fiber size, mononuclear inflammatory infiltrates, and endomysial or perimysial fibrosis. Histochemical investigation and SFEMG have revealed changes of the terminal innervation pattern consistent with reinnervation. Denervation could result either from involvement of the terminal nerve endings or from segmental necrosis of muscle fibers separated from the endplate region. Like EMG, histologic abnormalities often involve the paraspinal muscles predominantly or selectively. The inflammatory process of dermatomyositis may trigger the pathologic changes of IBM.[227]

High-dose steroid therapy retards the progression in most patients, but the remission may not last long, showing frequent clinical relapses.[228] In one series,[328] 30 of 50 patients experienced relapses during a follow-up period of up to 13 years. Some patients, if refractory to conventional steroid and immunosuppressive treatment, may respond to cyclosporin A[244] or high-dose IVIG.[187] Unlike in wallerian degeneration, spontaneous activity in myositis diminishes or disappears within a few weeks of successful steroid therapy. Symptoms of myositis may also improve after successful surgical resection of malignancy[403] or administration of anti-tumor-necrosis-factor.[171] Serial electrophysiologic evaluation can objectively assess patient response to various therapies. It also helps distinguish a recurrence of myositis from the emergence of steroid myopathy. Clinical recovery generally parallels improvement in EMG findings.

Inclusion Body Myositis

In this distinct but rarely recognized inflammatory disease of skeletal muscle,[276,378] the pathologic characteristics consist of inflammatory infiltrate surrounding healthy cells[84,85] and independent degenerative process with rimmed vacuoles.[12,189] These vacuoles show osmophilic membranous whorls and intracytoplasmic or intranuclear filamentous inclusions, which contain β-amyloid protein, two other epitopes of the β-amyloid precursor protein, and apolipoprotein E.[279] This phenomenon, therefore, differs from the extracellular deposits of amyloid in Alzheimer's disease. Cyclin-dependent kinase 5 may play a role in the formation of the inclusion body.[289] The rare occurrence of familiar cases adds further evidence for genetic susceptibility for sporadic IBM.[295]

Unlike dermatomyositis, the disease lacks the features of collagen vascular involvement, but some patients have evidence of associated autoimmune disease. Immune-mediated damage to dorsal root ganglia may cause unexpected sensory abnormalities in occasional cases.[143] Immunoreactivity with mumps virus antibodies has led to a postulate of a "slow" mumps infection[74] but without subsequent confirmation.[141,142] Mitochondrial DNA deletions may play a role in the pathogenesis, causing respiratory chain dysfunction in muscle fiber segments.[307] In a patient with sporadic Creutzfeldt-Jakob disuse and IBM, immunohistochemistry showed abundant disease-associated prion protein in the muscle.[212] In another patient, unique pathologic features included transthyretin immunoreactivity in prominent muscle blood vessel and amyloid deposits within vacuolated muscle fibers.[25]

Unlike other inflammatory myopathies, sporadic IBM, the most common acquired muscle disease in older individuals, causes slowly progressive muscular weakness and atrophy, which shows a distinct pattern of involvement and resists the conventional form of immunotherapy.[24,294] The disease frequently affects the distal muscles in men with early weakness of finger flexors, knee extensors, and foot dorsiflexors with considerable variability.[327] It progresses slowly, taking a benign clinical course, although symptoms worsen faster to disability when they begin after the age of 60.[324] Disorders associated with IBM include HIV infection[88] and POEM syndrome.[153]

As in other myositic conditions, EMG shows fibrillation potentials, positive sharp waves, and CRD at rest and a low-amplitude, short-duration MUP, which recruits early. In one series, quantitative studies of interference pattern showed changes consistent with myopathy in all 13 patients tested.[36] About one-third of cases have a mixed pattern consisting of large and small MUP, which some consider as highly suggestive of IBM.[193] Others advocate the use of macro

and surface EMG studies as a measure of disease progression.[34]

Hereditary IBM, which lacks inflammatory infiltrate, comprise a heterogenous group of distal myopathies, which may include Welander distal myopathy, tibial muscular dystrophy, Laing distal myopathy, Miyoshi distal myopathy, and Nonaka distal myopathy with rimmed vacuoles (see Chapter 27-2). The familial form usually, but not always, spares the quadriceps muscles, which the sporadic form severely affects.[296] Related disorders include distal vacuolar myopathy with complete heart block and no filamentous inclusions.[213] Familial IBM among Kurdish-Iranian Jews shows slowly progressive limb-girdle muscle weakness with a remarkable sparing of quadriceps muscles.[20]

Familial incidences related to consanguinity indicate a genetic cause with an autosomal recessive inheritance, some mapping to chromosome 9p1-q1 with mutations in the UDP-N-acetylglucosamine z-epimerase/N-acetylmannosamine kinase (GNE) gene.[55] In an American family with quadricep-sparing hereditary IBM, analysis for GNE revealed missense mutations not seen in sporadic cases.[435] Autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia, and rimmed vacuoles constitutes another variant of hereditary IBM.[90] Mutations of the valosin-containing protein gene (VCP) found in patients of Italian background may lead to a variable clinical phenotype for autosomal-dominant hereditary IBM associated with Paget's disease of bone.[149,215]

A small proportion of patients respond to corticosteroid or immunosuppressive therapy.[234] In refractory cases, other options include IVIG,[87] repeated immunoabsorption,[291] and low-dose whole-body or lymphoid radiation.[9,45,254] Oral methotrexate decreased serum CK activity without slowing down the disease progression.[28] A supervised progressive resistance training program may lead to gains in dynamic strength of the least weak muscles.[387] Tendon transfers may serve as an effective treatment of severe finger flexion.[445]

Other Myositis

Bacterial and viral infections of muscle occur less commonly than dermatomyositis or IBM. Neuromuscular complication of streptococcal myositis includes necrotizing fasciitis and focal myositis, and only rarely, generalized muscle weakness with multiorgan failure.[237] Parasitic infection prevails in tropical countries. In cysticercosis, taenia solium mostly affects the trunk muscles,[364] whereas, in trichinosis, trichinella spiralis preferentially invades the extraocular muscles.[93] An HIV-positive patient with fever, encephalitis, multiorgan dysfunction, and elevated serum CK level of obscure origin may have skeletal muscle toxoplasmosis.[146] Increased anti-toxoplasma antibodies in patients with idiopathic inflammatory myopathy probably indicate a concurrent rather than causal infection.[54]

Myositic conditions may also accompany systemic disorders such as histoplasmosis,[443] scleroderma,[115] Behçet's disease,[458] tuberculosis,[92] Crohn's disease,[373] and sarcoidosis.[231,332] Neuromuscular involvement in patients with legionnaire's disease includes myositis with an elevated serum CK level. The organisms may invade the muscle directly in some patients.[448] Biopsy-proven polymyositis may complicate severe poisoning by ciguatera fish toxin.[393] Muscle inflammation may follow the use of antigenic agent concomitant with a variety of other allergic reactions.[391]

A focal myopathy may mimic an entrapment neuropathy[125] as does acute exertional compartment syndrome.[236] Focal myositis, a benign inflammatory enlargement within a single skeletal muscle,[384] may also cause a localized painful swelling within the soft tissue sometimes as a treatable cause of compression neuropathy[7] or of dropped head syndrome.[48] The disease may involve any muscle of the limb, neck, abdomen, or face as an indolent lump.[60] In progressive unilateral hypertrophic myositis, the affected muscles show necrosis and variations in fiber size.[329] The focal region of abnormality shown by MRI corresponds to the confluent areas of necrosis and edema seen in muscle biopsy material. Histologic examination may also reveal interstitial fibrosis, lymphocytic infiltration, and scattered muscle fiber necrosis and regeneration. Complete recovery follows surgical removal of the lesion.

Focal myositis in the form of calf hypertrophy has developed in association with S1

radiculopathy, showing mixed neurologic and myopathic features in EMG.[394] Gallium citrate scintigraphy and MRI can localize such a focal myositis.[280] Chronic intramuscular injection of various narcotic analgesics such as pentazocine, meperidine, pethidine, piritramide, and heroin may cause a focal myopathy leading to muscle fibrosis.[449] Soft tissue sarcoma may mimic the focal myositis presenting as atypical limb pain.[91] Muscle infarction also begins with the acute onset of focal pain and swelling in the thigh as an unusual neuromuscular complication of diabetes.[37,49]

Any process that causes rapid destruction of striated muscle fibers may produce rhabdomyolysis, including infection, ischemia, exertion, trauma, toxin, medication, metabolic myopathies, and rarely calciphylaxis.[335] Of these, exertional rhabdomyolysis has a low incidence with smaller rate of complication than other causes.[6] Its symptoms include muscle pain, weakness, stiffness, and myoglobinuria. Acute rhabdomyolysis with myoglobinuria shares an elevated serum CK and other clinical profiles with acute myositis. In one series of 15 patients, however, only 5 had EMG abnormalities consistent with myopathy or myositis.[4]

7. OTHER MYOPATHIES

Critical Illness Myopathy

Neuromuscular disorders play an important role in prolonged ventilator dependency[389] Generalized motor deficits of this type include critical illness myopathy[226] and critical illness polyneuropathy (see Chapter 24-2). Of the two, acute myopathy predominates over acute axonal polyneuropathy as the cause of generalized weakness in intensive care units.[220] Diffuse weakness usually results as a complication of treatment with steroids or nondepolarizing blocking agents in patients with severe systemic illness such as renal failure, sepsis, or status asthmaticus.[219,258] A similar myopathy, however, can occur in patients with critical illness who have not received steroids or nondepolarizing neuromuscular blocking agent. Acute quadriplegic myopathy may also develop after administration of large doses of corticosteroid in patients with MG[318] or postoperatively following liver transplantation.[61,453]

Critical illness myopathy generally shows EMG changes suggestive of a necrotizing myopathy.[129] Some of these patients may have a characteristic pattern of evolution with early evidence of denervation followed by changes consistent with myopathy during recovery phase.[157] In most such cases, nerve stimulation elicits a small CMAP with a prolonged duration and, in some, defective NMT.[322] In one series, all 22 patients seen consecutively with critical illness weakness had an underlying myopathy based on direct muscle stimulation, quantitaive EMG, and motor unit number estimation (MUNE).[422]

Some investigators propose the use of direct muscle stimulation, which may reveal muscle membrane inexcitability in quadriplegic myopathy but not in critical illness polyneuropathy.[342,421] In one study using this technique, the authors identified 19 of 30 critically ill patients as having predominantly myopathic weakness.[229] In another series of 32 patients with critical illness myopathy, muscle fiber slowing and conduction block showed a correlation with the prolongation of CMAP duration and clinical severity.[5] Serial studies using paired stimulation technique to explore the excitability of individual muscle fibers help define the course of these pathophysiologic changes, which may parallel HypoPP.[5]

A muscle biopsy specimen shows prominent necrotizing fibers with an extensive loss of thick myosin filaments and relative preservation of thin actin filaments.[167,218] Immunocytochemical analysis reveals depletion of either fast or slow myosin[278] with some evidence of calpain-mediated proteolysis.[374] Apoptosis mediated by proteolytic proteases may play a role in the pathogenesis of acute quadriplegic myopathy.[103,353] Steroids may have suppressive effects on membrane excitability associated with a decline in muscle fiber conduction velocity as seen during high-dose methylprednisolone therapy.[428]

Myopathies Associated with General Medical Conditions

Amyloidosis may cause myopathy, although not as commonly as neuropathy.[383] Progressive amyloid myopathy has electron microscopic features distinct from the intracellular amyloid deposits

characteristic of sporadic or inherited IBM (see Chapter 27-6).[287] In the typical form, findings include pseudohypertrophic macroglossia and hoarseness of voice, although the absence of these features does not exclude the diagnosis. Other presenting features include respiratory failure with amyloid infiltration of the diaphragm[23] and dropped head syndrome with amyloid deposition in the cervical paraspinal muscles.[78] In one series of 17 patients, needle studies showed fibrillation potentials in 69% of muscles, most frequently in the gluteus medius and paraspinals, and an MUP consistent with myopathy in 72% of muscles.[350]

Patients with Marinesco-Sjögren syndrome may develop slowly progressive muscular weakness in addition to the typical features of cataracts, mental retardation, cerebellar atrophy, and skeletal abnormalities. Other characteristics include electrophysiologic findings consistent with myopathy, slightly elevated CK level, and myopathic changes with Type I fiber predominance in muscle biopsy.[206]

Although rare, proximal weakness, accompanied by EMG abnormalities, may result from extensive leukemic cell infiltration or discrete carcinomatous metastatic deposits in the affected muscle.[305] In paraspinal muscle metastasis, needle examination demonstrates marked segmental involvement of the posterior primary ramus with relative sparing of the anterior ramus.[217]

A primary myopathic condition predominantly affecting the entire axial musculature may cause dropped head syndrome and bent spine syndrome mostly in elderly patients who have decreased spine and shoulder muscle density and reduced force of their paravertebral muscles[225,303] Some of these patients may respond to prolonged immunosuppressant treatment.[348]

Controversies continue with the concept of myofascial pain and possible electrical activities recorded from needle electrode inserted in the tender area of the muscle.[77] An equally confusing entity termed *fibromyalgia*, or syndrome of aching muscles, often overlaps with an even more controversial entity, chronic fatigue syndrome.[203]

A spinal cord injury gives rise to morphologic and contractile changes in the muscles below the level of the lesion, showing a progressive drop in the proportion of slow myosin heavy chain.[47] Low volume-resistance exercise attenuates the decline in strength and muscle mass associated with immobilization.[302]

Other systemic illnesses that may involve the skeletal muscle include chorea-acanthocytosis,[184] dialysis-associated systemic fibrosis or scleroderma-like disease originally described as a purely cutaneous disorder,[233] McLeod syndrome,[194] and malnutrition.[180]

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28

Neuromuscular Diseases Characterized by Abnormal Muscle Activities

Abbreviations: AChR—acetycholine receptor, AD—autosomal dominant, ALS—amyotrophic lateral sclerosis, ATP—adenosines triphosphate, CACN—skeletal muscle calcium channel, CAV3—caveolin-3 gene, CCT—central conduction time, CIDP—chronic inflammatory demyelinating polyneuropathy, CLCN-1—muscle chloride channel, CMAP—compound muscle action potential, CMD—congential myotonic dystrophy, CMT—Charcot-Marie-Tooth disease, CRD—complex repetitive discharge, CRPS—complex regional pain syndrome, CSF—cerebral spinal fluid, CSP—cortical silent period, CTG—cytosine-thymine-guanine, DMI—myotonic dystrophy Type I, DMII—myotonic dystrophy Type II, EMG—electromyography, EPP—endplate potential, GABA—gamma aminobutyric acid, GAD—glutamic acid decarboxylase, GBS—Guillain-Barré syndrome, HFS—hemifacial spasm, HMSN—hereditary motor sensory neuropathy, HyperPP—hyperkalemic periodic paralysis, HypoPP—hypokalemic periodic paralysis, IgG—immunoglobulin G, LGMD—limb-girdle muscular dystrophy, MC—myotonia congenita, MEP—motor evoked potential, MFCV—muscle fiber conduction velocity, MG—myasthenia gravis, MMN—multifocal motor neuropathy, MND—motor neuron disease, MRI—magnetic resonance imaging, MUP—motor unit potential, NCS—nerve conduction study, NMT—neuromuscular transmission, PAM—potassium aggravated myotonia, PC—paramyotonia congenita, PIRC—percussion-induced rapid contraction,

PIMM—percussion-induced muscle mounding, PM—paramyotonia, PLM—periodic limb movement, PNH—peripheral nerve hyperexcitability, RLS—restless leg syndrome, RMD—rippling muscle disease, SCN4A—muscle sodium channel γ-subunit gene, SEP—somatosensory evoked potential, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy, SPS—stiff person syndrome, SP—silent period, TMS—transcranial magnetic stimulation, TSH—thyroid-stimulating hormone, VGKC—voltage-gated potassium channel

1. INTRODUCTION

Muscles may stiffen pathologically with lesions involving the muscle membrane, axon terminal, peripheral nerve trunk, spinal motoneurons, or central nervous system. Myotonia, or delayed relaxation of voluntarily or reflexively contracted muscle, develops as a characteristic clinical sign in several myogenic syndromes, such as myotonic dystrophy, myotonia congenita, paramyotonia congenita, and a form of periodic paralysis. Muscle activities without detectable muscle action potentials occur with contracture and rippling muscle disease. Muscle percussion may also induce electrically silent muscle mounding or stationary myoedema, considered physiologic with no implication of a neuromuscular disorder despite its traditional link to hypothyroidism. Involuntary muscle contraction also results from disorders of the peripheral nerve such as neuromyotonia, or continuous muscle fiber discharge, Schwartz-Jampel syndrome, and myokymia. Other lower motoneuron conditions with abnormal muscle activity include the common cramp, tetanus, tetany, and hemifacial spasm. In still other sustained muscle contractions, spontaneous discharges originate centrally as in the stiff person syndrome, disorders of involuntary movement, and seizure disorders.

Several electrophysiologic techniques help assess involuntary movement and determine the site of abnormal discharges. Nerve blocks will eliminate abnormal muscular activity originating in the central nervous system or the proximal part of the peripheral nerve. In this instance, repetitive nerve stimulation proximal to the block fails to induce the abnormal muscle activity. Discharges from the distal or terminal nerve segment cease after the block of neuromuscular transmission (NMT). In contrast, curarization does not affect abnormal discharges originating from the intrinsic muscle fibers. Some cramp syndromes display a distinctive pattern of abnormalities on electromyography (EMG). Others produce a normal interference pattern, although the subject has no voluntary control over the number and frequency of discharging motor units.

2. MYOTONIA

Advances in molecular biology have resolved some of the issues regarding classification of myotonia and periodic paralysis.[249,280] Three groups of disorders have emerged: (1) myotonic dystrophy Type I (DMI) associated with expanded run of trinucleotide sequence CTG, (2) proximal myotonic myopathy or myotonic dystrophy Type II (DMII) showing expanded run of CCTG, (3) dominant and recessive forms of myotonia congenita associated with disorders of muscle chloride channel (CLCN-1),[149,228,288,334] and (4) hereditary sodium channelopathies, which comprise the spectrum of disorders associated with missence mutations in the voltage-gated muscle sodium channel α-subunit gene (*SCN4A*).[281,377] This category includes (1) those with myotonia only, or potassium aggravated myotonia (PAM), (2) myotonia plus periodic paralysis, or paramyotonia congenita (PC) and hyperkalemic periodic paralysis (HyperPP), and (3) only attacks of paralysis or hypokalemic periodic paralysis Type II (HypoPP).[458] The *SCN4A* mutations result in gain of function defects whereby the mutant channels pass more sodium current than normal through an impairment of physiologic inactivation.[27] An increased sodium influx, in turn, causes either slight depolarization with hyperexcitability as evidenced by myotonia or sustained depolarization block manifested by paralysis.

In myotonia, the hyperexcitable muscle membrane, once activated, fires repetitively, inducing delayed muscle relaxation. Unlike cramps or spontaneous spasms, this type of prolonged muscle contraction causes no pain. Myotonic discharges, initiated by voluntary contraction, muscle percussion, or needle insertion, characteristically wax and wane at varying frequencies up to150 Hz. Decrementing amplitude, accompanied by shortening of the interspike interval, often gives the impression that motor unit potentials (MUPs) cannot keep up with the increasingly higher firing rate. Conversely, increments of amplitude tend to occur in association with a declining rate of discharges. These relationships, however, sometimes reverse, suggesting that different ionic mechanisms may dictate the amplitude and firing frequency (see Chapter 14-3). During volitional activity, myotonia may worsen initially but improve following a warm-up period, typically recurring at the beginning of the next voluntary movement after a period of rest. Percussion myotonia follows a brisk tap over the thenar eminence. Cold aggravates both post-activation and percussion myotonia. Myotonic muscles typically have reduced torques during maximal voluntary contraction and decreased mean amplitude of the compound muscle action potentials (CMAPs). Muscle action potentials decline further with repetitive nerve stimulation or after isometric exercise (see Chapter 18-8).

Myotonic discharge with or without clinical myotonia develops in a number of metabolic muscle diseases such as acid maltase deficiency, hyperthyroidism, hypothyroidism, and malignant hyperpyrexia (see Chapter 27-4 and 27-5). Myotonia and myositis may also constitute part of the symptom complex seen in paraneoplastic syndrome,[322] hypokalemic myopathy associated with glycyrrhizin-induced hypochloremia,[167] and a myopathy associated with the use of colchicine.[365] In all these entities myotonia plays neither a predominant nor an essential role as in myotonic dystrophy Types I and II (DMI and DMII), myotonia congenita (MC), or paramyotonia (PM).

The specific defect causing membrane hyperexcitability in myotonia remains unknown. Potassium ions accumulate in the transverse tubular system during activation of the muscle membrane, giving rise to a negative after-potential (see Chapter 2-3, Fig. 2-4 in Chapter 2). This degree of depolarization, although normally not large enough to generate an action potential, could initiate repetitive discharges in the myotonic muscle. In DMI, a combination of incomplete sodium channel inactivation and potassium ion accumulation in the T-tubule compartment may lead to myotonia and paralysis, although the relationship to the expanded CTG repeat remains undetermined.[55] Membrane instability may result from an abnormally low chloride conductance in the myotonia of goats or those induced experimentally with drugs.[395] In humans, only MC shows a low chloride permeability.[350]

Periodic paralysis results from reversible inexcitability of muscle membranes. The traditional classification distinguishes hypokalemic, hyperkalemic, and normokalemic types based on the serum level of potassium during a paralytic attack. All three categories share a number of clinical features, showing no direct cause-and-effect relationship between serum potassium level and paralytic events. Indeed, a given individual may have episodes of weakness associated with either hypokalemia or hyperkalemia. Of these, primary hereditary types consist of HypoPP and potassium-sensitive HyperPP or normokalemic periodic paralysis. The secondary acquired types include thyrotoxic HypoPP, acute or chronic potassium depletion and retention, hypokalemia caused by renal tubular acidosis, and chronic hypernatremia. In typical cases of periodic paralysis, nerve stimulation demonstrates a decrease in CMAP amplitude after several minutes of exercise. Patients with thyrotoxic HypoPP may show a dramatic improvement after treatment when they attain a euthyroid state.

During an attack of periodic paralysis, direct or indirect stimulation fails to excite the muscle membrane. An endplate potential (EPP) persists, although action potentials cease to propagate along the muscle fibers (see Chapter 13-4). In the HypoPP, application of calcium induces normal contraction in the muscle fibers stripped of their outer membranes.[115] Thus, inexcitability must result from dysfunction of muscle membrane rather than the contractile elements. An important finding common to HypoPP and HyperPP[47]

includes substantial depolarization of the resting membrane potential, presumably reflecting increased sodium conductance together with normal potassium and chloride conductance. These observations suggest that persistent inactivation of sodium channels leads to muscle fiber inexcitability at least in HypoPP. Interestingly, tetrodotoxin, a sodium channel blocker, cannot reverse the depolarization block.

Myotonic Dystrophy Type I

As one of the most common dominantly inherited muscular dystrophies, DM1 has an incidence of 1/8000. The responsible gene maps to serine/threonine protein kinase on chromosome 19q13.3, which normally has a run of 5–30 copies of the trinucleotide CTG sequence. In DMI, this repeat expands to more than 50 copies, showing a positive correlation between the repeat size and clinical severity,[420] the timing of cardiac complications,[5] and all-cause survival.[150] In one study using a computerized hand grip myometry,[300] leukocyte CTG repeat length also correlated positively to muscle relaxation time and negatively to measures of muscle strength. Thus, this expansion, located in the noncoding region of the RNA, must interfere with normal protein function by some as yet undetermined mechanism.

Trinucleotide repeats tend to expand during oogenesis, possibly accounting for genetic anticipation, or earlier onset of disease in subsequent generations, largely confined to the offspring of affected mothers. Less frequently, CTG repeat contraction can occur mostly during paternal transmissions.[338] In addition, mitochondrial inheritance of modifying genes or imprinting may play a role in material inheritance of congenital myotonic dystrophy. Studies of familial clustering suggest that factors other than CTG repeat length also play a role in the severity and progression of the disease.[151] In a patient with DMI, a laryngeal carcinoma showed CTG triplet expansion, which therefore may occur during acquired cell proliferation.[321] In one family with hereditary motor and sensory neuropathy (HMSN), 8 of 13 members also had signs of DMI, possibly implicating an allelic form of the myotonic dystrophy gene or two closely linked genes on chromosome 19.[396]

Typically, the illness begins in adolescence or early adult life with neuromuscular symptoms consisting of weakness and myotonia. Patients may have muscle stiffness and cramps, but distal weakness prompts them to seek medical advice. On questioning, they admit to difficulty with grip release, which they describe as more of an inconvenience than a disability. Weakness may begin in the hands and feet, but it eventually spreads to involve all the muscles, including the flexors of the neck. Both myopathic weakness and myotonia seen in oropharyngeal muscles play a part in dysphagia[118] and dysarthric speech.[87] In atypical cases with onset in late adulthood, the initial weakness may predominantly involve proximal rather than distal limb muscles.[218] Additional features may include frequent falls,[460] cardiac abnormalities,[298] disturbances of ocular motility,[443] gastrointestinal symptoms with bacterial overgrowth,[411] polyneuropathy,[449] sleep disorders,[356] personality disturbances,[92] nonalcoholic fatty liver disease,[390] and cognitive abnormalities associated with mild brain pathology, which remain relatively stable despite progressive motor deficits.[255]

Adult patients commonly have a hatchet-faced appearance, which results from relatively selective atrophy of the temporalis and masseter. Prominent wasting of the neck muscles, particularly of the sternocleidomastoids, gives rise to a swan neck. The head supported by a slender neck appears unstable. In recumbency, the patient cannot lift the head from a pillow against gravity. Facial weakness produces a blank expression and ptosis. In the absence of this characteristic appearance, milder cases of myotonic dystrophy may escape detection, although grip or percussion myotonia usually gives away the diagnosis. Myotonic phenomena become less prominent as the muscle wasting and weakness advance. Myotonia tends to diminish with continued exercise, and indeed the muscle may become almost normal clinically or electrically after repetitive testing.[238] Additional features include early frontal baldness, cataracts, gynecomastia, testicular or ovarian atrophy, and cardiac conduction defects. Neurogenic features as part of the generalized membrane abnormality include vocal cord paresis,[1] oculomotor abnormalities,[442] and cerebral involvement.[273,290]

Because of a highly variable penetrance, some subclinically affected individuals live normal lives. Most patients have a slowly progressive course with increasing weakness and myotonia that becomes notable in the second or third decade. Unusual response to certain medications such as barbiturates increases the risks of general anesthesia. Symptomatic patients have greater susceptibility to anesthetic and surgical complications.[265] Mexiletine at dosage of 150 to 200 mg three times daily over 7 weeks may provide some benefit in reducing handgrip relaxation time.[239] Patients with DM1 may benefit from aerobic training.[320] Therapeutic trials based on molecular mechanism of RNA toxicity may lead to the previously unforeseen possibility.[133]

Maternal transmission results in a high incidence of the congenital form of the disease characterized by poor feeding, respiratory distress, and facial diplegia. In this distinct entity, called congenital myotonic dystrophy (CMD), neuromuscular and systemic manifestations develop during the neonatal period in the offspring of mildly affected mothers.[197] The most characteristic symptoms during pregnancy include reduced fetal movements and polyhydramnios. In the neonatal period, infants have generalized hypotonia, facial weakness, hyporeflexia, and feeding and respiratory difficulties. These symptoms greatly diminish after a few weeks, although all affected children show psychomotor retardation. Some of these hypotonic infants may have no evidence of clinical or electrical myotonia until the age of 5 years or later. Weakness produces a triangular mouth in which the upper lip points upward in the middle. Many children have mental retardation, clubfeet, and diaphragmatic elevation. Infants frequently die of respiratory infections. Curiously, CMD rarely shows a paternal inheritance, appearing nearly always in children born to myotonic mothers. Approximately 10% of all the offspring and 20% of affected offspring from women with DM1 develop a congenital expression. If a mother has previously given birth to a child with this disorder, a subsequent child has an 80% risk of having the same.

Needle studies show myotonic discharges giving rise to "motorcycle" sounds (see Fig. 14-7 in Chapter 14) in all affected adults and approximately one-half of the relatives at risk for DMI. In 25 patients from 15 different families,[403] electrical myotonia occurred most frequently in the intrinsic hand muscles and orbicularis oculi, less commonly in the tibialis anterior and extensor digitorum brevis, and least frequently in the proximal and paraspinal muscles. In adults, the test helps to determine whether a patient with mild distal weakness and atrophy has DMI. Patients with partial syndrome, however, may lack clinical or electrical evidence of myotonia. During infancy and early childhood, patients may have neither characteristic clinical myotonia nor myotonic discharge. Needle studies may show a myopathic process with a low-amplitude, short-duration, polyphasic MUP. Tetanic muscle contraction evoked by a train of nerve stimuli gives rise to a lesser peak force, which then declines more slowly in patients with DMI as compared to normal subjects.[240] Automated analysis of such muscle force and relaxation time may help quantify myotonia better than maximum voluntary handgrip contraction.[241]

Other electrophysiologic findings include mild abnormalities in motor as well as sensory NCS and striking reduction in the number of functioning motor units. Patients may have a prolonged latency to reach peak velocity of pupillary light reflex and reduction in heart rate response to standing and in blood pressure response to sustained handgrip. All these may reflect skeletal and smooth muscle dysfunction rather than autonomic nervous system involvement. Despite slowing of peripheral motor conduction, central conduction time (CCT) tested by transcranial magnetic stimulation (TMS) remains within the normal range[79] or shows only a slight delay associated with increased threshold.[318]

Typical clinical presentation and family history usually suffice in diagnosing the condition. A DNA analysis based on the polymerase chain reaction technique and Southern blotting can estimate the size of the CTG repeat to disclose asymptomatic gene carriers, who may escape detection by neurologic examination, slit-lamp test, or EMG. A normal gene contains fewer than 30 repeats, whereas DMI allele has more than 50 repeats. Additional confirmatory features include an electrical pattern of repetitive

discharges, demonstration of lens opacities, and a degenerative change in muscle biopsy, which reveals Type I fiber atrophy and long chains of internal nuclei.

Myotonic Dystrophy Type II

Similar to DMI, characteristic findings of DMII or proximal myotonic myopathy, comprise myotonia, cataract, cardiac arrythmia, hypogonadism, and clinical anticipation of disease onset. Rebound nystagmus observed in some DMII patients suggests ocular myotonia.[2] Magnetic resonance spectroscopy (MRS) and MRI may reveal subclinical cardiomyopathy.[374]

Features distinct from DMI include proximal leg muscle weakness without striking muscular atrophy, mild, if any, facial involvement, sometimes severe muscle and joint pain, preservation of bulbar function and manual skills, and no signs of mental disturbance.[263,349,401] A congenital form of DMII, though rare compared to DMI,[85,272] may develop bilateral talipes equinovarus as the leading early symptom.[216] One patient with genetically proven DMII had focal asymmetric muscle weakness and abnormal EMG without myotonic discharges.[284]

Histopathological studies reveal preferential Type II fiber atrophy in DMII as compared to Type I fiber atrophy in DMI.[328,446] The spectrum of DMII findings also includes sudden cardiac death[375] and asymptomatic hyper-CK-emia, which, therefore, should prompt genetic investigation.[274] Despite the clinical similarities, genetic testing shows CCTG repeat on chromosome 3q in the noncoding part of the zinc finger protein 9 gene.[349,368,369,419]

In one series, all DMII patients had a normal short exercise test, which consistently showed postexercise CMAP declines in DMI cases.[367] In a series of 49 DMII patients, only 33 (67%) had diffuse myotonic discharges.[464] Thus, overreliance on this classical EMG finding may lead to delay in genetic diagnosis. In general, myotonic discharges worsen with heat and abate with cold, perhaps indicating a unique physiologic basis for muscle hyperexcitability.[368] In one study,[376] muscle pathology revealed myopathic abnormalities together with "denervation-like" changes and predominant Type II fiber atrophy in almost all 57 patients studied.

Myotonia Congenita

Genetic and clinical features distinguish three different varieties of myotonia congenita (MC). The first type originally described by Thomsen in four generations of his own family shows an autosomal dominant trait.[418] Patients with MC characteristically show stiffening and at times paralysis of the skeletal muscles during voluntary contraction after a period of rest. Loss of function mutations in *CLCN-1*, the gene encoding the skeletal muscle chloride channel on chromosome 7, reduces the chloride current, which normally stabilizes the muscle membrane by countering negative, or depolarizing, after-potential.[22,385] The resulting uninhibited membrane depolarization causes bursts of action potentials. The disease affects both genders equally, showing characteristic features of myotonia and calf hypertrophy with little or no loss of strength. Muscle biopsy materials reveal few or no degenerative changes. Myotonia appears in infancy or early childhood but remains mild throughout life. Occasional asymptomatic or mildly affected patients with EMG evidence of myotonic discharge indicate a high degree of genetic and clinical heterogeneity.[217]

The second, more common type, originally described by Becker,[25] appears in an autosomal recessive fashion, affecting men more frequently than women. More severe myotonia develops in the recessive type, which lacks chloride channels entirely, although the two varieties otherwise share similar clinical features. Electric after-activity results in slowed relaxation of the muscle.[178] In a third, rare type of myotonia congenita, the patient may have, in addition to myotonia, painful muscle cramps induced by exercise.[24] A mutation in the skeletal muscle voltage-gated *SCN4A* gene may also cause a painful congenital myotonia.[357]

The phenotypic spectrum of the MC ranges from mild myotonia disclosed only by clinical examination to severe and disabling myotonia with transient weakness and myopathy.[72] In general, symptoms often predominate in the lower limb, causing difficulty in ambulation. Movements begin slowly and with difficulty, especially

after prolonged rest. Although motor function improves to a normal level with continued exercise, this warm-up phenomenon induces no systemic effect. Thus, repetitive contraction of one set of muscles does not limber up another set of adjacent muscles. Despite the apparent weakness, muscle power returns to normal once myotonia disappears. Children commonly have restricted motor development. In some patients muscular hypertrophy develops as a result of continuous involuntary exercise, resulting in a Herculean appearance in contrast to the muscular wasting in myotonic dystrophy. This degree of hypertrophy, however, does not appear as commonly as previously publicized. The disease affects no other systems, allowing the patient to have a normal life expectancy.

Diagnosis depends on family history and clinical features, including readily demonstrable percussion myotonia. In equivocal cases, exposure to cold intensifies myotonic phenomenon as a useful provocative test. Muscle biopsy material reveals the absence of Type IIB fibers and the presence of internal nuclei, although to a lesser extent than in DMI. Painful muscle stiffness provoked by fasting or oral potassium administration may subside after intake of carbohydrate-containing foods. A contracted muscle shows electrical silence, or a contracture, probably resulting from some defect of muscle metabolism. In some patients, acetazolamide alleviates myotonia dramatically. Other patients with a resistance to one type of antimyotonic agent such as mexiletine or tocainide may respond well to another type of sodium channel blocking agent, for example, flecainide.[357]

Electrophysiologic studies play an important role in establishing the diagnosis of myotonia. In one study, 67% of the heterozygous carriers of recessive MC had electrical myotonia.[99] Repetitive nerve stimulation may cause a progressive decline in amplitude of the successively evoked CMAP, probably based on increasing muscle fiber refractoriness (see Chapter 18-8). This accounts for transient loss of strength observed clinically after a few muscle contractions against resistance. Unlike in myasthenia gravis (MG), the decremental tendency continues toward the end of a train, with a faster rate of stimulation producing a greater change. This phenomenon seen in both autosomal dominant and recessive varieties[73] shows a close association to the transient muscle weakness considered characteristic of this entity.[98] Prednisone may eliminate the electrophysiologic decrement.[62] Single-fiber studies show a progressive decline, sometimes leading to complete disappearance after direct stimulation of muscle fibers at 10 or 20 Hz.[219] A small percentage of normal muscle fibers may also show profound decrements in amplitude but without progressive waveform changes or conduction block characteristic of myotonic fibers.[428]

Hereditary Sodium Channelopathies

POTASSIUM-AGGRAVATED MYOTONIA

As implied by the name, potassium-aggravated myotonia (PAM), administration of potassium often produces dramatic worsening of this condition characterized by myotonia that often fluctuates temporally. Patients with this type of myotonia show no episodic weakness, paramyotonia, or dystrophy. Its variation includes, with overlapping signs and symptoms, myotonia fluctuans,[352] myotonia permanente,[230] acetazolamide-response myotonia,[336] and painful myotonia.[357,423]

PARAMYOTONIA CONGENITA

Paramyotonia congenita (PC) of Eulenburg[121] transmitted by a single autosomal dominant (AD) gene or as a de novo mutation,[136] affects both sexes equally. Gain-of-function mutations in the SCN4A gene on chromosome 17 cause a pathologic increase in sodium current, generating repetitive action potentials.[40,84] Homozygosity for this dominant mutation increases severity of the clinical impairment in the presence of 100% defective ion channels.[8] The same mutation may also affect cardiac repolarization.[326] Preexisting physiologic membrane depolarization induced by cold environment or with oral administration of potassium aggravates this tendency.[335]

The symptoms begin at birth or in early childhood, showing no improvement with age. Paradoxically, myotonia intensifies rather than remits with exercise[157] thus the name paradoxic

myotonia or paramyotonia. When exposed to cold, the patient may develop stiffness of the tongue, eyelids, face, and limb muscles. Electrical discharges may disappear with cooling, despite increasing muscular stiffness. Thus, the cold-induced rigidity may not always represent true myotonia. Attacks of flaccid weakness seen in cold-aggravated or potassium-aggravated myotonia resemble the spells of periodic paralysis. In various members of the same family, intermittent paralysis may occur without myotonia, or vice versa.

Laboratory findings include elevated or high normal levels of serum potassium. Acetazolamide therapy can reduce myotonic symptoms, although its administration may conversely trigger severe weakness in some patients. The lidocaine derivative, tocainide, can also suppress myotonia effectively, but it may cause reversible agranulocytosis. Mexiletine, another class 1b lidocaine derivative, also has clinical efficacy in several myotonic syndromes[58,186] In patients with muscle sodium channelopathies, depolarizing neuromuscular blocking agents such as succinylcholine can precipitate generalized myotonia. In contrast, an anesthetic agent, such as propofol, which decreases membrane excitability possibly by blocking sodium influx, may decrease myotonia[116,159]

Needle studies show myotonic discharges and, in some, fibrillation potentials on cooling.[157] On repetitive nerve stimulation CMAP amplitudes steadily decline. Cold induces a substantial fall in amplitude of the evoked potential, worsens the decremental tendency, and virtually abolishes myotonic discharges as well as voluntary recruitment of an MUP[186] Nerve stimulation fails to elicit muscle action potentials during episodes of paralysis, although the NCS shows no abnormalities between attacks. In one study[37] patients with PC showed reduced muscle fiber conduction velocity (MFCV) but normal degree of slowing after cold exposure. In one family with PC resulting from R1448C mutation in the SCN4A gene, pyridostigmine in doses of 60 mg three times daily abolished the postexercise CMAP decline and reduced the amplitude decrement to slow-rate repetitive stimulation.[207]

HYPERKALEMIC PERIODIC PARALYSIS

This autosomal dominant disorder, previously known as adynamia episodica hereditaria, affects the two genders equally with episodes of flaccid weakness that accompany an elevated serum potassium level. Paralysis typically follows a low carbohydrate intake or exercise. Gain-of-function mutations encoding sodium channel (*SCN4A*) on chromosome 17q23–25 enhance a persistent sodium current, possibly through slow inactivation coupled with enhanced activation.[27] Muscle weakness develops in response to physiologic membrane depolarization at elevated serum potassium.[54,173,452] Hyperkalemic or normokalemic type, when accompanied by myotonia, bares great resemblance to PC. The spectrum of clinical manifestations includes temperature-sensitive sodium channelopathy with heat-induced myotonia and cold-induced paralysis[404] and severe infantile HyperPP and PC associated with a *T704M* mutation.[42]

Spells of generalized hypotonia begin in infancy or early childhood. Sudden weakness develops after a short period of rest following exercise, upon exposure to cold, or after the administration of potassium. Further exercise or administration of carbohydrates temporarily delays what eventually becomes a more severe attack. Paralysis usually lasts less than 1 hour. Weakness probably results from muscle release of potassium rather than from the high serum level. Myotonia commonly involves the muscles of the face, eyes, and tongue. This finding suggests a linkage between HyperPP and PC. Both entities may appear in a single family, suggesting that they represent part of the spectrum of a single or closely related genetic disorder.[86]

Between attacks, EMG may reveal only increased insertional activity or show myotonic potentials and complex repetitive discharges (CRDs). During a paralytic episode, electrical or mechanical stimulation fails to excite the muscle despite increased irritability and myotonic discharges. In the presence of prominent myotonia, repetitive nerve stimulation may cause a decrement of CMAP, a tendency accentuated by cooling. Abundance of a low-amplitude,

short-duration MUP and early recruitment suggest progressive myopathy, which tends to develop at a time when attacks of paralysis decline in frequency. Muscle biopsy specimens show fiber size variability, internal nuclei, and vacuoles.[41]

Possible physiologic mechanisms underlying episodic paralysis[229] include reduced muscle membrane potentials at rest, reversible depolarization during the attacks, and neural hyperexcitability. Sustained immobility reduces the amplitude and area of electrically elicited CMAP, with the maximal effect occurring after 30 minutes. Prior intense muscle exercise may accentuate this to some degree. This appears to represent the electrophysiologic correlate of the characteristic symptom of weakness induced by rest after exercise (see Fig. 18-18 in Chapter 18).

HYPOKALEMIC PERIODIC PARALYSIS

In HypoPP, an autosomal dominant muscle channelopathy, episodes of flaccid paralysis develop in association with low serum potassium. The disease results from point mutations in calcium channel (*CACN*) or *SCN4A*encoding the skeletal muscle voltage-gated calcium or sodium channels with homologous pore-forming α subunits. Two common mutations in *CACN* and several mutations in *SCN4A* affect arginine residues in S4 segments that contribute voltage sensing.[266,458] Some of these patients show cold-induced shifts of voltage dependence in mutant *SCN4A*, causing periodic paralysis.[405] Autosomal dominant and sporadic HypoPP also results from mutations in the human skeletal muscle α1 subunit of the dihydropyridine-sensitive skeletal muscle *CACN*.[336] Loss-of-function mutations encoding *CACN* enhance channel inactivation, causing episodes of muscle weakness, particularly in response to lowered serum potassium. Thus, genetic abnormalities may affect calcium conductance in skeletal muscle, although how calcium channelopathies lead to paroxysmal weakness remains unknown.

Although variable in onset, episodes of paralysis typically begin in the second decade. During an attack, weakness starts in the legs, gradually spreading to all the muscles of the body, with the exception of the ocular muscles, diaphragm, and other respiratory muscles. Eyelid myotonia, originally described in HyperPP, may also appear in HypoPP. The episodes characteristically occur after rest, especially on waking in the morning. A heavy carbohydrate meal may precipitate the attack. Each paralytic episode, which may immobilize the patient totally, lasts several hours to a day, but a few days may elapse before a complete recovery. These attacks vary in frequency and severity but tend to remit after age 35 years. Despite a generally good prognosis and a normal life span, some patients die young, often with complications resembling malignant hyperthermia.[52] Rare familial cases of HypoPP have shown additional clinical and morphologic evidence of progressive muscular atrophy.[277]

Electrophysiologic studies during severe paralytic episodes reveal evidence of a decreased muscle excitability with preservation or enhancement of endplate noise (see Chapter 13-4) and reduced MUP recruitment. Electrical stimulation of the nerve elicits a reduced CMAP amplitude in proportion to the degree of weakness. Analogous to electrical recovery with repetitive stimulation, muscle strength improves temporarily after gentle exercise, followed by severe rebound weakness. A prolonged exercise test may document a gradual decline of CMAP, which serves as a measure of muscle membrane excitability.[7] Thyrotoxic patients with periodic paralysis also had a pronounced decrement, which improved if the patient attained a euthyroid condition.[414]

Administration of potassium chloride relieves the paralysis. Acetazolamide, which usually prevents paralytic attacks, may worsen the episode in some patients perhaps because of its kaliopenic effect.[26] Although this and other carbonic anhydrase inhibitors can cause nephrolithiasis, successful lithotripsy or surgical removal of renal calculus permits continued treatment.[413] Topiramate, an anti-epileptic drug known to have carbonic anhydrase inhibitory properties, also had a beneficial effect in decreasing the severity of paralysis attacks in an 11-year-old twin with HypoPP.[130] Between attacks, the patient has neither clinical nor electrophysiologic abnormalities except for the development of progressive myopathy, which shows a strong correlation to age but not to the history of paralytic attacks.[236]

OTHER PERIODIC PARALYSIS

Normokalemic periodic paralysis, a very rare condition, also seems to have an enigmatic relationship to potassium. Only a few reports have appeared since the original account[330] describing attacks of flaccid quadriplegia in infancy with normal serum levels of potassium. This condition probably qualifies as a variant of HyperPP, to which the clinical and genetic features closely resemble.[66] Loss-of-function mutations encoding potassium channel causes Andersen syndrome, a third type of periodic paralysis associated with cardiac arrhythmia and dysmorphic features.

Thyrotoxic periodic paralysis typically develops between 20 and 40 years of age in contrast to HypoPP, in which the onset of attack usually begins before age 20 and almost invariably before age 30.[148] Otherwise the two entities have indistinguishable clinical and biochemical findings. Paralytic attacks result from a preexisting abnormality of muscle membrane excitability rather than thyrotoxicosis.[6] Predominance in Oriental males suggests some genetic factors predisposing the muscle membrane for easy induction of paralytic attack under a slightly low potassium condition.[227] A thyrotoxic variety can occur as an isolated manifestation of incipient thyrotoxicosis.[457] In these patients, the general examination may reveal none of the features of thyrotoxicosis such as tachycardia, widening of the pulse pressure, ocular signs, skin changes, or weight loss.[148] The diagnosis then depends on a depression of thyroid-stimulating hormone (TSH) level; T3 and T4 levels may remain normal or only slightly elevated. Patients may respond to β-blockers but not to acetazolamide, the usual treatment for HypoPP.

3. MUSCLE ACTIVITES WITHOUT ACTION POTENTIAL

Contracture

The term *contracture* refers to intense mechanical muscle shortening in the absence of muscle action potentials. Thus, needle studies reveal no electrical activity in the contracted muscle. Ischemia induces contracture most commonly in patients with muscle phosphorylase or muscle phosphofructokinase deficiencies (see Fig. 12-3 in Chapter 12). In these entities, failure to produce adenosines triphosphate (ATP) possibly prohibits reaccumulation of calcium by the sarcoplasmic reticulum (see Chapter 12-2). Voluntary muscle contraction induces normal EMG but, after strong effort, the muscle relaxes only slowly over a period of 10 seconds. During this period the stiff muscle shows no electrical discharges. A normal MUP reappears if the patient voluntarily contracts the stiff muscle. Needle insertion or voluntary contraction initiates no myotonic discharge.

Rippling Muscle Disease and Myoedema

This condition first described in a Norwegian family with muscle irritability[422] characteristically shows percussion-induced muscle mounding (PIMM) and rapid contraction (PIRC), rippling, hyper-CK-emia, and muscle hypertrophy. Muscles display an unusual sensitivity to stretch, which may induce action potentials traveling entirely within the transverse and longitudinal tubular system.[221] This would result in myofiber shortening that propagates across a muscle, thus the name *rippling muscle disease* (RMD). In most reported patients, the involuntary muscle activities represented contracture, or electrically silent muscle contraction, whereas in others, rippling accompanied MUP discharges or bursts of short-duration, low-amplitude spikes, which resembled single muscle fiber discharges.[254] It may appear as an autosomal dominant condition[353,450] caused by incompletely mapped defect on chromosome 1q41 or by multiple missense mutations in caveolin-3 (*CAV3*) mapped to chromosome 3p25.[31] The cardinal clinical features in this entity, PIMM, PIRC, and muscle rippling, also vary considerably among members in the same family.[187] One form of RMD, called cardiac subtype, develops hypertrophic cardiomyopathy and arrhythmia with a dominantly inherited pattern.[353] Another form characterized by fatal arrhythmic cardiomyopathy and delayed bone age has an autosomal recessive inheritance.[214]

Association with seropositive MG[147,441] and autoimmune hemolytic anemia[301] distinguishes the autoimmune RMD from the hereditary forms. Other reported cases include sporadic RMD associated with *CAV3* mutations,[451] sporadic RMD unmasked by statin, which may cause an immune-mediated disruption of caveolar function,[18] and syndromes of *CAV3* and a mosaic pattern of dysferlin immunostaining.[379] In addition to RMD showing marked genetic and phenotypic heterogeneity, mutation of *CAV3* may give rise to LG muscular dystrophy (LGMD-1C), autosomal dominant families with asymmetric facial and proximal muscle weakness,[393] unilateral calf atrophy,[144] and distal myopathy and idiopathic hyper-CK-emia. Differential diagnosis includes myoedema, or electrically silent local bulge induced by tapping the muscle in a myoedematous or cachetic patient, and idiomuscular contraction or the brief fascicular contraction induced by tapping normal or partially denervated muscles. Some authors, based on a review of 39 members of a Swedish family, consider these percussion-induced phenomena as diagnostic of RMD even in the absence of hyper-CK-emia and rippling.[406]

4. SCHWARTZ-JAMPEL SYNDROME

Continuous muscle fiber activity occurs in osteochondromuscular dystrophy of autosomal recessive inheritance, originally described by Schwartz and Jampel.[381] The characteristic clinical features include short stature, muscular hypertrophy, diffuse bone disease, ocular and facial anomalies, and severe voluntary and percussion myotonia. Abnormalities seen in EMG resemble neuromyotonia or CRD. Unlike myotonia, the repetitive high-frequency discharges sustain without waxing or waning. They persist following nerve block or even nerve degeneration. Most but not all of the spontaneous activity disappears after administration of curare or succinylcholine.

5. MYOKYMIA

The term *myokymia*, first introduced to describe a patient with leg cramps[380] initially referred to spontaneous muscle contractions of the calves, thighs, chest, and arms. Others have used the term to include delayed muscle relaxation associated with continuous spontaneous motor unit discharges or, more broadly, manifestation of benign neuromuscular irritability. Different authors have since applied the name to muscle twitches in a variety of conditions, including lead poisoning, thyrotoxicosis, scleroderma, systemic infections, intoxications, and spinal cord lesions. Myokymia of the superior oblique muscle may cause micro tremor of the globe causing oscillopsia. Generalized myokymia with impaired muscle relaxation may develop in association with the syndromes of continuous muscle fiber activity (see Chapter 28-6), restless leg syndrome (see Chapter 28-15), muscular pain-fasciculation syndrome (see Chapter 28-7), and peripheral neuropathy (see Chapter 24-3). In autosomal dominant familial paroxysmal kinesigenic ataxia and continuous myokymia, patients have transient loss of coordination and balance lasting a few minutes. Associated features include a postural tremor of the head and hands, and fine rippling myokymia detected in about half of the cases.

According to current usage, myokymia has a distinctive clinical feature characterized by spontaneous repetitive contraction that involves narrow muscle bands for several seconds. Each segment of muscle, 1–2 cm in width, slowly contracts along the longitudinal axis. Independent irregular undulations along different strips give rise to the appearance of a cutaneous "race of worms." Although its electrical counterpart, myokymic discharge, varies slightly from one patient to another, the prolonged undulating movements all seem to result from brief tetanic contractions of repetitively firing single or multiple motor units. Myokymic discharges originating in motor axons usually occur alone without concomitant single muscle fiber discharges such as fibrillation potentials and positive sharp waves. In most limb myokymia, discharges arise focally at the site of a chronic peripheral nerve lesion. Less commonly, myokymic discharges result from biochemical, rather than structural, alterations, as the one seen in association with clozapine therapy[83] or timber rattlesnake envenomation.[45]

Myokymic discharges comprise two distinct EMG patterns. In the more common, discontinuous type, bursts of a single motor unit activity at 30–40 Hz last for 100–900 ms and repeat in semiregular intervals of 100 ms to 10 s (see Chapter 14-4). In the less common continuous type, rhythmic single or paired discharges of one or a few motor units recur with striking regularity at intervals of 100–200 ms. They do not typically wax or wane despite occasional association with myotonia. Neither the clinical myokymia nor the electrical counterpart changes substantially with sleep, volitional movement, rest, percussion, electrical stimulation, or needle movement. Reminiscent of hypocalcemic tetany, reducing serum-ionized calcium enhances myokymic discharges.[153] In contrast, xylocaine infusion of a peripheral nerve trunk blocks the discharges. Thus, myokymic potentials result from an alteration in membrane excitability at one of the various sites along the motor axon. Most likely, these ectopic discharges arise from terminal branches of the nerve fibers showing prolonged conduction block.[361]

Myokymic discharges occur in a heterogenous group of disorders, including, most notably, demyelinating conditions such as Guillain-Barré syndrome (GBS)[264] and radiation plexopathy,[164] but also, to a lesser, disorders of axonal degeneration.[206] Thus, this abnormality represents a nonspecific neuronal response to injury. Other conditions associated with limb myokymia include spinal stenosis,[71] nerve root compression,[53] subarachnoid hemorrhage,[38] celiac disease,[33] and neurocysticercosis.[32] Facial myokymia usually suggests segmental demyelination[316] as in multiple sclerosis[382] (see Fig. 14-12A in Chapter 14) or pontine glioma[155,215] but may also occur in hypothyroidism,[237] brain death,[370] and a systemic disorder called familial dyskinesia and facial myokymia.[129] It also appears in association with Bell's palsy,[30] syringobulbia,[348] meningoradiculitis,[139] and polyradiculoneuropathy (see Fig. 14-12B in Chapter 14).[439]

6. NEUROMYOTONIA

Peripheral nerve hyperexcitability (PNH) characterizes a group of heterogenous disorders involving the peripheral nerve in patients with a high propensity for developing an autoimmune disorder.[364] Isaacs[182,183] originally described two patients with progressive painless stiffness and rigidity of the trunk and limb muscles, which represents an idiopathic severe acquired form of PNH. Subsequent authors referred to this entity either as the Isaacs syndrome, or more descriptively, as continuous muscle fiber activity, neuromyotonia, neurotonia, or generalized myokymia. Still others used the now abandoned term *pseudomyotonia* to distinguish persistent muscle activity of peripheral nerve origin from true myotonia, which represents disorders of the muscle membrane. The disease usually appears sporadically without a precipitating factor or following a viral infection.[409] Symptoms begin at any age, although rarely in the neonatal period. Similar sustained muscle contraction may develop focally in the trigeminal nerve distribution following radiation of its motor branch.[103]

A few reports describe hereditary forms of sustained muscle activity in association with a neuronal type of Charcot-Marie-Tooth (CMT) disease[440] and other forms of sensorimotor or motor neuropathy[137,160] as well as epilepsy with or without episodic ataxia.[234] Continuous muscle activity has also appeared in patients with distal spinal muscular atrophy (SMA),[57] central pontine myelinolysis,[4] chronic inflammatory demyelinative polyneuropathy (CIDP),[314] multifocal motor neuropathy (MMN),[444] myasthenia gravis (MG),[168,261] amyotrophic lateral sclerosis (ALS), and Morvan's syndrome with autonomic and central nervous system dysfunction.[243] Other disorders recognized as a paraneoplastic syndrome associated with neuromyotonia include thymoma,[445] small cell lung cancer, Hodgkin's lymphoma,[220,448] plasmacytoma, and renal cell and bladder carcinoma.[185] Clinical evidence for a possible autoimmune etiology include the presence of oligoclonal bands in the spinal fluid, improvement following plasma exchange, association with thymoma and MG, raised anti-acetylcholine receptor (AChR) antibody titers, and induction by penicillamine. These clinical data, taken together with physiologic changes observed in mice injected with patients' immunoglobulin G (IgG), suggest an antibody-mediated

autoimmune mechanism.[165,306,421] Other entities possibly associated with production of the autoantibodies include spinal epidural abscess[250] and chronic graft-versus-host disease after bone marrow transplantation.[235] In fact, in acquired neuromyotonia, now considered an antibody-mediated channelopathy, 50% of patients develop autoantibodies to voltage-gated potassium channels (VGKCs).[447]

In milder forms of the syndrome, the abnormal activity appears restricted in degree and distribution, for example, isolated finger flexion[291] persistent facial myokymia,[156] and focal muscle twitching, especially in the legs. Asynchronous contraction of single or multiple motor units may produce generalized myokymia. In a severe form, continuous and excessive muscle contraction may give rise to an abnormal posture, hyporeflexia, and rigid arms with the wrist flexed and the fingers extended. The patient moves slowly and deliberately, as if imitating a slow motion picture. Stiffness seems to vary from one movement to the next. Excessive sweating occurs, probably as the result of continuous muscle activity. Enlarged muscles likely reflect activity-induced hypertrophy.

In myotonia, abnormal muscle activity occurs only after voluntary or induced muscle contraction. In contrast, as one of several causes of visible movement, neuromyotonia results from spontaneously occurring peripheral nerve discharges often accentuated by voluntary muscle contraction. Thus, patients with neuromyotonia suffer from sustained or repetitive spontaneous activity of the muscle fibers. In addition, the affected muscles stiffen and fail to relax completely following voluntary contraction. The motor activity persists during sleep, general or spinal anesthesia, or after procaine block of the peripheral nerve. Local administration of curare eliminates the activity. Intramuscular injection of the botulinum toxin can also eliminate or greatly diminish the discharges.[100] These findings suggest that the high-frequency discharge originates at various sites along the motor axon, but more commonly within the terminal branches.[251] Increased strength-duration time constant found by threshold tracking technique (see Chapter 10-4) may contribute to the axonal hyperexcitability responsible for ectopic activities.[50,252]

Needle studies reveal neuromyotonic discharges, or spontaneous motor unit firing rhythmically and continuously in all involved muscle groups. Waveforms of varying configuration usually appear at high frequencies up to 300 Hz, showing a marked decrement in successive amplitude. This produces a unique musical sound, "pings" that differ from other spontaneous potentials or myotonic discharge.[222] In addition to neuromyotonia, EMG abnormalities consist of fasciculation potential, often firing twice or three times forming doublet and triplet and myokymic discharges or multiple single unit discharges that have a high intraburst frequency, the bursts themselves occurring irregularly.[306] During voluntary contraction, many motor units fire successively with overlap. Artificially induced ischemia or electrical stimulation of the nerve may abruptly initiate the spontaneous discharge. Other electrophysiologic abnormalities include repetitive after-discharges following each stimulation of motor axons.[13,435] A marked Type I myofiber predominance probably represents conversion of Type II fibers to Type I fibers from continuous neuromyotonic stimulation.[154]

Diphenylhydantoin and carbamazepine render beneficial effects in most but not all patients.[9,14,183] Therapeutic options also include gabapentin[101] and intravenous administration of methylprednisolone to reduce the spasm.[188] Increased sensitivity to a nondepolarizing muscle relaxant seen in some patients may result from downregulation of AChR in response to chronic high ACh concentration.[142]

7. CRAMPS AND RELATED DISORDERS

Physiologic cramps seen in otherwise asymptomatic individuals represent briefly sustained, painful, or painless involuntary contractions lasting seconds to minutes[192,282] This definition excludes such repetitive movements seen in tremor, chorea, hemiballisms, or myoclonus and isolated muscle twitches associated with fasciculation potentials or CRD. Painful cramps, which commonly involve the calf muscles in healthy subjects, usually start after maintaining a certain posture and improve by rubbing or lengthening the muscle. Numerous

predisposing factors include salt depletion, other causes of hyponatremia, hypocalcemia, and vitamin deficiency. Repetitive magnetic coil stimulation of the tibial nerve over the ankle at 4 to 20 Hz regularly induces muscle cramps, which may serve useful in physiologic studies.[56] Leg and foot muscles have different cramp susceptibility based on excitability measures using muscle motor point stimulation.[286] Electrical stimulation cramp threshold frequency correlates well with the occurrence of skeletal muscle cramps.[279]

Cramps also constitute an essential part of a symptom complex of hereditary[351] or sporadic cases[94] of the muscular pain- or cramp-fasciculation syndrome. In the familial variety that affects both genders, the symptoms appear as an autosomal dominant inheritance during the first or second decade. Exercise-induced painful cramps predominantly involve the hands and feet, sometimes leading to more generalized symptoms. Involvement of the esophagus may cause difficulty in swallowing.[43] Nonfamilial types affect either gender with onset of symptoms during the third to seventh decades. Although painful cramps primarily occur in the calves, fasciculations develop in the lower limbs diffusely.

Painful intermittent cramps also characterize the rare syndrome of progressive muscle spasm, alopecia, and diarrhea,[371] which affects women more frequently than men. Involuntary muscle spasm involves the limb muscles initially and then the neck, trunk, and mastication muscles several years later. The spontaneous discharges, which probably originate centrally, resemble tetani, although serum calcium levels remain normal. The symptoms begin at about age 10 years and slowly progress, leading to malnutrition and possibly death. Skeletal muscle cramps, either spontaneous or induced by ischemia or exercise, also accompany a broad spectrum of other illnesses. For example, muscle cramp constitutes an early feature of motoneuron disease (MND), sciatica, and peripheral neuropathies.[65] Patients with certain inborn errors of metabolism may complain of exertional cramps, but not as an essential symptom.

In muscular pain fasciculation syndrome, NCS may show decreased velocities and increased distal latencies. Supramaximal stimulation of the nerve may produce showers of electric potentials following the CMAP, which abate with application of curare but not by nerve block.[392,407] Repetitive nerve stimulation also commonly induces afterdischarge lasting longer than 500 ms in normal controls without subjective cramps and in patients with peripheral neuropathy (see Chapter 18-8).[39] In EMG studies, muscle cramps consist of high-frequency irregular motor unit discharges at rates ranging from 40 to 60 Hz and occasionally reaching 200–300 Hz. These activities involve a large part of the muscle synchronously as opposed to asynchronous firing of motor units during voluntary muscle contraction. Despite effective inhibition by nerve block or spinal anesthesia, repetitive nerve stimulation distal to the block still induces cramping.[29] These findings suggest a peripheral origin.

Carbamazepine therapy partially suppresses hyperexcitability of the peripheral nerve.[407] Tocainide also reduces disabling muscle spasms and cramps associated with conditions characterized by neuromuscular irritability.[337] Quinine sulfate, though useful, poses some worrisome side effects.[282] Other possibly beneficial agents include vitamin B complex, Naftidrofuryl, and calcium channel blockers such as diltiazem.[203] Transcutaneous nerve stimulation may relieve severe muscle cramps as reported in a patient with muscle hypertrophy and fasciculation potentials.[283]

8. TETANUS

The toxin of Clostridium tetani usually travels from wound to central nervous system via blood or retrograde axonal transport. Other unusual sources of infection include malignant, hypoxic necrotic tumors and very rarely, a benign skin neoplasm.[196] After an incubation period of 1–2 weeks the patient develops either generalized or localized manifestations of neuromuscular irritability. Its stimulatory effect closely resembles strychnine, which competes with glycine for receptors in the spinal cord and higher structures.[391] The patients develop, in addition to hyperirritability of limb muscles, spasm of the masticatory muscles, or trismus, and facial grimacing, or risus sardonicus. The symptoms may worsen within a few

days but improve in several weeks except for possible chronic manifestations of tetanic contraction. Neonatal tetanus still poses a health hazard in developing countries as an important, preventable cause of death.[125,209]

Tetanus toxin presumably blocks postsynaptic inhibition in the spinal cord and brainstem, thereby increasing the excitability of the alpha motoneurons. The continuous motor unit discharges seen in EMG resolves during sleep, with administration of general or spinal anesthesia, and after peripheral nerve block. The shortened or absent silent period (SP) probably results from failure of Renshaw inhibition (see Fig.9-11 in Chapter 9). This characteristic electrodiagnostic feature of tetanus seldom occurs in other disorders with motor unit hyperactivity.[354] Reduction in the SP induced by transcranial magnetic stimulation (TMS) suggests impaired inhibitory mechanisms at multiple levels.[456] Although the exact pathophysiology awaits further clarification, the muscle spasms and rigidity almost certainly result from the effect of tetanus toxin on the central nervous system. This notwithstanding, some clinical and electrophysiologic findings suggest peripheral nerve involvement in severe tetanus.[383] Increased jitter and block in single-fiber electromyography (SFEMG) implies a presynaptic defect of NMT in human tetanus.[128] In one series of 40 patients seen after recovery from tetanus, electrophysiologic studies revealed evidence of mild subclinical axonal polyneuropathy.[247]

9. TETANY

The physiologic term *tetanus* also describes tetany caused by hypocalcemia and alkalosis. Decreased extracellular calcium increases sodium conductance, which leads to membrane depolarization and repetitive nerve firing. Hypomagnesemia and hyperkalemia also induce carpopedal spasm. Tetanic contraction abates with infusion of curare, but not with peripheral nerve block. Thus, the spontaneous discharge seems to occur at some point along the distal segment of the peripheral nerve. Various maneuvers precipitate clinical or electrical neuromuscular irritability, such as Chvostek's sign and peroneal sign by a gentle tap over the facial nerve and the lateral surface of the fibula, and Trousseau's sign by artificially induced forearm ischemia. Needle studies reveal a grouped, asynchronous MUP firing at a rate of 4–15 Hz, with periods of relative silence in between.

10. HEMIFACIAL AND HEMIMASTICATORY SPASM

Idiopathic hemifacial spasms (HFSs) typically occur in middle age, showing female sex and left-sided predominance.[75] In a service-based prevalence study in Oslo, Norway, the total prevalence of 9.8 per 100,000 increased with age to 39.7 among those older than 70 years.[312] Vascular compression of the facial nerve plays an important role, showing some association to cortical hypertension.[90,91] Magnetic resonance imaging (MRI) and tomographic angiography can identify vascular compression in most patients.[172] Symptomatic HFS as a late complication of Bell's palsy probably accounts for 5%–7% of all cases,[408] although one series reports 23%.[75] The same syndrome may also accompany posterior fossa tumors compressing the brainstem[36] or trauma to the facial nerve.[260]

The diagnosis of hemifacial spasm depends on visual inspection or EMG recording of abnormal movements. Involuntary twitching ordinarily begins in the upper and lower eyelid, spreading gradually to involve the remainder of the orbicularis oculi and other facial muscles. In advanced cases, spasm increases in severity and frequency, resulting in sustained contraction of several muscles on the affected side of the face. Volitional activation of one muscle results in synchronous involuntary discharges of other muscles (see Chapter 8-6). Thus, for example, the eyebrow rises during eye occlusion as originally described by Babinski.[397] Unlike focal convulsion of the face, which tends to march, the spasmodic movement, which often follows blinking, consists of simultaneous rapid twitching in several facial muscles on the affected side. Less commonly, the involved muscles may show prolonged contraction with irregular fluctuation. Synkinesis found in hemifacial spasm serves to differentiate these entities from other motor disorders, such as essential blepharospasm, facial dystonia, focal

seizures, and myokymia. In none of these conditions does stimulation of the supraorbital nerve elicit a blink reflex in facial muscles other than orbicularis oculi.

A possible therapeutic regimen includes, in addition to carbamazepine, botulinum toxin injection to induce muscle weakness, thus diminishing or abolishing the spasm without demonstrable effect on ectopic or ephaptic transmission in the facial nerve. Despite some side effects that include, in order of frequency, facial weakness, facial bruising, diplopia, ptosis, and various other mild complaints,[454] this preferred treatment provides effective relief of spasm for a mean duration of 19 weeks in one series.[131] Reduction of orbicularis oris spasm following botulinum toxin injection to the orbicularis oculi suggests that trigeminal afferent input alters the excitability of facial motoneurons.[315]

The frequency of repetitive motor unit discharges seen in HFS typically varies between 200 and 400 Hz, although some patients have a slower irregular pattern in the range of 20–40 Hz. Polygraphic studies reveal progressive diminution of spasmotic movements with deepening sleep stages, becoming lowest in REM sleep.[296] Central inhibitory processes may account for this partial decline. Inhalation anesthesia, which normally abolishes R1 and R2 of the blink reflex, however, fails to suppress the spasm.[293] A number of investigators have suggested various pathophysiologies underlying the HFS. Although the published accounts lack complete accord, spontaneous bursts of discharges may result from either hyperexcitability of the facial nucleus after axonal injury[293,432] or ectopic excitation at the site of injury.[311] The beneficial effects of surgical decompression suggest the primary site of involvement in the facial nerve rather than the nucleus, although hyperexcitability of the facial motoneurons could develop as the result of a peripheral lesion.

Electrically elicited blink reflex[12,210,309] can document synkinesis by demonstrating the presence of R1 and R2 components not only in the orbicularis oculi but also in the orbicularis oris, platysma, or other muscles innervated by the facial nerve (see Chapter 8-6, Fig. 8-15). A temporal variability of synkinetic responses characterizes idiopathic HFS in contrast to the highly reproducible results seen after aberrant regeneration of the degenerated facial nerve in Bell's palsy.[12,210] The findings suggest ephaptic transmission, or cross-talk, between axons as a physiologic mechanism responsible for synkinesis. Focal slowing secondary to demyelination constitutes an important prerequisite for ephapses in experiments with squid axons. This mechanism may play a role in some patients with an increased latency of R1 on the affected side[308] but not in others showing a normal latency.[210]

In the presence of ephaptic transmission, stimulation of one branch of the facial nerve may evoke a delayed response in muscles innervated by another branch.[410] In one study, following stimulation of the zygomatic or marginal mandibular branch of the facial nerve, simultaneous recordings from the orbicularis oculi and mental muscles confirmed transmission of impulses between the two branches.[310] If such a lateral spread results from ephapses, the onset latency of the delayed response should equal the antidromic and orthodromic conduction to and from the presumed site of the lesion. The measured latency, however, exceeded the sum by a few milliseconds, with an inference that the spread occurs at a more proximal site like the facial nucleus.[293] Intraoperative recordings also suggested backfiring of the facial motoneurons as the cause of the abnormal muscle response, which a properly timed blink reflex can eliminate at the facial nucleus.[292] In one study, paired stimuli used to elicit lateral spread during microvascular decompression evoked a constant second response after a fixed refractory period, suggesting a cross-transmission at the site of vascular compression.[462] In another similar study using a collision technique, delayed responses represented ectopic re-excitation of the involved axons in some recordings and backfiring of an alpha cell in others.[362]

Stimulation of the supraorbital nerve normally activates only a fraction of the motoneuron pool destined to innervate the orbicularis oculi muscle. Thus, the size of the CMAP evoked by direct stimulation of the facial nerve far exceeds that of the reflexively activated Rl. Increased amplitude of Rl found in hemifacial spasm suggests lateral spread of the impulse, activating more fibers

contained in the zygomatic branch. Synkinetic responses of Rl and R2 in the mental muscle, not ordinarily involved in the blink reflex, further support the theory of lateral spread of impulses to other fibers. In one study, [297] eliciting R1-like response in the orbicularis oris after stimulation at the supraorbital foramen, displacement of the stimulation site toward the extracranial origin of the facial nerve caused a progressive shortening of response latency. These features indicate antidromic conduction in the facial nerve motor axons followed by axon-axonal activation of the fibers innervating the lower facial muscles. This finding stands in contrast to the conclusion that trigeminal afferent input, rather than antidromic activation of the facial nerve, mediates the abnormal muscle response elicited by stimulation subthreshold to excite motor fibers.[287] Paired-shock technique reveals an upward shift of the R2 recovery curve not only on the side of spasm[110] but also on the unaffected side, suggesting enhanced excitability of the facial motoneurons and brainstem interneurons.[433] The presence of after-activity and late activity implies autoexcitation of the involved fibers.[308] Enhanced reflex responses on the affected side of the face also suggest hyperexcitability of the facial nucleus.[434] Unfortunately, none of these findings conclusively distinguish ephaptic or ectopic discharges along the motor fibers from facilitation of the facial nucleus.[362]

Spontaneous discharges of this type may affect the masseter muscles, causing hemimasticatory spasm. This rare disorder of the trigeminal nerve develops alone or in association with facial hemiatrophy[204,415] producing paroxysmal involuntary contraction of the jaw-closing muscles unilaterally. Needle studies demonstrate irregular bursts of MUP identical in pattern to those observed in hemifacial spasm. Electrophysiologic findings suggest ectopic excitation of the trigeminal motor root or its nucleus, an abnormality analogous to HFS.[15]

11. STIFF PERSON SYNDROME

The stiff person syndrome (SPS) characterized by rigidity and spasm from autoimmune encephalomyelopathies[119] usually affects adult men and women sporadically except for a rare congenital form.[13,269] Muscle stiffness develops insidiously, progressing from tightness to painful, sustained contraction, often inducing hyperlordosis of the lumbar spine in well-established cases. The spasm has some predilection for the pelvic and shoulder girdle muscles involving the lower more than the upper limbs and, unlike tetanus, usually sparing the facial muscles. The tightness of the chest muscles may interfere with breathing and swallowing. Painful spasms occur spontaneously or in response to sudden noise or other stimuli. Co-contraction of agonistic and antagonistic muscles may immobilize the limbs in unnatural positions. Inversion and plantar flexion of the feet reflect the overpowering force of the posterior versus anterior calf muscles. Movement, either active or passive, aggravates the pain. The excessive muscle contraction resembles physiologic cramps, although it involves many muscle groups simultaneously and continuously. The SPS may mimic hysteria with facial grimacing, unusual posture, and muscle cramps, all superficially resembling voluntary contractions. The conspicuous absence of other neurologic abnormalities may strengthen this erroneous impression. Close observation reveals the pathologic nature of the powerful spasms that supercede any voluntary contraction. Indeed, fractures of the long bones have resulted.

Needle studies show a sustained interference pattern in agonistic as well as antagonistic muscles. The persistent electrical activity associated with painful muscle cramps probably originates in the central nervous system. The spasm and spontaneous discharges disappear during sleep, with administration of general or spinal anesthesia, following procaine block of the peripheral nerve or after infusion of curare.[275] Increased central excitability leads to enhanced exteroceptive reflexes, including cutaneously elicited responses such as the blink reflex, showing an R1 bilaterally rather than ipsilaterally and, with higher intensity, R3 components following the normal R2 responses (see Chapter 8-3).

The exact neurophysiologic mechanism underlying the abnormal discharge remains unknown. Clinical similarities with chronic tetanus initially suggested a possible relationship

between these two entities. Tetanus toxin causes hyperexcitability of motor units by blocking spinal inhibitory postsynaptic potentials. Similarly, the motoneuron pool may become hyperexcitable in the absence of the inhibitory spinal mechanisms in the SPS. Unlike those with tetanus, however, patients with this syndrome have a normal SP.[256,400] Abnormal spread of various brainstem reflex resembles exaggerated startle, a feature considered characteristic of familial hyperekplexia with disturbed reflex excitation.[208] The recovery cycle of the blink reflex also indicates an increase in brainstem excitability.[294] Other physiologic findings reported in SPS include a diminution in vibration-induced inhibition of H reflex and normal presynaptic period for reciprocal inhibition.[132] Administration of baclofen[398] or diazepam (Valium) markedly diminishes rigidity and associated electrical discharges by suppressing interneurons at spinal and supraspinal levels.

Some SPS patients have an autoimmune pathogenesis with autoantibodies against glutamic acid decarboxylase (GAD), an enzyme present in GABAergic neurons, serum, and cerebrospinal fluid (CSF).[82] This autoantigen located in the GABA-producing neurons[177] may explain occasional association between this syndrome and neurologic symptoms caused by inhibition of GABA synthesis.[104] These patients also often suffer from insulin-dependent diabetes mellitus, a finding consistent with the expression of GAD in pancreatic β cells.[394] These findings suggest autoimmune origin of SPS, although one study reports two asymptomatic newborns, despite a high anti-GAD antibody titer transferred from their mother with typical SPS.[305] Motor cortex hyperexcitability tested by TMS correlated with anti-GAD autoimmunity.[211] Treatment with plasma exchange and immunosuppressants benefits some patients,[81,176,233] further strengthening the autoimmune hypothesis. In one patient, the use of the anti-CD20 antibody, rituximab, induced a lasting clinical remission.[17] Class I evidence exists to support the prescription of IVIG to treat SPS.[105]

Subsets of SPS comprise stiff trunk syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity.[74,134] In a familial SPS associated with GAD65, the father had an appendicular form and the daughter, axial form characterized by episodic opisthotonus.[51] Some SPS patients with antiamphiphysin autoantibodies have autoimmune paraneoplastic syndrome,[268,459] occasionally associated with rhabdomyolysis.[327] In one large series, 116 of 621 patients had anti-GAD antibodies, whereas 11, all women, had anti-amphiphysin antibodies, showing a high correlation to breast cancer.[122,304] This condition, which is strongly associated with cervical region stiffness, female sex, EMG abnormalities, and benzodiazepine responsiveness, may also respond to steroids and can dramatically improve with cancer treatment.

Other conditions described in association with stiff-person-like features include cerebellar disease,[345] thymoma and MG,[307] pernicious anemia and diabetes mellitus,[111] nocturnal myoclonus and epilepsy,[262] focal cortical atrophy with increased CSF gammaglobulin,[253] multiple myeloma following autologous bone marrow transplantation,[70] and sudden death.[143,289] Some of these symptoms may represent a variant called progressive encephalomyelopathy with rigidity and myoclonus.[271]

12. DYSTONIA AND BOTULINUS TOXIN THERAPY

The term *dystonia* can describe a clinical sign, a symptom, or a syndrome. Dystonia has two characteristic features distinct from other involuntary movements: sustained muscle contractions and the twisting nature of abnormality. Combined, these induce abnormal posture, giving rise to patterned torsional movement, as implied by the phrase "torsion dystonia." In one series, more common idiopathic type without identifiable underlying cause showed an estimated overall prevalence of 329 per million, including 294 cases of focal dystonia.[455] Primary torsion dystonia consists of generalized dystonia, formerly known as dystonia musculorum deformans; focal dystonia such as blepharospasm, torticollis, and writer's cramp, the three main entities encountered in practice; and multifocal or segmental dystonia. The underlying abnormality in torticollis also involves central motor programming for head position, rather than the activity of individual

neck muscles. The use of the asymptomatic hand may provoke dystonic movements of the contralateral symptomatic hand. This phenomenon, termed *mirror-movement dystonia*, provides further evidence for the presumed central origin of dystonia. Exteroceptive suppression reflex seen in sternocleidomastoid muscle after stimulation of the infraorbital branch of the trigeminal nerve also suggests abnormalities of brainstem interneurons.[339]

The reduction of brain GABA, an inhibitory neurotransmitter, may explain the clinical symptomatology of focal dystonia.[232] The symptom may also appear secondary to other neurologic conditions such as structural lesions of the basal ganglia,[68] cerebral palsy, complex regional pain syndrome (CRPS),[437] and exposure to toxins. Focal dystonia with some familial occurrence include cervical dystonia, Meige syndrome, writer's cramp, and other task-specific dystonia.[194] Advances in molecular technology have led to discoveries of GAG deletion in the DYT1 gene at the chromosome 9q34 causing dystonia with distinguishable clinical phenotypes.[44] Other linkages reported include the DYT7 gene to chromosome 18p, DYT6 gene to chromosome 8, and DYT13 gene to chromosome 1p.[431] A mutation in the gene encoding GTP cyclohydrolase caused dopa-responsive dystonia and neuroleptic malignant syndrome as a result of central dopaminergic blockade.[180] Segregation analyses of adult-onset blepharospasm and cranial-cervical dystonia suggest an autosomal-dominant transmission with reduced penetrance or polygenic inheritance.[89,195]

Dystonia-plus syndromes comprise the phenotype of dystonia and additional neurologic features. These include myoclonic dystonia[10]; three types related to parkinsonism, dopa-responsive dystonia,[399] rapid-onset dystonia,[123] and X-linked recessive dystonia or Lubag[3,146]; and two varieties of paroxysmal dystonia,[303] kinesigenic dystonia and dystonic choreoathetosis.

Peripheral entrapment and brachial plexopathy can give rise to distal, action-induced involuntary postures of the hand with focal dystonia. Such causes of secondary dystonia include pronator teres syndrome, radial nerve palsy, lower brachial plexus lesion, median nerve compression, and thoracic outlet syndrome.[340] Focal dystonia may follow soft tissue injury, suggesting a role of altered sensory information from a painful limb, which disturbs motor performance.[202] Spasmodic torticollis may develop in association with eighth nerve lesions.[46] Peripheral nerve injuries, often trivial, may trigger the causalgia-dystonia syndrome, producing burning pain, allodynia, hyperpathia and vasomotor, sudomotor and trophic changes, as well as a fixed dystonic posture.[34,438] Some believe this distressing syndrome results from a true organic disorder of the central nervous system, whereas others stress a psychogenic origin. Psychogenic and organic dystonia share similar cortical and spinal physiologic abnormalities, which, therefore, may represent a consequence rather than a cause of dystonia.[120]

Diagnosing focal hand dystonia in musicians challenges medical professionals.[360] In one series of 672 musical instrumentalists, 7% of patients with playing-related disorders had focal dystonia; 64%, musculoskeletal disorders; and 23%, peripheral nerve problems.[226] Ulnar neuropathies seen commonly in musicians may predispose them to focal dystonia.[60,359] Task-specific hand cramps also develop during writing, typing ,and piano and guitar playing. Familial aggregation of dystonia and other movement disorders in relatives of patients suggests a genetic contribution to musicians' dystonia with phenotypic variability, including focal task-specific dystonia.[372]

In these patients, EMG shows generalized muscle spasms with co-contraction of agonist and antagonist muscles, the findings characteristic of a focal dystonia. In musician's cramp, dystonic muscle showed less facilitation of motor evoked potential (MEP) induced by muscle vibration. This finding together with reduced inhibition of the antagonistic muscle may imply alteration of sensorimotor integration.[358] In one series,[378] 58 of 84 musicians experienced improvement from botulinum toxin injections. Sensory training using braille reading may alleviate deficits in spatial discrimination and improve disability in patients with focal dystonia.[465] Severe tardive dystonia may respond to pallidal deep brain stimulation.[429]

Surface EMG of the orbicularis oculi helps classify the pattern of blepharospasm to

distinguish it from apraxia or focal eyelid dystonia.[193] Video EMG allows an integrated approach to identity overactive neck muscles in patients with cervical dystonia.[302] In one study,[248] electrical impedance myography (see Chapter 13-8) may effectively differentiate normal subjects from dystonia patients by quantifying muscle asymmetries. Multichannel recordings reveal a characteristic pattern of co-contraction of the agonist and antagonist muscles of the forearm and hand in writer's cramp.[347] Oscillatory pallidal local field potential activity correlates with involuntary EMG in dystonia.[63] Different techniques of TMS showed abnormal cortical synaptic plasticity in dystonic patients with enhanced potentiation.[276] In somatosensory evoked potential (SEP) studies, N30 shows an increased amplitude in dystonia patients in contract to decreased amplitude in Parkinson's disease.[346]

Studies of movement-related potentials show an abnormal cortical processing of voluntary muscle relaxation in patients with focal hand dystonia.[463] Patients with writer's cramp show decreased contingent negative variation for finger extension in the affected and unaffected hands, but not for neck movement.[162] Patients with writer's cramp show postcontraction depression of physiologic reciprocal inhibition in the forearm muscles.[198,332] Blink reflex recovery curves characteristically show increased excitability of R2 in patients with blepharospasm and generalized dystonia.[110] Shortened cortical silent period (CSP) elicited in facial muscles (see Chapter 20-6) may also reflect hypoexcitability of cortical inhibitory neurons in cranial dystonia.[80] These findings together with anomalous somatosensory homunculus seen in patients with hand dystonia suggest abnormal cortical plasticity as a contributing factor in the development of dystonia.[21] Other electrophysiologic features reported in writer's cramp include abnormal spinal interactions from hand afferents to forearm muscles.[245]

Botulinum toxin injections effectively relieve symptoms of focal dystonias such as blepharospasm,[161,324] jaw opening dystonia,[108] torticollis,[224] writer's cramp,[28,373] and other hand dystonia.[190,436] The use of needle EMG facilitates identification of dystonic muscles.[295] A high-density surface EMG-guided study may help target botulinum toxin toward the muscle's endplate zone to increase its effect.[78,223] In addition to its indirect influence on the spinal cord through the action on the intrafusal pathway,[199,453] the toxin may transiently alter the excitability of the cortical motor areas by reorganizing the inhibitory and excitatory intracortical circuits.[141] This action would facilitate the effect of botulinum toxin A in poststroke spasticity.[200,201]

Botulinum toxin injections may cause increased jitter values and histologic evidence of mild muscle atrophy in distant limb muscles.[35,76] Such remote effects also involve autonomic function, showing mild abnormalities of cardiovascular function, far more often after botulinum toxin type B than after type A.[106] Despite the concerns of subclinical effects on uninjected sites, repeated botulinum toxin treatment may benefit patients with MG and cervical dystonia.[126] Some patients become clinically resistant after repeated injections, probably with production of anti-toxin antibodies.[107] The frequency of treatment and the injection of a higher weight-adjusted maximum dose per treatment constitute the most significant risk factors for antibody formation.[171] Lower protein load seems to reduce the risk of antibody formation.[191] Pre- and postinjection amplitude ratio of the extensor digitorum brevis CMAP elicited by peroneal nerve stimulation may serve to quantitate resistance to botulinum toxin.[145]

13. MYOCLONUS

Cortical, subcortical, spinal, and, less frequently, peripheral lesions can induce myoclonus defined as a sudden, brief, involuntary muscular contraction.[363,387] Myoclonus occurs not only as idiopathic seizures[461] but also in a group of heterogeneous disorders such as progressive myoclonus epilepsy of Unverricht-Lundborg, Lafora body disease, and myoclonus epilepsy with ragged-red fibers.[387] Other entities associated with myoclonus include Rett syndrome,[152] akinetic-rigid syndrome,[64] corticobasal degeneration,[49,416] hereditary neuropathy with liability to pressure palsy,[384] and posttraumatic stimulus suppressible myoclonus of peripheral origin.[11] Mechanical irritation of brachial plexus can also precipitate rhythmic myoclonus in the arm.[20] Detailed

electrophysiologic analyses help elucidate the origin of the discharge to identify different forms of myoclonic jerks.[386,387] Treatment, which depends on the type of myoclonus, usually consists of valproic acid, clonazepam, and piracetam.[213]

Abnormal sensory motor cortical discharges can cause a wide range of clinical motor phenomena.[285] Brief muscle jerks probably involve cerebral cortical mechanisms, which also account for the abnormal enhancement of SEP and premotor cortical potentials time-locked to the preceding spontaneous or action-induced jerking.[386] The site of abnormality in the sensory motor cortex probably dictates the varied pattern of motor responses seen in spontaneous or stimulus-sensitive myoclonus or focal motor epilepsy. Other related entities of interest include cortical tremor, defined as a type of reflex myoclonus associated with a giant SEP, enhanced long-loop reflex asterixis,[412] exaggerated 16–20 Hz motor cortical oscillation,[430] and premyoclonus cortical spikes recorded by jerk-locked averaging.[181,317,424]

Various SEP studies have revealed enhanced cortical excitability for 20 ms just after the myoclonus, followed by suppression throughout the postmyoclonus period. These findings indicate a pathologic enhancement of certain early cortical components seen normally.[389] Similar waveforms and scalp topography imply that the giant SEP and myoclonus-related cortical spikes may have a common,[390] if not identical,[96] physiologic mechanism. Paired-pulse TMS showed a decrease in physiologic intercortical inhibition, and digital stimulation markedly facilitated test MEP at interstimulus intervals ranging from 25 to 40 ms, both indicating sensory and motor cortex hyperexcitability.[259]

Paroxysmal axial spasm arises in propriospinal systems intrinsic to the spinal cord.[48] This type of spinal myoclonus may also present as thoracoabdominal muscle jerks showing rostral propagation.[67] Segmental myoclonus may rise in the spinal cord after various viral infections, including herpes zoster radiculitis. Usually abnormal movements follow the rash, but myoclonus may precede herpes zoster involving the same segments.[212] Studies of lumbosacral SEP by paired stimulation has revealed increased spinal cord excitability in a patient with rhythmic segmental myoclonus.[102]

14. MIRROR MOVEMENT

In congenital mirror movements, an MUP generated by voluntary movement shows normal temporal characteristics, duration, and recruitment pattern on the normal and mirror sides. These findings suggest a similar motor command for both voluntary and mirror movements. As one of the possible mechanisms of mirror movements, abnormally branched fast-conducting corticospinal tract fibers may project to motoneuron pools on both sides of the spinal cord.[124,267] A shortened contralateral silent period seen in this condition implies bilateral activation of the hand motor cortex.[69] In one case, a unilateral stretch of distal but not proximal arm muscles gave rise to bilateral long-latency reflex.[127] This finding indicates that a transcortical mechanism plays a role in the generation of long-latency stretch reflexes in distal but not in proximal arm muscles. In eliciting mirror movements, two distal muscles of the same patient may show different patterns of motor control.[19]

15. RESTLESS LEGS SYNDROME

Patients with restless legs syndrome (RLS) have an uncontrollable urge to move the legs when lying in bed or during periods of prolonged rest.[23,112,427] A large survey confirmed the high prevalence (10.6%), female preponderance, and underrecognition of RLS.[175] Dysesthesias in the legs either closely precede or follow occurrences of irresistible leg movements. Upper-limb restlessness may develop in RLS, and rarely as the initial symptom.[59,135] Periodic limb movements (PLMs) may occur in sleep, although the frequency decreases from wakefulness to sleep stages 1 and 2.[61,170] Familial cases may have an autosomal recessive linkage on chromosome 12q13–23 or 14q13–21.[231] Despite the high concordance, the disease severity, age of onset, and symptom descriptions often vary between monozygotic twins.[319]

In his original report, Ekbom[112] described two forms of RLS, one with pain, termed *crurum dolorosum* and the other with paresthesias, known as *crurum paresthetica*. Histologic studies

indeed identify two forms of RLS, one triggered by painful dysesthesias associated with small sensory fiber neuropathy, late onset, and no family history, and the other with an earlier onset age, positive family history, and evidence of large-fiber neuropathy.[329] Clinical studies may overlook the syndrome, which may present with symptoms suggestive of a peripheral neuropathy,[313] although some authors question prominent causal relationship between neuropathy and RLS.[109] Other conditions associated with RLS include spinal anesthesia,[174] regional low brain iron levels with hemochromatosis,[158] idiopathic hyper-CK-emia [93] and pregnancy.[258]

In one series,[179] eight consecutive patients seen with the primary complaint of leg movement had mild axonal neuropathy. One study found RLS in 10 of 27 CMT II and 1 of 17 CMT I cases, showing a positive correlation to patients' sensory symptoms.[140] A retrospective study revealed RLS in 33 of 99 diabetic neuropathy patients with association to small-fiber sensory symptoms and burning feet.[138] In a series, 11 (39.3%) of 28 CIDP patients had RLS compared with 2 (7.1%) of 28 age-matched controls.[344] In another study,[366] 5% of patients with polyneuropathy had RLS. In another series, RLS occurred more frequently in hereditary neuropathy (19.4%) compared with acquired neuropathy (9.2%) or controls (8.2%), although all over prevalence remained the same between 245 neuropathy patients and the same number of age-matched controls.[166,331]

In patients with RLS, short interstimulus paired transcranial magnetic stimulation showed a significant decrease in inhibition together with increase in facilitation of intracortical excitability.[341] A shortened CSP also suggests an impaired supraspinal inhibitory system.[117] The number of muscles contracted correlates with arousal from sleep.[88] Other electrophysiologic abnormalities reported include an increase in F-wave duration and shortened cutaneous silent period.[184] The recruitment pattern indicates the engagement of different independent and sometimes unsynchronized generators along the entire spinal cord for each PLM in sleep.[333] In most patients, however, muscle contractions show a constant order of propagation, descending or ascending the spinal segments.[425] This and other electrophysiologic patterns seem to indicate the spinal origin of the involuntary limb movements.

Several lines of evidence suggest the involvement of the dopaminergic system in the pathogenesis.[95] Treatment with gabapentin[163] or dopaminergic agonists[170] may provide an effective relief of the symptoms. Dopamine agonist targeting the dopamine D3 receptor subtype has a higher efficacy in PLM and RLS than a drug that preferentially targets D2 receptor subtype.[257] Pergolide substantially improves PLM and subjective sleep disturbance.[426] Reduction of antiparkinsonian medication during subthalamic nucleus deep brain stimulation may unmask symptoms of RLS.[205]

16. TREMOR

Clinical characteristics also allow subdivision of tremor into three types: (1) rest tremor seen in Parkinson's disease, which changes in frequency and phase only with different hand position[225]; (2) the intention or coarse ataxic tremor that occurs as the limb approaches a target, representing dysmetria; and (3) the action or postural tremor seen during a maintained limb position or during voluntary movement. Some authors use the joint name *action tremor* to include intention tremor that also occur during voluntary muscle activation. Action tremor, the most prevalent of the three types, has three subdivisions based on the underlying mechanism: (a) physiologic tremor accentuated by stress, drugs, or toxins; (b) symptomatic tremor associated with various disorders such as hereditary motor and sensory neuropathy, adult-onset idiopathic dystonia, parkinsonism, myoclonus, other metabolic conditions, Wilson's disease, and vitamin E deficiency; and (c) essential tremor consisting of autosomal dominant and sporadic varieties. Accelerometric recording and spectral analysis help classify hand tremor by establishing amplitude and frequency of oscillation.

Accumulated evidence indicates the involvement of the cerebellum in the generation of parkinsonian rest tremor, which may depend on the interaction between nigrostriatal-pallido-thalamic and cerebellothalamic systems.[246] Mechanical factors such as the hand position determine the peak

frequency of physiologic tremor,[343] whereas the degree of motor unit synchronization dictates the amplitude of oscillation.[242] Passive transmission of mechanical oscillation from the upper arm and forearm, however, may not necessarily account for physiologic tremor in the hand and fingers.[299] Symptomatic tremors have varied pathophysiologies unique to the underlying disorders.[244] Patients with anti-myelin-associated glycoprotein and peripheral neuropathy often develop a distinct form of neurogenic tremor.[325] Distal ulnar neuropathy at Guyon's canal may initiate finger tremor, although the mechanical basis remains obscure.[402]

The pathophysiology of tremor includes mechanical and central components for physiologic tremor, reflex-mediated clonus or voluntarily produced oscillations for psychogenic tremor, rhythmic activities of the olivocerebellar circuits for palatal and essential tremors, and basal ganglia loop for parkinsonian and dystonic tremor.[97,342] Upper-limb tremor induced by thoracic surgery suggests a peripheral generator.[77] Essential tremor ranks as one of the most common adult neurologic disorders, although its estimated prevalence varies depending on the choice of diagnostic criteria. Approximately 8% of young and elderly control subjects have an EMG-acceleration pattern consistent with mild essential tremor.[114] Early essential tremor qualitatively resembles the 8–12 Hz component of physiologic tremor, but its frequency decreases with time and advanced essential tremor has a frequency of 4–8 Hz.[113] Established treatments for essential tremor include propranolol and primidone [16] and, as an alternative to medication, stereotactic surgery. Some advocate botulinum toxin injection to cervical and forearm muscle to control head and hand tremor.[189]

The EMG examination serves as a tool for differentiation of tremor. The group with synchronous patterns includes some patients with essential, cerebellar, and enhanced physiological tremors. The group with alternating patterns includes some patients with essential tremor and cerebral and psychogenic tremors.[278] The ability of TMS to reset both postural tremor in Parkinson's disease and essential tremor suggests an intracortical origin of oscillation.[323] Patients with essential tremor have normal cortical excitability judged by CSP, which shows a similar duration as in control subjects.[355] Coherence analysis of EMG signals in essential tremor suggests dynamic right-left synchronization of central oscillators.[169] Despite its name, orthostatic tremor may not always develop related to the upright posture.[417] This tremor shifts from low to high frequencies with forceful muscle contractions,[270] making it distinct from essential tremor.

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PART IX

Interpretation of Study Results

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Studies for the Pediatric and Geriatric Population

Abbreviations: AChR—acetylcholine receptor, CMAP—compound muscle action potential, E1—active electrode, E2—reference electrode, EMG—electromyography, GBS—Guillain-Barré syndrome, LEMS—Lambert Eaton myasthenic syndrome, MG—myasthenia gravis, MUP—motor unit potential, NCS—nerve conduction study, SEP—somatosensory evoked potential, SFEMG—single-fiber electromyography, SMA—spinal muscular atrophy, SNAP—sensory nerve action potential

1. INTRODUCTION

Even an experienced physician may find electrophysiologic examination of a distressed child challenging. Yet we must perform the evaluation with confidence to minimize the anxiety of the family. Careful planning of the intended approach based on clinical diagnosis in question facilitates the process of assessment. A wide range of reference values reflecting the differing rates of neuromuscular maturation among children poses unique problems and limitations.[45,46,59,79] Adequate knowledge of pediatric neurology greatly improves the clinical practice of electromyography (EMG) and nerve conduction studies (NCSs) in this age group.[17,27] Although physical activity modifies the course of age-related motor changes, declining motor function associated with aging includes decreased motor performance and muscle strength.[11]

Pediatric population may have neuropathic process not seen in adulthood. For example, possible causes of isolated sciatic neuropathy in childhood include, in addition to compressive lesions, injury in utero,[76] complication of umbilical vessel catheterization,[73] traction injuries during breech delivery,[81] entrapment by a fibrovascular band,[90] gluteal intramuscular injection,[19] and various other conditions such as stretch injury during operation, puncture wound, lymphoma, and eosinophilic vasculitis.[48]

Electrophysiologic studies, though poorly tolerated in children, play an important role in establishing the diagnosis.[80] For example, used

early on in the first few days after birth, such studies can separate the rare brachial plexus palsies that occurred during the intrauterine period from weakness caused by the events at the time of birth. A repeat study, if conducted before possible reinnervation complicates the EMG interpretation, would identify neurotmesis and avulsion much earlier than 3 months of age, the crucial time in the assessment of nerve injury for possible surgical intervention.[70]

2. PRACTICAL APPROACH

Helpful additions to the ordinary adult instrumentation include pediatric-sized surface discs, finger-clips, and ring electrodes for recording; and bipolar probe for stimulation. An excessive application of conduction cream increases shock artifacts. For needle studies, a standard 30 mm, 28-gauge concentric electrode generally provides adequate information. When recording with monopolar needle (E1), the use of an intramuscular rather than surface reference electrode (E2) may reduce interference. Studies performed in an electrically noisy location, like intensive care units, call for a solid grounding. An incubator required to maintain the infant's body temperature may cause a major electrical interference.

A thorough explanation of the procedure to the parents maximizes their cooperation and reduces unnecessary fear. They must understand that the studies, although uncomfortable for the child, do not cause excessive pain. The physician must establish a good rapport by discussing the purposes of the study and describing each step in some detail. Demonstrating a conduction study on a parent may help relieve anxieties. The parents who recognize the usefulness of the study will usually assist the physician by controlling the child. Some choose to stay and may even hold the infant on their lap during the examination. They should understand in advance that they may have to leave, depending on the progress of the examination and the degree of their tolerance.

With clear explanation using appropriate terminology, most children can understand the need for the procedure. Distraction with stuffed animals or other toys may help young children. An older child usually cooperates better if encouraged to participate in the process by listening to the loudspeaker and observing the response build on the oscilloscope. They may help the examination by "hearing" the muscle and "watching" it twitch. Teenagers should receive full information regarding the study to avoid an element of surprise for either needle or nerve stimulation studies.

A physical examination before the study will establish developmental reflexes of an infant or functional skill in an older child. Once lost, the examiner rarely regains cooperation during needle exploration. Thus, a routine examination should begin with more easily tolerated NCSs, which provide important maturational information.[10,63] Minimal stimuli suffice to excite the superficially located peripheral nerves. For the more threatening needle EMG, the child should receive an honest forewarning about pain to avoid any distrusts. Some use the words "pin" instead of "needle" and "pinch" instead of "stick" to distract the child's attention from the electrodes. As stated earlier, children may become fascinated with the noise the muscles make, which often encourages their participation in the evaluation. For a comprehensive study, the needle examination must survey proximal and distal muscles in addition to the segment of concern. Single-fiber electromyography (SFEMG) depends on stimulation techniques for children aged 7 or younger who cannot provide optimal voluntary contraction (see Chapter 16-3).

A short, well-executed evaluation often eliminates the need for premedication, which limits the assessment of motor unit recruitment patterns. For routine study, most advocate the use of analgesia only in distress-prone children of a young age. In one survey of a pediatric population,[36] behavioral problems during the study showed a positive correlation with younger age, uncooperative attitude with previous painful procedures, negative experiences with medical or dental care, and fear and anxiety expressed by their mother about the electrical studies. Children aged 2–6 years showed extreme behavioral distress in 35% of examinations conducted without major pain medication.[37] This group may benefit from sedation. Premedication also has its place for repetitive stimulation and extended needle studies of spontaneous and insertional activity. Sedation,

analgesia, and general anesthesia all have some risks, requiring appropriate support devices. In our laboratory, we never sedate restrainable infants younger than 1 year old (although we sometimes sedate the parents). Most children 1–5 years old receive chloral hydrate 50 mg/kg, 30 minutes before the procedure. This dose usually produces enough effect for motor and sensory NCS without rendering the child too sleepy to recruit motor units during needle EMG. Administration of Demerol, another commonly prescribed drug, tends to oversedate the child.

We often underestimate the perception of pain from procedures, which looms large for children.[2] The anguish caused by pain could leave a persisting fear of future medical interventions. Making the study as comfortable as possible helps reduce the negative experience, rendering the investigation less stressful to the child (and the examiner).

3. MATURATIONAL PROCESS AND AGING

Table 29-1 summarizes the results of one series showing a steep increase in conduction of the peroneal nerve through infancy and a slower maturation of the median nerve during early childhood.[29] Tables 29-2, 29-3, and 29-4 summarize a set of normal values for motor and sensory studies, phrenic nerve latencies, and F-wave values in children. Table 29-5 summarizes the results of one study, [62] showing a reduction in the mean conduction rate of about 10% at 60 years of age.

Nerve Axons and Myelin Sheath

Peripheral nerve myelination, which begins at about the 15th week of gestation, continues throughout the first 3–5 years after birth. Myelinated nerve fibers mature at the same rate whether in utero or ex utero,[63] exhibiting no accelerated myelination just after birth.[86] The axons also mature during the prenatal and postnatal period, beginning at 20 weeks gestation and reaching a maximum between ages 2 and 5 years.[86] Conduction velocities increase in proportion to the myelin sheath thickness, which directly correlates to the diameter of the axon. In the phrenic nerve, the number of myelinated axons doubles from birth to 1 year of age[85] showing no further increase thereafter. The nodes of Ranvier also undergo remodeling, with a gradual lengthening of the internodal distances that peaks at about 5 years of age.[34]

Conduction velocities calculated from the onset latency increase linearly with the diameter of the largest axon, maintaining a ratio of 6:1.[12] Thus, infants of different weights but the same gestational age have a similar conduction velocity. Therefore, NCS helps distinguish premature babies from full-term infants with a small birth weight.[23] In the newborn, the distal motor latencies decrease with the increasing gestational age.[91] At birth, the median, ulnar, and peroneal nerves show a conduction velocity at approximately half the normal adult values, with an average of 27 m/s. Premature infants have an even slower rate, ranging from 17 to 25 m/s in the ulnar nerve and from 14 to 28 m/s in the peroneal nerve.[13] The values

Table 29-1 Normal Motor Nerve Conduction Velocities (m/s)

AGE	ULNAR NERVE	MEDIAN NERVE	PERONEAL NERVE
0–1 week	32 (21–39)	29 (21–38)	39(19–31)
1 week to 4 months	42 (27–53)	34 (22–42)	36 (23–53)
4 months to 1 year	49 (40–63)	40 (26–58)	48(31–61)
1–3 years	59 (47–73)	50 (41–62)	54 (44–74)
3–8 years	66 (51–76)	58 (47–72)	57 (46–70)
8–16 years	68 (58–78)	64 (54–72)	57 (45–74)
Adults	63 (52–75)	63 (51–75)	56 (47–63)

(Modified from Gamstorp.[29])

Table 29-2 Motor and Sensory Nerve Conduction Studies: Normal Values in Infants

	NO.	CMAP/SNAP· AMPLITUDE (mV/μV)	CONDUCTION VELOCITY (m/s)	DISTAL LATENCY (ms)	DISTANCE (cm)
1) *Neonate*					
Motor					
Ulnar	56	1.6–7	20–36.1	1.3–2.9	1–3.4
Median	4	2.6–5.9	22.4–27.1	2–2.9	1.9–3
Peroneal	4	1.8–4	21–26.7	2.1–3.1	1.9–3.8
Sensory					
Median	10	7–15 (A)	25.1–31.9	2.1–3	3.8–5.4
		8–17 (O)	—	—	—
Sural	1	8	—	3.3	5.5
Medial plantar	3	10–40	—	2.1–3.3	4.4–5.8
2) *1–6 months*					
Motor					
Ulnar	22	2.5–7.4	33.3–50	1.1–3.2	1.7–4.4
Median	6	3.5–6.9	37–47.7	1.6–2.2	2.1–4.1
Peroneal	10	1.6–8	32.4–47.7	1.7–2.4	2.5–4.1
Sensory					
Median	11	13–52 (A)	36.3–41.9	1.5–2.3	4.3–6.3
		9–26(0)	—	—	—
Sural	2	9–10	—	1.7–2.3	5.8
Medial plantar	2	17–26	35.4–35.7	1.5–1.9	4.5–5.5
3) *7–12 months*					
Motor					
Ulnar	28	3.2–10	35–58.2	0.8–2.2	1.9–4.6
Median	13	2.3–8.6	33.3–46.3	1.5–2.8	1.9–4.3
Peroneal	19	2.3–6	38.8–56	l.4–3.2	2.2–5.5
Sensory					
Median	15	14–64 (A)	39.1–60	1.6–2.4	5.5–6.8
		11–36 (0)	—	—	—
Sural	5	10–28	40.6	1.7–2.5	5.8–7.6
Medial plantar	6	15–38	39.4–40.3	1.9–2.7	6.5–7.9
4) *13–24 months*					
Motor					
Ulnar	53	2.6–9.7	41.3–63.5	1.1–2.2	2.4–4.8
Median	16	3.7–11.6	39.2–50.5	1.8–2.8	2.2–4.3
Peroneal	36	1.7–6.5	39.2–54.3	1.6–3.5	2.2–5.8
Sensory					
Median	29	14–82 (A)	46.5–57.9	1.7–3	5.7–9.1
		7–36(0)	—	—	—
Sural	9	8–30	—	1.4–2.8	4.5–8.6
Medial plantar	12	15–60	42.6–57.3	1.8–2.5	6.1–9.3

A, antidromic; O, orthodromic; SNAP, sensory nerve action potential; CMAP, compound muscle action potential (Modified from Miller and Kurtz.[63])

Table 29-3 Phrenic Nerve Latency for Different Age Groups (Both Sides)

AGE RANGE	*n*	MEAN ± SD
0–6 months	45	6.0 ± 1.6
6 months to 1 year	34	5.0 ± 1.2
1–2 years	34	4.8 ± 0.8
2–5 years	34	4.9 ± 0.8
5–10 years	34	5.5 ± 0.8
10–18 years	20	6.3 ± 1.2

(Modified from Russell, Helps, and Helms.[71])

at 23 to 24 weeks of fetal life average roughly one-third those of newborns with a normal gestational age,[18,63,77] which gradually approaches the normal neonatal values toward the conceptional age of 40 weeks. In premature infants, motor and proprioceptive conduction show a different time course of maturation when plotted according to the expected date of birth.[8]

Conduction velocities, roughly half the adult value in full-term infants, increase rapidly during the first year of life, when the process of myelination advances.[86] It then changes more slowly, reaches the adult range at age 3–5 years (Fig. 29-1), and plateaus by 4–5 years of age.[30,57,63,86,91] The nerves conduct 7–10 m/s faster in the arms than in the legs in older children and adults,[44] but not in newborns, who show average velocities of 20–30 m/s in both the upper and lower limbs. The ulnar and peroneal nerves mature most during the first 6 months of life, whereas the median nerve shows a slower development until the age of 1–3 years.[4] The modest velocity difference between the ulnar and median nerves gradually disappears by age 4 or 5. At about 3 years of age all ulnar nerve values reach the lower adult range.[86] In one study (Table 29-3),[71] phrenic nerve latencies showed a curvilinear relationship with age, averaging 6.0 ms at 0–6 months, falling to 4.8 ms between 1 and 2 years, then rising to 6.3 ms between 10 and 18 years of age. In another study,[43] the latency gradually decreased from 6 to 8 ms at birth to about 5 ms at the age of 1 year. In older children and adolescents from age 3 to 19 years, both motor and sensory conduction velocities tend to increase slightly in the upper limb and decrease in the lower limb as a function of age and growth in length.[57]

The peripheral somatosensory pathways develop at a faster rate than the central pathways measured by somatosensory evoked potential (SEP).[94] Cortical SEP matures, reflecting conventional age primarily during the first 3 weeks of life, although the trend continues throughout the first 2 years.[25,31,61] In the same process, the compound muscle action potential (CMAP) triples in size as compared to nerve conduction, which doubles in velocity.[86] Orthodromic compound sensory nerve action potentials (SNAPs) recorded proximally may comprise two distinct peaks in infants representing two groups of maturationally

Table 29-4 Range of Normal Values for F-Wave Latencies in Infants

MONTHS	NERVE	NO.	LATENCY (ms)	DISTANCE (cm)
1–6	Ulnar	1	17	21
	Peroneal	2	22–25	35–36
7–12	Ulnar	6	13–16	21–30
	Median	3	13–16	23–30
	Peroneal	3	19–23	20–47
	Tibial	2	19–24	43–48
13–24	Ulnar	10	14–17	25–39
	Median	4	14–18	22–27
	Peroneal	10	21–26	30–53
	Tibial	9	25–26	42–52

(Modified from Miller and Kurtz.[63])

Table 29-5 Normal Latencies (ms) and Conduction Velocities (m/s) in Different Age Groups (mean ± SD)

NERVE	AGE 10–35 YEARS (30 CASES)		AGE 36–50 YEARS (16 CASES)		AGE 51–80 YEARS (18 CASES)	
	SENSORY	MOTOR	SENSORY	MOTOR	SENSORY	MOTOR
Median nerve						
Digit–wrist	67.5 ± 4.7		65.8 ± 5.7		59.4 ± 4.9	
Wrist–muscle		3.2 ± 0.3*		3.7 ± 0.3*		3.5 ± 0.2*
Wrist–elbow	67.7 ± 4.4	59.3 ± 3.5	65.8 ± 3.1	55.9 ± 2.6	62.8 ± 5.4	54.5 ± 4.0
Elbow–axilla	70.4 ± 4.8	65.9 ± 5.0	70.4 ± 3.4	65.1 ± 4.2	66.2 ± 3.6	63.6 ± 4.4
Ulnar nerve						
Digit–wrist	64.7 ± 3.9		66.5 ± 3.4		57.5 ± 6.6	
Wrist–muscle		2.7 ± 0.3*		2.7 ± 0.3*		3.0 ± 0.35*
Wrist–elbow	64.8 ± 3.8	58.9 ± 2.2	67.1 ± 4.7	57.8 ± 2.1	56.7 ± 3.7	53.3 ± 3.2
Elbow–axilla	69.1 ± 4.3	64.4 ± 2.6	70.6 ± 2.4	63.3 ± 2.0	64.4 ± 3.0	59.9 ± 0.7
Common peroneal nerve						
Ankle–muscle		4.3 ± 0.9*		4.8 ± 0.5*		4.6 ± 0.6*
Ankle–knee	53.0 ± 5.9	49.5 ± 5.6	50.4 ± 1.0	43.6 ± 5.1	46.1 ± 4.0	43.9 ± 4.3
Posterior tibial nerve						
Ankle–muscle		5.9 ± 1.3*		7.3 ± 1.7*		6.0 ± 1.2*
Ankle–knee	56.9 ± 4.4	45.5 ± 3.8	49.0 ± 3.8	42.9 ± 4.9	48.9 ± 2.6	41.8 ± 5.1
H reflex, popliteal fossa		71.0 ± 4.0		64.0 ± 2.1		60.4 ± 5.0
		27.9 ± 2.2*		28.2 ± 1.5*		32.0 ± 2.1*

*Latency in milliseconds. (Modified from Mayer.[62])

distinct sensory fibers.[91] Earlier changes in the proximal rather than distal nerve segments tend to shorten the H-reflex and F-wave latencies more quickly than the distal latencies.

Conduction velocities begin to decline after 30 to 40 years of age, but the values normally change by less than 10 m/s by the 60th year or even the 80th year.[84] In one series measuring at two points separated by 5 years,[88] median and ulnar sensory nerve study showed a decrease in amplitude of 2.3 and 1.8 μV, an increase in onset and peak latencies of 0.07 and 0.04 ms and 0.11 and 0.06 ms, and a decrease in conduction velocity of 1.1 and 0.7 m/s. Aging also causes a diminution in amplitude and changes in the shape of the evoked potential (Table 29-6).[28] The latencies of the F wave and SEP also gradually increase with advancing age, probably reflecting preferential loss of the largest and fastest conducting motor units.

Type I and Type II Muscle Fibers

Nerve fibers, which determine muscle fiber properties, reach the elongated myoblasts at 6 weeks of gestation and form the neuromuscular junction at 10 weeks. Initially, the large Type II fast twitch muscle fibers outnumber the smaller Type I slow twitch fibers. This relationship reverses gradually with increased growth of Type I fibers after the nuclei migrate peripherally during the first 10–15 weeks of gestation. By 15–20 weeks, Type I fibers, larger in diameter, match the Type II

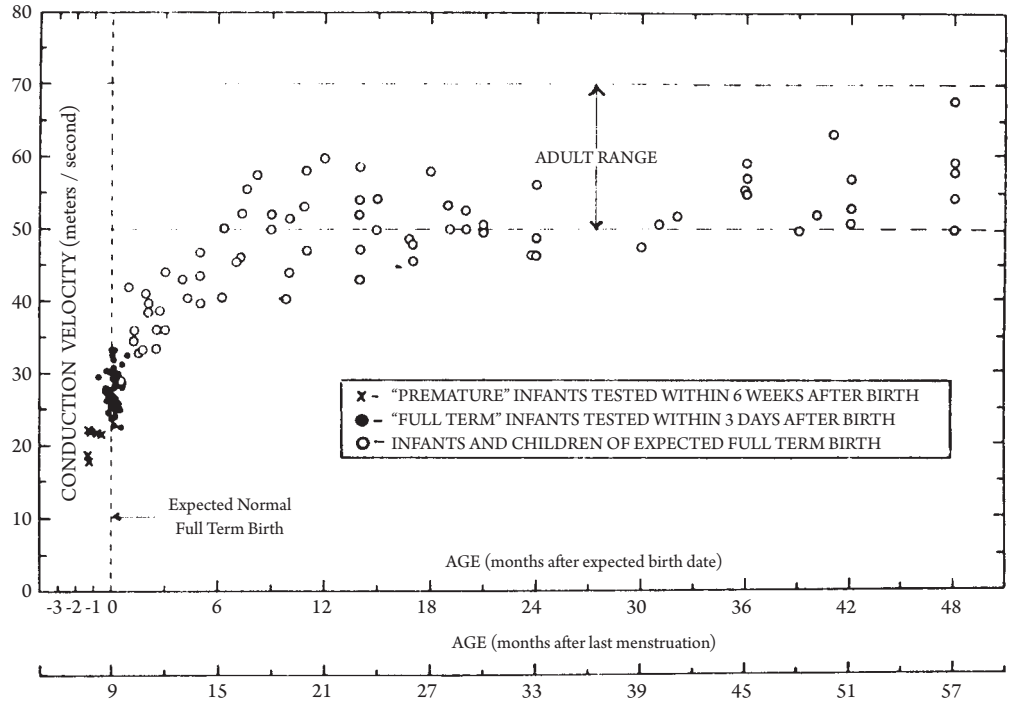

FIGURE 29-1 Relation of age to conduction velocity of motor fibers in the ulnar nerve between the elbow and wrist. Velocities in normal young adults range from 47 to 73 m/s with most values between 50 and 70 m/s. Ages plotted indicate month after expected birth date based on calculation from the first day of last menstruation. (From Thomas and Lambert,[86] with permission.)

fibers in number.[27] Muscle fibers mature not only during intrauterine life but also after birth.[60] The increased proportion of Type II fibers in adults may result from a transformation of Type I to Type II fibers.[60] Quantitative ultrasonography may help evaluate muscle thickness and its ratio to subcutaneous fat thickness, and muscle echo intensity in children.[69,74]

The maturational factors also influence the interpretation of EMG in newborns and infants. Careful quantification of the motor unit characteristics constitutes a useful aspect of the needle examination. It often serves as a means of distinguishing among acute, subacute, and chronic stages during the course of a neuropathic process. Abnormal motor units in children may result not only from diseases of the nerve or muscle, as in adults, but also from deranged development of the neuromuscular system. Proper assessment of motor unit potentials (MUPs) in health and disease, therefore, requires the knowledge of the maturational sequence of the nerve and muscle.

4. NERVE CONDUCTION STUDIES

The same anatomic landmarks used in adults apply when placing stimulating and recording electrodes in children. Active (E1) and reference (E2) leads placed 2 cm apart are best suited for recording from the small hands in the newborn. For motor conduction studies, a disc electrode placed on the thenar or hypothenar eminence serves as the active electrode (E1), and a ring electrode wrapped around the long or little finger, as the reference (E2). For technical reasons, most electromyographers test the median and ulnar nerves in the upper limb and the peroneal and tibial nerves in the lower limb. Table 29-5 summarizes normal values for different age groups.

Studies should include at least one sensory nerve, especially in the assessment of a diffuse process. These include median, ulnar, and sural SNAP, all easily elicited in newborns.[63] In the upper limb, orthodromic studies consist of stimulating

Table 29-6 Comparison of Conduction Studies Between Younger Group (*n* = 52, 10–40 years) and Older Group (*n* = 52, 41–84 years)

NERVE TESTED		NO. OF NERVES	AGE 29.7 ± 6.9 YEARS (MEAN ± SD)	NO. OF NERVES	AGE 54.0 ± 10.5 YEARS (MEAN ± SD)	P VALUE
Peroneal						
M amplitude	(mV)	104	5.4 ± 1.5	98	5.0 ± 1.3	0.03*
M latency	(ms)	104	3.7 ± 0.9	98	3.7 ± 0.7	0.98
MNCV	(m/s)	104	49.5 ± 5.4	98	47.8 ± 3.8	0.01*
F latency	(ms)	44	47.1 ± 5.3	42	47.6 ± 4.9	0.68
FWCV	(m/s)	44	60.6 ± 7.7	42	59.9 ± 7.6	0.66
F number	(#)	10	8.5 ± 1.7	29	9.7 ± 3.1	0.19
Tibial						
M amplitude	(mV)	104	6.7 ± 2.0	100	5.9 ± 1.5	0.001*
M latency	(ms)	104	3.5 ± 0.6	100	3.6 ± 0.6	0.23
MNCV	(m/s)	104	48.6 ± 4.2	100	49.1 ± 4.9	0.52
F latency	(ms)	74	47.9 ± 4.1	74	48.3 ± 4.6	0.63
FWCV	(m/s)	74	58.3 ± 6.2	74	57.5 ± 6.8	0.49
F number	(#)	25	11.6 ± 3.4	27	12.4 ± 2.6	0.39
H amplitude	(mV)	53	1.4 ± 0.8	43	1.2 ± 0.8	0.20
H latency	(ms)	53	29.8 ± 2.3	50	30.7 ± 2.0	0.04*
Sural						
S amplitude	(μV)	53	20.9 ± 8.0	50	17.2 ± 6.7	0.01*
S latency	(ms)	53	2.7 ± 0.3	50	2.8 ± 0.3	0.16
SNCV	(m/s)	53	52.5 ± 5.6	50	51.1 ± 5.9	0.23

F number, number of responses out of 16 trials; FWCV, F-wave conduction velocity in the proximal segment; MNCV, motor nerve conduction velocity in the distal segment. The older group showed significantly reduced amplitude for all the nerves tested with no changes in conduction characteristics except for peroneal MNCV and tibial H latency. (Modified from Kimura.[51])

the digits and recording from the median or ulnar nerve at the wrist or elbow. Because of its length, the use of the long finger reduces the stimulus artifact in studying the median nerve. Antidromic recording of digital potentials elicited by proximal stimulation generally yields more stable results for median, ulnar, radial, and musculocutaneous nerves in the upper limb and sural nerve in the lower limb. In cooperative children, quantitative thermal perception testing may also uncover small nerve fiber dysfunction to complement sensory conduction studies.[39]

Stimulation with a needle electrode lowers the shock intensity, reducing the stimulus artifact. The use of a relatively large ground, such as a band electrode placed around the wrist or ankle, may accomplish the same result. Other useful strategies to minimize the shock artifact include lowering the impedance by cleansing the skin, decreasing the surface spread of current by limiting the amount of conduction cream applied to the electrodes, and altering the direction of the current by rotating the anode around the cathode. Stimulation at the digits or palm may initially trigger a grasp reflex in infants causing movement artifacts, which usually habituate with repeated trials.

In infants with very short limbs, any movement hinders the measurement of the nerve length

under study, especially if fat hides the usual bony landmarks. When dealing with a nerve segment several centimeters in length, an error of only 1 cm will result in a 20%–25% velocity change. Immobilizing the limb properly throughout the study improves the accuracy of NCS. Despite the inherent difficulty, nerve stimulation technique serves its purpose, for example, by showing the presence of a normal SNAP, which excludes a lesion distal to the dorsal root ganglion. Here, studies add important information even without calculation of the forearm sensory conduction velocity. The same applies for motor nerve stimulation, which helps assess the number of functional axons distal to the site of lesion. Neonates with poor temperature homeostasis should remain in an incubator during the study. Older children may perspire profusely with anxiety and crying, making the limb unexpectedly cool with evaporation.

5. LATE RESPONSES

Table 29-4 summarizes normal F-wave latencies for infants up to 2 years of age.

Late responses elicited by distal stimulation add usefully to the evaluation of the peripheral nerves in infants (see Chapters 7 and 9). The unique advantages include a higher rate of abnormalities accumulated over the longer conduction distance and a greater reproducibility reflecting smaller measurement errors in percentage. Submaximal stimulation gives rise to a constant H reflex, whereas supramaximal shocks evoke F waves with variable waveforms and latencies.[64]

The test also helps establish maturational changes in the proximal versus distal nerve segment.[89] Preterm neonates have slower H-reflex conduction velocity compared to full-term babies.[65] Normal values for the soleus H reflex established in 83 preterm and term infants include the latency (mean ± SD) of 19.2 ± 2.16 ms for conceptional ages 31 to 34 weeks, 16.7 ± 1.5 ms for ages 35 to 39 weeks, and 15.9 ± 1.5 ms for 40 to 45 weeks.[10] These results reflect the degree of myelination in infants of increasing conceptional age, showing progressive latency diminution despite a longer reflex pathway associated with growth. In one study of 103 elderly subjects aged 60–80 years, the H reflex elicited in 92% of the population showed an average latency of 30.8 ± 2.6 ms (mean ± SD) on the right and 30.7 ± 26 ms on the left, with the upper limit of normal side-to-side difference of 1.8 ms.[26]

The H reflex, although elicitable from most muscles in infancy, undergoes progressive central inhibition, showing consistent recording only from the calf muscle toward the end of the first year. In one study, for example, stimulation of the ulnar nerve elicited an H reflex in most full-term infants, but not after 1 year of age.[86] When tested using the H-reflex latency, the sensory fibers of the ulnar nerves conducted approximately 10% faster than the motor fibers between wrist and elbow in the newborn.[86]

Supramaximal stimulation of any peripheral motor nerve evokes the F wave in full-term newborns. In one series, the F waves of the abductor pollicis brevis, elicited in 100% of trials, showed a higher F/M amplitude ratio and more uniform waveforms than in adults.[65] The F-wave latencies change with both maturation and growth,[10,63] showing a decrease during the first year and a progressive increase, thereafter, in proportion to the limb length.[30] In one study,[75] F-wave latencies of the median nerve averaged 16.0 ± 1.5 ms (mean ± SD) for infants less than 3 months of age, and 14.4 ± 1.6 ms for youngsters between 4 months and 2 years of age. In another series,[64] the minimal F-wave latency of the median nerve averaged 17 ms in neonates (1 to 28 days), 15 ms in infants (1 month to one year), and 16 ms in children (2 to 12 years). In children, the minimal F-wave latency remains relatively constant during the first 3 years of life because rapid change in conduction velocity compensates for the increase in arm length. The F-wave latency then increases until about the 20th year of life, when it reaches 95% of its maximal value.[56] An older group of subjects have longer F-wave latencies than the young healthy subjects.[67]

6. BLINK REFLEX

Table 29-7 summarizes various aspects of direct response, and R1 and R2 components of the blink reflex in 30 neonates compared with those

Table 29-7 Studies of Facial Nerve and Blink Reflex (mean ± SD) in 30 Healthy Neonates as compared to 30 Healthy Adults

	FACIAL NERVE STIMULATION		SUPRAORBITAL NERVE STIMULATION			
	DIRECT RESPONSE		R_1 COMPONENT		R_2 COMPONENT	
	NEONATES	ADULTS	NEONATES	ADULTS	NEONATES	ADULTS
Latency (ms)	3.30 ± 0.44*	3.15 ± 0.28	12.10 ± 0.95†	10.60 ± 0.82	35.85 ± 2.45†	31.30 ± 3.33
Difference between two sides (ms)	0.32 ± 0.33*	0.14 ± 0.17	0.38 ± 0.22	0.31 ± 0.31	1.79 ± 1.36	2.14 ± 1.76
Amplitude (mV)	0.48 ± 0.30	1.21 ± 0.77	0.51 ± 0.18†	0.38 ± 0.23	0.39 ± 0.19†	0.53 ± 0.24
Ratio (right/left)	0.95 ± 0.56	1.03 ± 0.45	1.00 ± 0.33	1.04 ± 0.96	1.15 ± 0.64	0.99 ± 0.53

*$p < .05$, †$p < .01$.

In neonates, as in adults, the blink reflex elicited by unilateral stimulation consisted of an early ipsilateral component, R1, and a late bilateral component, R2. Stimulation of the supraorbital nerve elicited R1 in all but 3 of the 113 infants. Despite a considerably shorter reflex arc, the neonates had a greater latency than the adults. Stimulation of the supraorbital nerve elicited R2 bilaterally in all adults but only in two-thirds of neonates, mostly on the side ipsilateral to the stimulus. The presence or absence of R2 and its amplitude depended to a considerable degree on the intensity of stimulation, that is, the stronger the shock, the larger the size of R2. (Modified from Kimura, Bodensteiner, and Yamada.[52])

established in 30 older subjects aged 7–67 years (average age, 31 years).

Despite extensive studies in adults, only a few reports dealt with the maturational pattern of blink reflexes in infants and children.[15,40] We also reported our experience with newborn infants less than 3 days of age to establish normal ranges of the early and late blink reflex, R1 and R2, and the direct response elicited by stimulation of the facial nerve.[52] Before initiating the study, we had anticipated various technical problems that might make testing difficult in small neonates. These concerns not withstanding, optimally applied low-intensity stimuli elicited R1 without even awakening the infant in light sleep. A higher intensity shock used to elicit R2 while keeping the infants fully awake posed a greater challenge. Strong facial nerve stimulation required to elicit a direct response caused more technical difficulties than weak trigeminal nerve stimulation to evoke a blink reflex.

As in adults[53] the blink reflex elicited by unilateral stimulation basically consists of an early ipsilateral component, R1, and a late bilateral component, R2 (see Figs. 8-1 and 8-5 in Chapter 8). A comparable study showed R1 in all but 3 of the 113 infants.[52] Despite a considerably shorter reflex arc, the neonates have a greater latency than the adults (Fig. 29-2). Stimulation of the supraorbital nerve elicits R2 bilaterally in all adults but only in two-thirds of neonates, mostly on the side ipsilateral to the stimulus (Fig. 29-3)[6,15,52] and rarely in premature babies.[35,83] The presence or absence of R2 and its amplitude depend to a considerable degree on the intensity of stimulation, that is, the stronger the shock, the larger the size of R2.

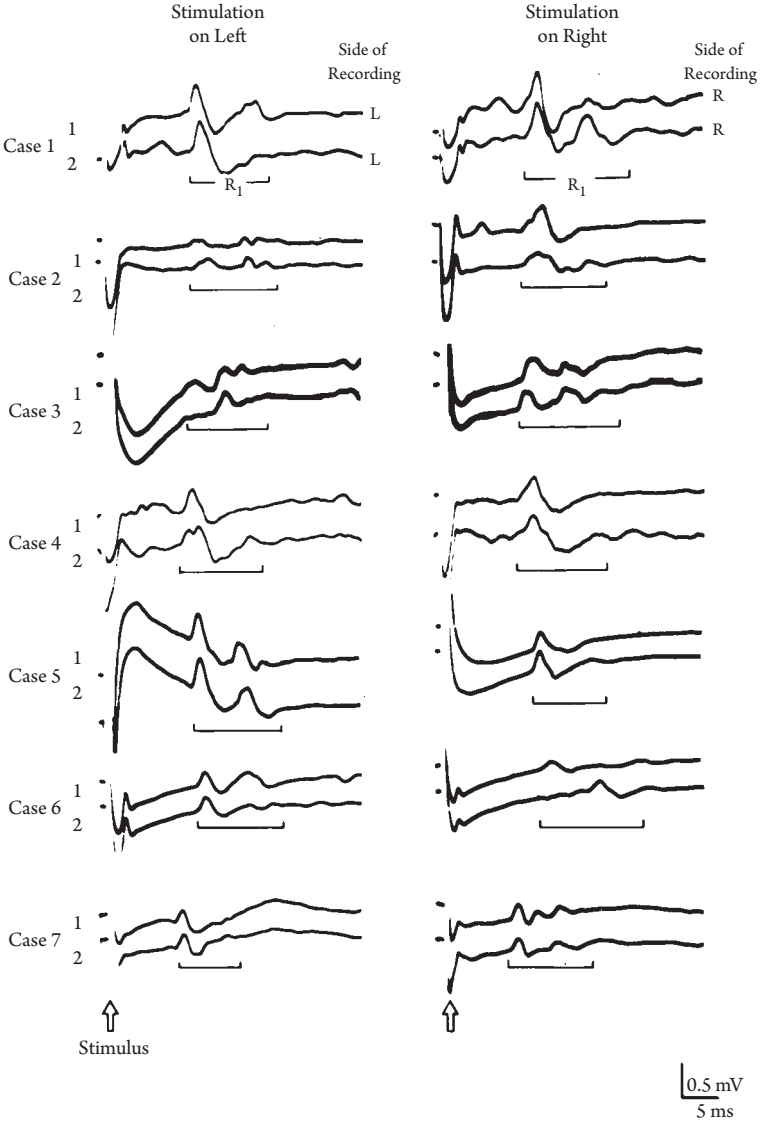

FIGURE 29-2 R1 component (*brackets*) of electrically elicited blink reflex in seven newborn infants, recorded form the orbicularis oculi muscle on the side of the stimulus (*arrows*). Tracings depict two successive trials in each subjects, showing consistency of R1 response. Neonates often have polyphasic R1 with prolonged duration at times showing more than one component, separated by brief intervals (Cases 2 and 5, *left*). If a submaximal stimulus fails to elicit the initial peak of R1, measurements to the second peak may show an erroneously increased latency (Case 6, *right*, second tracing). (Modified from Kimura, Bodensteiner, and Yamada.[52])

The presence of R1 in most newborn infants provides the evidence for maturation of the oligosynaptic pontine pathway at birth. Similarly, R2 elicited on the side of stimulus in two-thirds of neonates indicates at least partial establishment of the polysynaptic connection. A comparatively greater latency of the direct response and of R1 in infants suggests incomplete myelination of the trigeminal and facial nerves. Conduction velocities in full-term infants average roughly half of those of adults. Thus, despite considerably shorter reflex pathways in infants, the latency of R1 exceeds the adult value by approximately 1.5 ms (Table 29-7). By about 6 years of age, the R2 components in children parallel those in adults in consistency and excitability[15,40] This corresponds

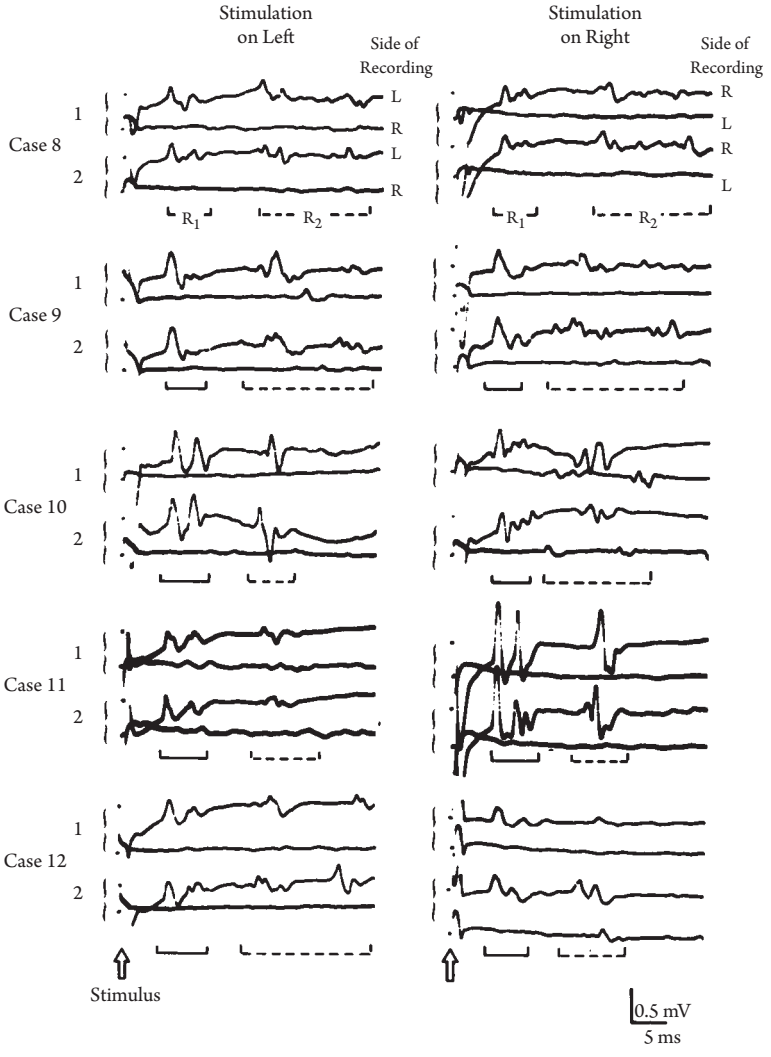

FIGURE 29-3 R1 (*solid brackets*) and R2 components (*broken brackets*) of electrically elicited blink reflex in five newborn infants, recorded from orbicularis oculi muscle on both sides after unilateral stimulation (*arrows*). Each subject had two successive right-sided stimuli (*right half*) followed by two successive left-sided stimuli (*left half*) to show consistency of reflex responses. All five infants showed R1 and ipsilateral R2 with small or absent contralateral R2 (Cases 9 and 11, left; Cases 10 and 12, right). (Modified from Kimura, Bodensteiner, and Yamada.[52])

with the time of completion of brainstem myelination in children.

Measuring the latency of R1 can aid in assessing lesions of the brainstem, and the trigeminal and facial nerves in infants.[82] In contrast, R2 has little clinical value at this age because of its maturational variability. Of the two electrically elicited blink reflex components, the bilateral R2 bears a great resemblance in latency and duration to the corneal reflex elicited with tactile stimulation. As an inference, therefore, an absent or asymmetric corneal reflex provides a questionable clinical sign in neonates.

7. TESTS OF NEUROMUSCULAR TRANSMISSION

In testing neuromuscular transmission, repetitive nerve stimulation performed with the infant's arm

immobilized on a pediatric arm board serves as the primary electrodiagnostic method to quantitate clinical findings.[16] The same criteria apply to pediatric and adult populations except for infancy (see Chapter 18). In younger children, sedation facilitates limb immobilization with restraining straps or tapes. A warm blanket may help to maintain surface temperature monitored with a thermistor. It takes less intensity to achieve supramaximal stimulation in children than in adults. The use of a needle inserted close to the nerve minimizes intensity variability related to muscle contraction. For recording, a pair of surface electrodes is better suited for the evaluation of full responses, although a subcutaneously placed needle or wire may suffice as a substitute despite its restricted recording radius.

As in adults, the proximal limb muscles and facial muscles usually provide the highest yield. Repeat studies and testing multiple nerves help confirm an abnormality by establishing reproducibility. With mild sedation, the procedure does not necessarily awaken the child. Stimulation begins at a slow rate, usually 2–3 Hz, as in adults. Children under 6 years of age usually cannot voluntarily exercise the muscle. The test of posttetanic potentiation and exhaustion, therefore, must include a brief train of stimuli usually at rates of 20–50 Hz for 1–5 seconds under adequate sedation. For the same reason, SFEMG also depends on stimulation technique and not on voluntary contraction (see Chapter 16-3).

Compared with adults, infants have different physiologic responses to repetitive stimulation, reflecting immature neuromuscular junctions at birth. In one series of 17 newborns, including 6 premature infants[54] continuous stimulation for 15 seconds and at a rate of 1–2 Hz induced no change in amplitude. With an increased stimulus rate, 5 of 8 infants had at least 10% facilitation at 5–10 Hz, and 12 of 17 infants had a decremental change averaging 24% at 20 Hz. Premature infants showed exhaustion at rates greater than 20 Hz, possibly because of inadequate neuromuscular reserves. Although greatest in the premature infants, all 17 had reduction, averaging 51% at 50 Hz. Despite a reduced margin of safety, normal newborns showed neither decrement at a rate of 2–10 Hz nor facilitation at 20–50 Hz. Thus, stimulation at 5 Hz or less evoked a stable response in all healthy infants.

Children suffer from the same disorders of neuromuscular junctions as adults (see Chapter 26-4). These include myasthenia gravis (MG), botulism, Lambert-Eaton myasthenic syndrome (LEMS), and drug-induced conditions. Infants may also have congenital myasthenia gravis, which may show a series of two or more repetitive responses to a single stimulus (see Fig. 18-10 in Chapter 18). This finding should prompt the electromyographer to perform further studies with repetitive stimulation. As an experiment of nature, 20% of infants born of myasthenic mothers have transient myasthenia following transplacental transfer of antibody. Children with transient neonatal MG have elevated antiacetylcholine receptor antibodies (AChR), which serves as one of the best indicators of the disease.[66] Anti-AChR antibody assays, however, fail to adequately discriminate this condition from prepubertal onset juvenile MG with high frequency of seronegativity.[3,92]

8. ELECTROMYOGRAPHY

A pediatric size concentric electrode has a diameter of 0.30 mm as compared to a standard electrode with a diameter of 0.45 mm. In one study,[9] comparison between these two types of electrode showed no clinically relevant differences in assessing an MUP. The examination of an infant must often deviate from the routine order of steps recommended for a cooperating adult. If the child tolerates testing well, study the insertional and spontaneous activities initially, as in adults. Infants tend to maintain relaxed postures of the extensor muscles, such as the gastrocnemius in the legs and triceps in the arms, which, therefore, serve well when looking for spontaneous discharges. Passive shortening of the muscle can achieve enough relaxation for this part of the examination. Studies of the less active intrinsic foot and hand muscles also suffice for the evaluation of resting states in a diffuse process. The distal muscles, with a large motor point zone, tend to show frequent endplate spikes, which may confuse the issue. Their irregular high-frequency pattern of discharges, however, stands in contrast

to fibrillation potentials, which fire regularly at a slower rate (see Chapter 13-4).

If the infant resists, assess the MUP associated with the movements first. The initial insertion usually induces a maximal volitional contraction, allowing the evaluation of the recruitment pattern of motor units in infants. Studies of motor units should, therefore, center on the flexor muscles, which tend to fire reflexively as part of a withdrawal response. The most commonly tested include the tibialis anterior and biceps brachii. If necessary, the use of primitive reflexes helps activate flexor responses. Evaluation of generalized diseases may consist of studying a certain group of muscles at rest and another group of muscles during contraction. Unilateral, segmental, or focal processes call for a more complete assessment, with sedation if necessary. In infants, the needle must clear a large amount of adipose tissue to reach the muscle.

Compared with adults, infants and young children have smaller muscle fibers and less fiber density, rendering the MUP lower in amplitude and shorter in duration. With a 5- to 8-fold increase in fiber diameter, MUP amplitude increases 2- to 5-fold in size during life.[72] In infants 3 years old or younger, the amplitude ranges from 200 to 700 μV, usually not exceeding 1 mV.[22,72] This makes a subtle myopathic change difficult to detect. In contrast, infants with neurogenic atrophy show a definite dropout of motor units in number, which causes the rapid firing of a large MUP in conjunction with a recognizable late recruitment. In fact, a needle study shortly after birth may readily document intrauterine onset of a neuropathic process in patients with infantile spinal muscular atrophy (SMA).[49] The same also holds in the study of neonatal brachial plexus palsy in detecting the pattern of abnormalities, which helps select appropriate patient care. Although reinnervation may complicate the interpretation, electrophysiologic studies would identify the type of plexus injury before 3 months of age, the crucial time for possible surgical intervention.[1,5,38,70]

For these reasons, needle studies in infants detect neurogenic patterns of weakness more accurately than myogenic features.[20] This distinction particularly holds in infants who normally show a small-amplitude, short-duration MUP. Besides, documenting an early recruitment poses a considerable difficulty during irregular muscle contraction. In one series, EMG and biopsy results showed a good correlation in 14 of 15 infants with Werdnig-Hoffman disease and in 3 of 3 with congenital infantile polyneuropathy, but in only 4 of 10 infants with myopathy.[21] Thus, in the study of a floppy infant (see Chapter 29-10), myopathic disorders tax the electromyographer more than neurogenic conditions.[20] Although subtle changes call for careful reassessment before resorting to an invasive procedure, patients with suggestive but inconclusive evidence of a myopathic disorder benefit from muscle biopsy for confirmation. As in adult cases, electromyographers should err on the normal side of interpretation of infants, based on the principle that patients have no abnormalities unless proven otherwise.

9. SOMATOSENSORY AND MOTOR-EVOKED POTENTIALS

The same technical principles apply for infants as for adults (see Chapter 19) in eliciting an SEP for study of the peripheral nerve, spinal cord, brainstem, and cerebral cortex,[93] but studies in neonates utilize lower stimulation rates of 1–2 Hz combined with higher stimulus intensity.[25,31] Short-latency SEP peaks in infants and children resemble those of adults (Fig. 29-4). Studies of preterm and term infants,[31,50,58,78,94] however, show a considerable variability in latency and waveform during the first few years of life, which reflects a complex maturational process of the central pathways. In contrast, the latencies of the peripheral and lumbar potentials correlate positively with age and height, yielding a predictable nomogram (Fig. 29-5).[33] In general, the peripheral part of the sensory pathway reaches the adult range at 3–4 years of age and the central part, at school age.[87] Group means of the median SEP indicate minor differences in waveform and latency between the genders.[42]

The peak latency of N9, generated at brachial plexus, decreases exponentially with age during the first year and increases with height thereafter.[7] The interpeak latency N9-N11, which measures conduction between the brachial plexus and dorsal column, decreases with age, whereas

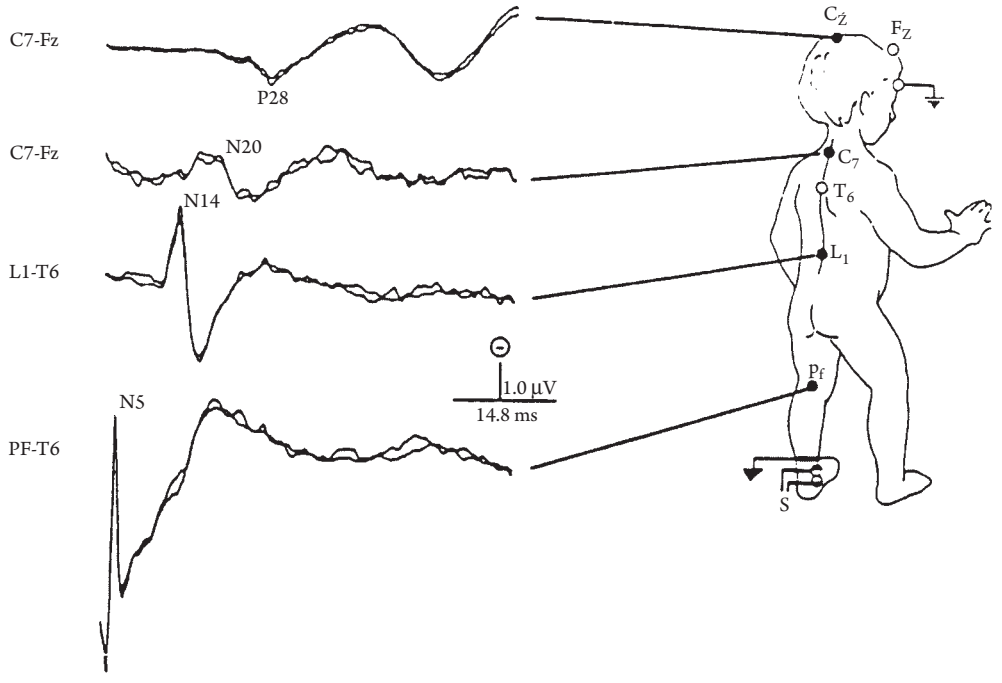

FIGURE 29-4 Tibial nerve somatosensory evoked potential simultaneously recorded at various sites after stimulation at the ankle. The labels show the surface polarity and mean peak latencies observed in 32 normal young subjects (age = 1–8 years, height = 82–130 cm). Electrode placement included popliteal fossa (Pf), first lumbar (Ll), and seventh cervical (C7) vertebral spinous processes, and Cz (2 cm behind Cz) referenced to either Fz or the sixth thoracic vertebral spinous process (T6). (Modified from Gilmore, Bass, and Wright.[33])

the N11-P13 interval, which represents the brainstem conduction to the cervico-medullary junction, shows no change during 4 years of life.[7] The central conduction time (mean ± SD), measured from the cervical area (N13) to the primary cortical response (NI), remains relatively constant (5.66 ± 0.44 ms) from 10 to 49 years of age. It increases approximately 0.3 ms between the fifth and sixth decades, with no further change thereafter.[41] Stimulation of the lower-limb nerves elicits spinal evoked potentials more easily in infants than in adults.[32,58] Both latency and amplitude of middle-latency SEP increase substantially with age.[95] The age also influences the detection thresholds to noxious heat as measured by verbal rating scale. Contact heat-evoked potentials, showing a negative correlation with age, corroborate this finding.[14]

Magnetic stimulation shows a markedly increased threshold in infancy, decreasing to the adult level at 8 years old or thereabout.[55] The onset latency reaches adult values at about 11 years old, and then increases linearly with age from the second to the ninth decade, involving both the central and peripheral motor pathways.[24] The amplitude also declines gradually with increasing years.

10. THE FLOPPY INFANT

Despite some overlap, pediatric and adult neuromuscular diseases vary considerably. Most infants referred for neurologic evaluation have a floppy infant syndrome rather than radiculopathies or mononeuropathies that abound in adult practice.[21] Up to 80% of floppy infants have a central nervous system cause, showing hypotonia but not weakness per se. Neuromuscular disorders presenting as acute floppy infants in critical care units include SMA, postvaccine poliomyelitis, intrauterine Guillain Barré syndrome (GBS), infantile botulism,

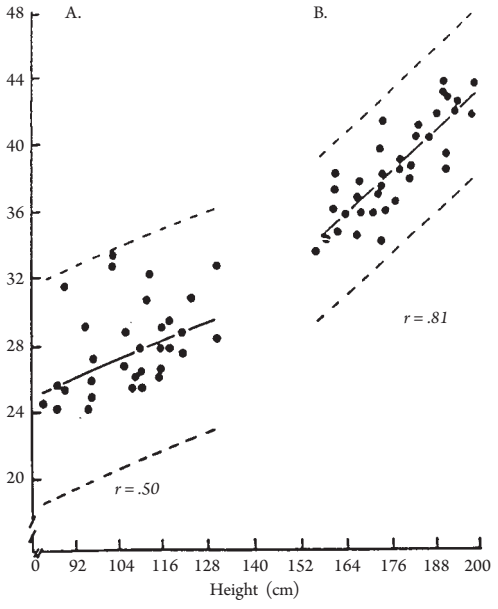

FIGURE 29-5 The correlation of height to cortical evoked potentials (P28 in children and P37 or P40 in adults). (*A*) During growth and development (1–8 years old). (*B*) During adulthood (18–40 years old). (Modified from Gilmore, Bass and Wright.[33])

and severe myopathies, such as myotonic dystrophy and glycogen storage disease.[47] Experienced pediatricians can differentiate central hypotonia from neuromuscular dysfunction clinically and by means of electrodiagnosis (see Chapter 27).

In contrast to the normal newborn with well-defined muscular tone and the ability to suck and swallow, a floppy infant has minimal or limited skeletal muscle activity despite full eye movements and a bright look. The limp head, arms, and legs form an inverted U when lifting the child from the prone position by the examiner's hands. These infants with weak bulbar motor function tend to develop recurrent episodes of aspiration pneumonia. Some infants may appear normal at birth but show delayed developmental milestones, not holding up the head, rolling over or sitting up during the first 3–6 months.

Electrophysiologic evaluation helps distinguish central and peripheral neurogenic abnormalities and myogenic disorders. In a retrospective review of 51 hypotonic infants younger than 1 year old,[68] final diagnoses included SMA or Werdnig Hoffman disease,[72] myopathy,[34] infantile botulism,[91] benign congenital hypotonia,[12] and some types of central nervous system disorders.[86] Studies revealed appropriate neuropathic or myopathic findings in all these categories except for the last two, which showed normal findings. In another series of 41 infants who had muscle or nerve biopsy or both,[20] 23 had SMA accurately defined by EMG. Some patients with myopathy had classical features, whereas others had either normal or nonspecific changes. The abnormalities of sensory conduction led to a diagnosis of hypomyelinating neuropathies in 5 infants.

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30

Data Analysis and Reporting

Abbreviations: EMG—electromyography, ESPRIT—European Strategic Program on Research in Information Technology, ESTEEM—European Standardized Telematic Tool to Evaluate EMG Knowledge Based Systems and Methods, KANDID—Knowledge Based Assistant for Neuromuscular Disorder, MUNIN—Muscle and Nerve Inference Network, MUP—motor unit potential, NCS—nerve conduction study, SNAP—sensory nerve action potential

1. INTRODUCTION

Most neurophysiologic evaluations in the clinical setting make a comparison between a patient finding and some set of normative data. Thus, the quality of such a database plays an essential role for diagnostic accuracy and yields.[19] Established control values should accompany a detailed description of the technique for clinical use.[17] The compilation of normative data must conform to the established principles, even if it takes tedious effort to deliver a standardized test to a large number of healthy subjects.[18,35,36,37,44] A population study of patients with carpal tunnel syndrome (CTS) and radiculopathy[34] has shown that an electrodiagnostic study has an important impact on the treatment choice and clinical outcome.

2. ACQUISITION OF REFERENCE VALUES

Control Values

Normative data comprise a set of values derived from disease-free individuals. In contrast, the term "reference" usually indicates either a normative or disease control. Patients referred to the laboratory for evaluation of clinical signs or symptoms may have "normal results." Despite values within the "normal range," these patients do not belong to a normal group. To judge some patients as normal on the basis of test results for inclusion into a normative database represents a circular argument and thus defeats its own purpose. Similarly, patients with disease or injury unrelated to the

study in question cannot serve as normal subjects because the apparently unaffected limbs may have subclinical involvement, and because systemic effects of treatments may influence the test outcome. Furthermore, the population with illness may well contain a higher proportion than normal of preexisting conditions that, even if subclinical, may affect the test outcome.

Statistical Analysis

In as much as the population variables conform to a bell-shaped Gaussian distribution, statistical analysis shows an identical value for mean, median, and mode. The Gaussian distribution, though generally symmetrical, tends to fall asymmetrically to the baseline at both ends, reflecting a small proportion of extremely high and low values, or outliers. These values dictate "the range," which, unlike other methods for deriving normative data, critically depends upon only two individual values, the lowest and the highest, essentially disregarding all other sample data. Extreme values may represent subclinical diseases or technical errors, making the range less useful as an index of normative limits. A non-Gaussian distribution, though not ideal, can still serve as a control value after statistical manipulations. For example, the natural or base 10 logarithms, or square root, will render positively skewed distributions more Gaussian. The mean and standard deviations of the transformed data, if converted back to original units, set up normative limits for clinical application. Some authors advocate other statistical maneuvers such as application of quantile regression.[16,33]

The Gaussian distribution, customarily set at ±2 SD about the mean, includes 95.44% of the entire population. About 5% of normative values falling outside these limits represent false-positive test results, half at either end of the range. Performing multiple independent tests on a single patient increases the likelihood of finding an "abnormal" value.[35,41] The overall chance equals the sum of the probabilities in each of the individual tests.[35] If each measurement allows a 2.5% rate of false-positivity using 2 SD as the criterion, then an examination that consists of 10 independent electrophysiologic measurements has a probability of 1 in 4 (25%) of turning up one or more abnormal values on the bases of chance alone.

False-Positive and False-Negative Results

False-positive outcomes present a major problem for clinical application. In general, therefore, we prefer to err on the side of false negativity, calling more borderline abnormalities normal than the reverse. We also emphasize to our referring physicians that a normal study does not rule out any apecific disorder based on our belief that "absence of evidence constitutes no evidence of absence." The incidence of false positivity will decrease with the use of a broader limit, for example, mean ± 2.5 SD. In this case the false-positive rate falls to about 1% in aggregate, at the cost of a correspondingly higher rate of false negativity.[19] Excessive overlap between normative data and disease-reference values precludes the use of a broader normative range because false negativity increases to such an unacceptable level so as to make the study useless.

Despite considerable overlap between the control and patient population, powerful statistical tests may show a significant difference comparing, as a group, the values in normal and diseased subjects. Such scientific conclusions, though valid, provide only limited practical applications in assessing individuals. In the clinical context, a single patient value must fall outside the established normative limits to declare its abnormality with reasonable confidence. Common sense dictates in questioning an isolated borderline abnormality just outside the normal limit, a surprise result unrelated to the patient signs and symptoms, and a pattern of abnormalities inconsistent with each other and with the clinical signs and symptoms. Unexpected findings that make little sense call for reevaluation of the patient, scrutinizing possible errors in the interpretation of clinical or electrophysiologic data or both in an effort to resolve the discrepancy.

3. EXPERT SYSTEMS AND QUALITY DEVELOPMENT

Electromyographers face difficult challenges in considering a vast amount of constantly

increasing knowledge in electrodiagnostic medicine. Computer-based methodology has helped the development of automated expert systems for use in some electrodiagnostic assessments. This type of analysis may complement the routine laboratory procedures, aiding the less-experienced examiner in time-efficient detection of abnormalities. Various expert systems, although still in the developmental stage, may provide quick access to pertinent information that facilitates the decision-making process. The use of such a device can reduce interlaboratory variation, which results from differences in the quality of training and technical preference of investigators. This approach may also help standardize physiologic evaluations in formulating a diagnostic impression. Adherence to acceptable practice guidelines of electrodiagnosis ensures better quality control, which plays an essential role in the effective operation of an expert system.[21]

KANDID

One such system, Knowledge Based Assistant for Neuromuscular Disorder Diagnosis, or KANDID, runs on an IBM-compatible PC and assists clinical neurophysiologists during their examinations. The system processes the data in two steps: it converts raw data into a pathophysiological statement, and then matches this statement to a disorder knowledge base. To maintain an iterative cycle of planning, testing, and diagnosing, the clinician must provide data of sufficient quality and decides when to stop the electrodiagnostic examination.

A prospective European multicenter field trial tested the validity of KANDID at seven independent laboratories.[23] The agreement level among nine clinical neurophysiologists who participated in 159 electrodiagnostic examinations averaged 81% for pathophysiologic conclusions and 61% for diagnostic categories. The pronounced interexaminer variation reflected regional differences in epidemiology, examination techniques, reference values, interpretations, and planning strategies.

ESTEEM

The experience with KANDID led to a multicenter project called ESTEEM, or European Standardized Telematic Tool to Evaluate EMG Knowledge Based Systems and Methods. This project used a multicenter database of neuromuscular cases to obtain diagnostic consensus by expert electromyographers and to establish standardized guidelines of electrodiagnostic practice for an acceptable expert system. As a prototype for an electrophysiology platform, ESTEEM also integrated different tools within the laboratory telematically communicating pertinent data at various posts within one hospital as well as among different institutions.

Studies of the ESTEEM database in 81 patients established the degree of observer variation in interpreting individual tests. Despite a good overall agreement among physicians who assessed 735 muscles and 726 nerve segments, a considerable disagreement emerged in determining specific pathophysiology in general and in diagnosing demyelination in particular. For the consensus procedure of ESTEEM, the moderator discarded all of the information except for electrodiagnostic data and related reference values.[42] The selected experts then interpreted the data in each case with respect to pathophysiologic conclusions and overall diagnosis. The experts must agree with the diagnosis before transferring the case to the consensus database. If not, the diagnosis given by the majority went back to the minority for a second interpretation, and when necessary, a panel discussion, leading to a consensus for nearly all cases. Based on ESTEEM experience of 572 peer-reviewed electrodiagnostic examinations, the collaboration has produced a set of criteria now in use at the centers involved in the project.[40] The use of ESTEEM multicenter database also led to the recognition that not all the physicians use the same classification of polyneuropathy.[39,43]

MUNIN

Another EMG expert system, Muscle and Nerve Inference Network (MUNIN), uses a causal probabilistic network in contrast to the rule-based KANDID.[14,32] The microhuman prototype[14] includes a limited "microhuman" anatomy and a small number of nerve lesions. The system gives a detailed description of the most important groups of generalized disorders affecting

the muscle and nerve, as well as commonly used measures of electromyography (EMG) and nerve conduction studies (NCSs). For diagnostic purposes, a probabilistic inference engine "reasons" to proceed from test results to different aspects of pathophysiology and to neuromuscular disorders. It can also provide causal reasoning in the opposite direction, from disorders to pathophysiology, and to expected test results. At the end of a 5-year project sponsored by the European Strategic Program on Research in Information Technology (ESPRIT) program, evaluation of its diagnostic performance revealed generally satisfactory results in 30 cases covering a wide range of neuromuscular disorders. The seven expert electromyographers who evaluated the system concluded that MUNIN performed at a level similar to an experienced neurophysiologist.[15]

Compared to KANDID, MUNIN does not explicitly formulate the planning of an examination. Such an interaction, if available based on the probabilities provided by the system, would help direct the physician toward a proper course of action. Compared to 39% disagreement for KANDID in 159 cases collected in a field trial, electromyographers expressed no serious discrepancies between MUNIN and the majority opinion in any of the 11 cases evaluated by peer review. This system, which utilizes very few clinical findings, accepts no cases with a limited EMG study performed only to confirm a clinical diagnosis. Methodologic and population differences make it difficult, if not impossible, to compare MUNIN and KANDID regarding their diagnostic accuracy and dependability.

Interlaboratory Communication

The diversity of electrodiagnostic practices necessitates studying the differences between various existing techniques. For example, some physicians use quantitative EMG and near-nerve technique for NCS, and others use qualitative needle examination and surface electrodes to record SNAP. To improve the quality of studies, expert systems must consider these widely variable patterns of practices[22] and standardize terminology for pathophysiologic interpretations and diagnoses. To facilitate interaction among different laboratories via the Internet, the ESTEEM project developed an EMG communication protocol.[26] It consists of general data, examination techniques, reference values, pathophysiologic conclusions, and diagnoses. Its implementation of several computer programs allows an exchange of data among laboratories despite the use of different techniques and reference values. This consensus database may help develop an expert system, which integrates all tools concerned and generates a report independent of specific instrument and telematic programs.[43]

4. REPORTING TO THE REFERRING PHYSICIAN

Electrodiagnostic studies constitute an extension of the clinical neurologic evaluation. Thus, although existing guidelines apply to approximately 90% of situations for testing common problems,[11,13,25] the patient's particular situation calls for incorporation of individualized planning. A well-organized report should reflect this unique testing process based on the clinical history and physical examination.

General Consideration

The report should use generally accepted language such as those included in the glossary published by AANEM (2001). It should address the questions posed by the referring physicians using the language appropriate to their level of expertise in electrodiagnostic medicine. To improve general understanding, it must avoid abbreviations or jargons familiar only to those working in electrophysiology, such as "SNAP" for sensory nerve action potential or "MUP" for motor unit potential.

All reports must identify the patient by name, date of birth, and the hospital registration number. A well-organized report should provide the referring physician with a confirmation of the clinical diagnosis, precise localization of the lesion, quantitative rather than qualitative description of the abnormality, and its type and distribution. A typical report form consists of three portions: (1) tabular presentation of the data for both NCS and EMG, (2) succinct summarization of the

abnormalities and, when appropriate, normalities presented in the table, and (3) interpretation of the results in the clinical context, usually stating whether the findings support or refute the clinical diagnosis under consideration (see Tables 30-1 and 30-2).

Tabular Presentation of Data

Modern equipment, using computerized networking, automatically captures numerical data into a tabulated document. This type of electrical reporting, now preferred in most academic centers, also facilitates their entry into the electronic medical record. Tables, commonly used in computer-generated reports, should provide easy-to-read data with clear headings, descriptors, and measurement units. Numerical data must convey an appropriate level of accuracy, for example, 54 m/s and 3.4 ms, not 53.6 m/s and 3.41 ms, which give erroneous impression of significance (see Chapter 11-7). Both motor and sensory NCS should indicate the side, name of the nerve, and measured or calculated values for all the segments tested. Tabular presentation of EMG should include the side and name of the muscle, insertional activity, spontaneous discharges, if any, motor unit waveform, recruitment, and interference pattern. Most North American laboratories now employ disposable monopolar or concentric needles for routine clinical studies. The use of reusable or other specialty needles deserves a special mention for documentation.

For the common tests performed, a listing of the laboratories normal reference value helps recognize the degree of abnormality. A number of factors can influence relevance of these values, which may lead to inappropriate interpretation of the data. The modifying factors include temperature, age, gender, height, weight, and body mass index. In addition, the report should describe side-to-side comparisons, which may influence the interpretation of the results. Although not commonly practiced, some advocate the use of percentiles and normal deviates to express the test abnormalities[20] and others, electroneurography index.[38] In our laboratory (Tables 30-1 and 30-2), we tabulate temperature-adjusted motor and sensory latencies and conduction velocities, subtracting or adding 4% of the measured value for each degree below 32°C (see Chapter 5-6). The table also includes individually adjusted reference values for F-wave latencies based on a height-latency nomogram (see Chapter 7-4 and Appendix Figs. 1-1 and 1-2).

These reports can also provide images of the waveforms if requested by the referring physician who has enough expertise to analyze the recorded responses. Including figures with waveforms also helps evaluate the results of a subsequent study whether conducted by the same or another laboratory.

Summary of Findings

The narrative summary, which follows the tabulated data, should list pertinent abnormalities, drawing a relationship between physiologic changes and anatomic localization. It should mention normal findings that influence the interpretation. The report should build a rational explanation to support a single localization of the lesion identified by a number of techniques during the evaluation. Accurately performed measurements should show internal consistency. Deviation from this rule often suggests an unusual, yet unidentified condition or technical problems, prompting reassessment. If further clinical or electrophysiologic evaluation fails to clarify the discrepancy, which even experts sometimes experience, the report should so state for future reference. An isolated abnormality that does not seem to fit in the overall evaluation of findings may, or may not, suggest two independent disease processes. These exceptional features deserve a special mention in the hope that further studies may solve the issue. In discussing the distribution of abnormalities, possible anatomic variation and anomalies need a clear explanation. Comments should include deviation from the usual range of values for temperature, height, and weight, which may preclude the use of the ordinary reference values.

Concluding Remarks

The concluding impression should state the most likely diagnosis based on electrophysiologic data

Table 30-1

F-15 Electromyography and Electrodiagnosis
File most recent sheet of this number ON BOTTOM

Date
Name
Hosp#.
BirthDate

Motor Nerve Conduction Data

Values @ 32°C calculated based on 4%/degree change

Nerve (muscle)	Side	Site	Latency ms	Norm	Amplitude* mV	Norm	Segment	Distance mm	NCV m/s	@32	Norm	Temp °C
Median (APB)	Right	Palm	1.7	<2.4	8.9	>3.5	Palm					33.1
		Wrist	3.6	<4.2	8.8	>3.5	Palm-Wrist	80	42.1		>38	
		Elbow	8.1	<8.8	8.7	>3.5	Wrist-Elbow	230	51.1		>48	
		Axilla	10.7	<11.6	8.6	>3.5	Elbow-Axilla	140	53.8		>51	
Ulnar (ADM)	Right	Wrist	2.6	<3.4	10.1	>2.8	Wrist					33.1
		Below Elbow	6.8	<7.5	9.8	>2.8	Wrist-Below Elbow	240	57.1		>49	
		Above Elbow	8.4	<9.6	9.6	>2.8	Below Elbow-Above Elbow	100	62.5		>50	
		Axilla	9.9	<11.7	9.5	>2.8	Above Elbow-Axilla	100	66.7		>53	
Radial (EIP)	Right	Forearm	2.0	<3.4	4.0	>3.5	Forearm					33.1
		Above Elbow	4.7		3.9	>3.5	Forearm-Above Elbow	200	74.1		>51	
		Erb's Point	9.0		3.7	>3.5	Above Elbow-Erb's point	320	74.4		>58	
Phrenic (Diaphragm)	Right	SCM	6.7	8.0	3.6	>0.4						33.1
	Left	SCM	6.9	8.0	3.5	>0.4						33.1
Peroneal (EDB)	Right	Ankle	4.1	<5.5	6.5	>2.5	Ankle					32.2
		Below Knee	10.9	<12.9	6.2	>2.5	Ankle-Below Knee	320	47.1		>40	
		Above Knee	13.0	<14.9	6.1	>2.5	Below Knee-Above Knee	100	47.6		>40	
Peroneal (TA)	Right	Below Knee	3.0		3.6							32.2
		Above Knee	5.2		3.5		Below Knee-Above Knee	100	45.5			
Tibial (AH)	Right	Ankle	5.1	<6.0	14.0	>2.9	Ankle					32.2
		Knee	14.2	<15.1	13.5	>2.9	Ankle-Knee	420	46.2		>41	
Femoral (VL)	Right	Groin	3.5	<4.6	8.9			140				32.2
	Left	Groin	3.4	<4.6	8.9			140				32.2

*Side to side difference must be <50%

Sensory Nerve Conduction Data

Values @ 32 °C calculated based on 4%/degree change

Nerve	Side	Site	Latency ms	Norm	Amplitude* uV	Norm	Segment	Distance mm	NCV m/s	@32	Norm	Temp °C
Median (Index finger)	Right	Palm	1.5	<1.9	25.5	>20	Palm					33.1
		Wrist	3.1	<3.5	21.4		Palm-Wrist	80	50.0		>44	
		Elbow	7.1	<7.9	20.1		Wrist-Elbow	230	57.5		>53	
Ulnar (Small finger)	Right	Wrist	2.4	<3.1	24.5	>18	Wrist	140	58.3		>44	33.1
		Below Elbow	6.5	<6.9	20.1		Wrist-Below Elbow	240	63.2		<53	
		Above Elbow	7.7	<8.7	19.5		Below Elbow -Above Elbow	100	66.7		>55	
Med-Uln (Ring finger)	Med	Wrist	2.9	**	24.5							33.1
	Ulnar	Wrist	2.7	**	20.2							33.1
Radial (Snuff)	Right	Forearm	1.7	<2.4	27.1	>7	Forearm					33.1
Sup.Peroneal	Right	Ankle	2.1	<4.6	10.0	>6	Ankle					32.2
Sural (lat.mal)	Right	Mid-Calf	3.1	<3.5	12.6	>10	Ankle	140	45.2		>39	32.2

*Side to side difference must be <50% **Latency difference must be <0.4ms

F-Wave Data Values @ 32°C calculated based on 4%/degree change

Height	165.0cm

With stimulation at elbow and knee

Nerve	Side	Stim.Site	Rec.Site	Min. Latency ms	@32	Norm	Distance mm	F-Velocity m/s	Norm	F-Ratio	Norm	Temp °C
Median	Right	Wrist	APB	25.9		<28.0	490	58.3	>56	1.0	0.82 -1.14	33.1
Ulnar	Right	Wrist	ADQ	26.0		<28.0	490	59.0	>55	1.0	0.87 -1.23	33.1
Peroneal	Right	Ankle	EDB	45.8		<49.2	780	49.1	>43	1.3	0.87 -1.23	32.2
Tibial	Right	Ankle	AH	48.1		<49.2	780	47.4	>44	1.2	0.87 -1.33	32.2

Values @ 32°C for the M-latency and R1 latency calculated based on 4%/degree change

Nerve	Side	Facial Nerve Stimulation					Blink Reflex						
		M-Amplitude* mV	Norm	M-Latency** ms	@32	Norm	R1-Latency† ms	@32	Norm	iR2-Latency ms	@32	cR2-Latency ms	@32
	Right	1.2	>0.6*	3.5		<4.1**	10.2		<12.5†	27.9		29.1	
	Left	1.1	>0.6*	3.3		<4.1**	10.1		<12.5†	28.3		29.5	

*Side to side differencemust be <50%, **Side to side difference must be <0.6ms, †Side to side difference must be <1.2ms, i=ipsi c=contra

Repetitive Stim Amplitude Data

Nerve	Side	Amplitude mV	Rate	Change (%)	Post Tetanic Change (%)	Delay	Max.Change (%)
Median	Right	8.8	3Hz	0	0	0-3min	0

Repetitive Stim Area Data

Nerve	Side	Area ms	Rate	Change (%)	Post Tetanic Change (%)	Delay	Max.Change (%)
Median	Right	6.1	3Hz	0	0	0-3min	0

EMG Needle Findings

Muscle	Side	Insert.	Fibs.	PSW	Amp.	Dur.	Poly.	Recruit.	Interfer.	Fascic.	CRD	Myot. Dis.	Other
FDI	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Pronator T.	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Biceps	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Triceps	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
C- Parasp.	Right	Normal	0	0						0	0	0	0
Glut. Med	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Quads	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
TA	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Gastoc.	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
LS- Parasp.	Right	Normal	0	0						0	0	0	0

Results

NCS: Normal nerve conductions studies.

EMG: Normal needle electromyography.

Impression: Normal study.

I, Dr. Jun Kimura, certify that I was present during the examination and concur with the findings and interpretation of this report. Signature: Jun Kimura, MD Date:

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Table 30-2

F-15 Electromyography and Electrodiagnosis
File most recent sheet of this number ON BOTTOM

Date
Name
Hosp#.
BirthDate

Motor Nerve Conduction Data

Values @ 32°C calculated based on 4%/degree change

Nerve (muscle)	Side	Site	Latency ms	Norm	Amplitude* mV	Norm	Segment	Distance mm	NCV m/s	@32	Norm	Temp °C
Median (APB)	Right	Palm	2.6	<2.4	3.4	>3.5	Palm					31.0
		Wrist	5.0	<4.2	3.1	>3.5	Palm-Wrist	80	33.3	34.6	>38	
		Elbow	9.9	<8.8	2.8	>3.5	Wrist-Elbow	230	46.9	48.8	>48	
		Axilla	12.7	<11.6	2.6	>3.5	Elbow-Axilla	140	50.0	52.0	>51	
Ulnar (ADM)	Right	Wrist	3.6	<3.4	2.7	>2.8	Wrist					31.0
		Below Elbow	8.6	<7.5	2.5	>2.8	Wrist-Below Elbow	240	48.0	49.9	>49	
		Above Elbow	11.0	<9.6	2.1	>2.8	Below Elbow-Above Elbow	100	41.7	43.4	>50	
		Axilla	12.9	<11.7	2.0	>2.8	Above Elbow-Axilla	100	52.6	54.7	>53	
Peroneal (EDB)	Right	Ankle	6.0	<5.5	1.6	>2.5	Ankle					30.5
		Below Knee	14.2	<12.9	1.2	>2.5	Ankle-Below Knee	320	39.0	41.3	>40	
		Above Knee	16.9	<14.9	1.1	>2.5	Below Knee-Above Knee	100	37.0	39.2	>40	
Peroneal (TA)	Right	Below Knee	3.2		2.1							30.5
		Above Knee	6.0		2.0		Below Knee-Above Knee	100	35.7	37.8		
Tibial (AH)	Right	Ankle	5.3	<6.0	2.8	>2.9	Ankle					30.5
		Knee	16.3	<15.1	2.3	>2.9	Ankle-Knee	420	38.2	40.5	>41	

*Side to side difference must be <50%

Sensory Nerve Conduction Data

Values @ 32°C calculated based on 4%/degree change

Nerve	Side	Site	Latency ms	Norm	Amplitude* uV	Norm	Segment	Distance mm	NCV m/s	@32	Norm	Temp °C
Median (Index finger)	Right	Palm	2.0	<1.9	15.2	>20	Palm					31.0
		Wrist	4.0	<3.5	10.2		Palm-Wrist	80	40.0	41.6	>44	
		Elbow	8.5	<7.9	8.7		Wrist-Elbow	230	51.1	53.1	>53	
Ulnar (Small Finger)	Right	Wrist	3.3	<3.1	9.8	>18	Wrist	140	42.4	44.1	>44	31.0
		Below Elbow	8.0	<6.9	8.7		Wrist-Below Elbow	240	51.1	53.1	<53	
		Above Elbow	10.0	<8.7	5.2		Below Elbow-Above Elbow	100	50.0	52.0	>55	
Sural (lat.mal)	Right	Mid-Calf	3.8	<3.5	3.6	>10	Ankle	140	36.8	38.3	>39	30.5

*Side to side difference must be <50% **Latency difference must be <0.4ms

F-Wave Data Values @ 32°C calculated based on 4%/degree change

Height 165.0cm

With stimulation at elbow and knee

Nerve	Side	Stim.Site	Rec.Site	Min. Latency ms	@32	Norm	Distance mm	F-Velocity m/s	@32	Norm	F-Ratio	Norm	Temp °C
Median	Right	Wrist	APB	31.7	30.4	<28.0	490	50.2	52.2	>56	0.98	0.82-1.14	31.0
Ulnar	Right	Wrist	ADQ	32.5	31.2	<28.0	490	51.0	53.0	>55	0.87	0.87-1.23	31.0
Peroneal	Right	Ankle	EDB	53.5	50.3	<49.2	780	39.3	41.7	>43	1.2	0.87-1.23	30.5
Tibial	Right	Ankle	AH	59.1	55.6	<49.2	780	40.0	42.4	>44	1.2	0.87-1.33	30.5

EMG Needle Findings

Muscle	Side	Insert.	Fibs.	PSW	Amp.	Dur.	Poly.	Recruit.	Interfer.	Fascic.	CRD	Myot. Dis.	Other
FDI	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
TA	Right	Incr.	+2	+2	Incr.	Normal	50%	Reduced	-2*	0	0	0	0
Gastoc.	Right	Normal	0	0	Normal	Normal	<20%	Normal	Full	0	0	0	0
Ft. Intrinsic	Right	Incr.	+2	+2						0	0	0	0

*Rapid Firing

Results

NCS: Nerve conduction studies revealed low amplitude motor and sensory responses with delayed latencies and slowed conduction velocities as well as increased F-wave latencies

EMG: Needle electromyography showed denervation in the right tibialis anterior and foot intrinsic muscles.

Impression: Findings support the clinical diagnosis of axonal sensorimotor polyneuropathy.

I, Dr. Jun Kimura, certify that I was present during the examination and concur with the findings and interpretation of this report. Signature: Jun Kimura, MD Date:

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and clinical information. This section should identify the type of abnormalities in the context of the patient's clinical condition. For a referring physician knowledgeable in using the electrodiagnostic information, a straightforward statement suffices to indicate whether the results support the clinical diagnosis under consideration. For example, it should simply state that the findings support the clinical diagnosis of axonal sensorimotor polyneuropathy. Not all referring physicians have sufficient knowledge to appreciate the results of electrodiagnostic studies. In these situations, the report must elaborate on how one has reached the particular conclusion to document the relationship between the clinical findings and electrodiagnostic results. For example, it should state that mild slowing of sensory and motor conduction velocities, reduced size of responses, and evidence of muscle denervation all support the clinical diagnosis of axonal sensorimotor neuropathy.

If appropriate, this section should also indicate prognosis of the neuromuscular disorder under consideration and the possible need of follow-up studies for additional electrodiagnostic assessments to clarify difficult diagnosis.[24] Some patients will not tolerate the testing, which limits the choice of procedures and affects the scope of interpretation for the lack of complete data. The report should identify these situations with appropriate guidance for repeat electrodiagnostic testing with special preparation such as sedation, if necessary.

5. ETHICAL CONSIDERATIONS IN CLINICAL PRACTIICE

Ethical principles in medical practice, by design, protect the rights of patients as summarized in an updated version of *Fundamental Elements of the Patient–Physician Relationship*, published by the Council of Ethical and Judicial Affairs of the American Medical Association.[30] To ensure high standards of medical practice,[27] and to enforce ethical standards for practitioners, the American Association of Electrodiagnostic Medicine (AAEM) has also published a series of guidelines,[1,2,4–6,9,28] position statements,[3,7,10,29] and a summary of the current recommendations.[12] This section will briefly review important aspects of these documents whose general principles apply to any practice of electrodiagnostic medicine. Specific details may, however, differ from one place to another in such areas as consultant–patient relationships, conflict of interest related to clinical research, compensation for electrodiagnostic services, and professional misconduct.[30,31]

A medical consultant must recognize the patient's right to receive information about the benefits, risks, and costs of an examination; to refuse all or part of the electrophysiologic examination; and to ask for a copy of the summary of the medical report. The patient's medical needs should constitute the sole indication for the performance of electrodiagnostic services, not his or her race, religion, nationality, or gender. A particular diagnosis, specifically those related to HIV infection or other communicable disease, must not preclude electrodiagnostic evaluation, if indicated for the care of the patient. A clinical research project requires approval of an Institution Review Board. A written informed consent for the protocol should include declaration of external sponsorship and compensation to the consultant, if any.

A physician should not charge an excessive fee for the electrophysiologic examination and should avoid billing for unnecessary services. As a guideline, a reasonable fee should reflect the difficulty of the technique, skill and time required for the study, customary charges in the locality for similar services, experience of the physician, and quality of the examination. In addition, each laboratory should consider setting an appropriate upper limit for the total amount of charge per patient. The AAEM guidelines[2,3,11] outline a maximum number of specific tests necessary for a physician to arrive at a diagnosis in at least 90% of cases, thus establishing reasonable charges in most instances. The fee scale should conform to the principles of the current environment to contain costs.

Thoughtfully written reimbursement guidelines will positively impact the patient care. Poorly written policies may lead to bad medical judgments based on inadequate information. The

AANEM[8] recommends the following minimum standards:

1. Electrodiagnostic testing must be medically necessary.
2. Testing must be performed using electrodiagnostic equipment that provides assessment of all aspects of the recorded signals. Studies performed with devices designed only for "screening purposes" rather than diagnosis is not acceptable under this policy.
3. The number of tests performed must be the minimum needed to establish an accurate diagnosis.
4. NCSs must be either (a) performed directly by a physician or (b) performed by a trained individual under the direct personal supervision of a physician. Direct personal supervision means that the physician is in close physical proximity to the electrodiagnostic laboratory while testing is under way, is immediately available to provide the trained individual with assistance and direction, and is responsible for selecting the appropriate NCSs to be performed.
5. Needle studies must be performed by a physician specially trained in electrodiagnostic medicine, as these tests are performed and simultaneously interpreted.

Adopting the American Medical Association's Principles of Medical Ethics, the AANEM guidelines[2] state that "consultants should not knowingly ignore a colleague's incompetence or professional misconduct," to protect the public from an impaired physician. The organization has in place a mechanism to conduct a formal hearing on charges of professional misconduct and to pursue a disciplinary process based on established policies and procedures. Each practitioner must maintain the highest of standards in ethical conduct and adhere to the enforcement policies for fairness and due process.

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PART X

Appendices

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Appendix 1

Myotome, Normal Values for Nerve Conduction Studies, and DVD Description

I MYOTOMES AND NORMAL VALUES

A Tables of Myotomes

Table 1-1 Muscles Innervated by the Cranial Nerves and Cervical Plexus*

NERVE	MUSCLES	BRAINSTEM			ROOT		
Oculomotor nerve	Levator palpebrae	**Midbrain**	Pons	Medulla	C2	C3	C4
	Superior rectus	**Midbrain**	Pons	Medulla	C2	C3	C4
	Medial rectus	**Midbrain**	Pons	Medulla	C2	C3	C4
	Inferior rectus	**Midbrain**	Pons	Medulla	C2	C3	C4
	Inferior oblique	**Midbrain**	Pons	Medulla	C2	C3	C4
Trochlear nerve	Superior oblique	**Midbrain**	Pons	Medulla	C2	C3	C4
Trigeminal nerve	Masseter	**Midbrain**	Pons	Medulla	C2	C3	C4
	Temporalis	**Midbrain**	Pons	Medulla	C2	C3	C4
	Pterygold	**Midbrain**	Pons	Medulla	C2	C3	C4

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-1 Muscles Innervated by the Cranial Nerves and Cervical Plexus* (Continued)

NERVE	MUSCLES	BRAINSTEM			ROOT		
Abducens nerve	Lateral rectus	Midbrain	**Pons**	Medulla	C2	C3	C4
Facial nerve	Frontalis	Midbrain	**Pons**	Medulla	C2	C3	C4
	Orbicularis oculi	Midbrain	**Pons**	Medulla	C2	C3	C4
	Orbicularis oris	Midbrain	**Pons**	Medulla	C2	C3	C4
	Platysma	Midbrain	**Pons**	Medulla	C2	C3	C4
	Digastric and stylohyoid	Midbrain	**Pons**	Medulla	C2	C3	C4
Glossopharyngeal nerve	Laryngeal	Midbrain	Pons	**Medulla**	C2	C3	C4
Vagus nerve	Laryngeal	Midbrain	Pons	**Medulla**	C2	C3	C4
Accessory nerve (cranial root)	Laryngeal	Midbrain	Pons	**Medulla**	C2	C3	C4
Hypoglossal nerve	Tongue	Midbrain	Pons	**Medulla**	C2	C3	C4
Accessory nerve (spinal root)	Sternocleidomastoid	Midbrain	Pons	Medulla	**C2**	**C3**	C4
	Trapezius upper	Midbrain	Pons	Medulla	C2	**C3**	**C4**
	Trapezius middle	Midbrain	Pons	Medulla	C2	**C3**	**C4**
Cervical plexus	Trapezius lower	Midbrain	Pons	Medulla	C2	**C3**	**C4**
Phrenic nerve	Diaphragm	Midbrain	Pons	Medulla	C2	**C3**	**C4**

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

Table 1-2 Muscles Innervated by Brachial Plexus and Upper-Limb Nerves*

NERVES	MUSCLES	ROOT							
Anterior primary rami									
Brachial plexus									
Dorsal scapular nerve	Rhomboid, major, minor	C2	C3	C4	**C5**	C6	C7	C8	T1
	Levator scapulae	C2	*C3*	*C4*	**C5**	C6	C7	C8	T1
Suprascapular nerve	Supraspinatus	C2	C3	C4	**C5**	*C6*	C7	C8	T1
	Infraspinatus	C2	C3	C4	**C5**	*C6*	C7	C8	T1
Axillary nerve	Teres minor	C2	C3	C4	**C5**	*C6*	C7	C8	T1
	Deltoid, anterior, middle, posterior	C2	C3	C4	**C5**	**C6**	C7	C8	T1
Subscapular nerve	Teres major	C2	C3	C4	**C5**	**C6**	C7	C8	T1
	Subscapularis	C2	C3	C4	*C5*	**C6**	C7	C8	T1
Musculocutaneous nerve	Brachialis	C2	C3	C4	**C5**	*C6*	C7	C8	T1
	Biceps brachiI	C2	C3	C4	**C5**	**C6**	C7	C8	T1
	Coracobrachialis	C2	C3	C4	C5	*C6*	**C7**	C8	T1
Long thoracic nerve	Serratus anterior	C2	C3	C4	**C5**	**C6**	**C7**	C8	T1

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-2 Muscles Innervated by Brachial Plexus and Upper-Limb Nerves* (Continued)

NERVES	MUSCLES	ROOT							
Anterior thoracic nerve									
Lateral pectoral nerve	Pectoralis major (clavicular part)	C2	C3	C4	**C5**	**C6**	C7	C8	T1
Medial pectoral nerve	Pectoralis major (sternocostal part)	C2	C3	C4	C5	**C6**	**C7**	C8	T1
	Pectoralis minor	C2	C3	C4	C5	**C6**	**C7**	**C8**	T1
Thoracodorsal nerve	Latissimus dorsi	C2	C3	C4	C5	**C6**	**C7**	**C8**	T1
Radial nerve	Brachioradialis	C2	C3	C4	*C5*	**C6**	C7	C8	T1
	Extensor carpi radialis longus	C2	C3	C4	*C5*	**C6**	*C7*	C8	T1
	Extensor carpi radialis brevis	C2	C3	C4	C5	*C6*	**C7**	*C8*	T1
	Triceps, long, lateral, middle heads	C2	C3	C4	C5	*C6*	**C7**	*C8*	T1
	Anconeus	C2	C3	C4	C5	C6	**C7**	*C8*	T1
Posterior interosseous nerve	Supinator	C2	C3	C4	C5	**C6**	*C7*	C8	T1
	Extensor carpi ulnaris	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Extensor digitorum communis	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Extensor digiti minimi	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Abductor pollicis longus	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Extensor pollicis longus	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Extensor pollicis brevis	C2	C3	C4	C5	C6	**C7**	*C8*	T1
	Extensor indicis	C2	C3	C4	C5	C6	**C7**	*C8*	T1
Median nerve	Pronator teres	C2	C3	C4	C5	*C6*	**C7**	C8	T1
	Flexor carpi radialis	C2	C3	C4	C5	*C6*	**C7**	C8	T1
	Palmaris longus	C2	C3	C4	C5	*C6*	**C7**	*C8*	T1
	Flexor digitorum sublimis	C2	C3	C4	C5	*C6*	**C7**	*C8*	T1
	Abductor pollicis brevis	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Flexor pollicis brevis (superficial)	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Lumbricals I & II	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Opponens pollicis	C2	C3	C4	C5	C6	C7	*C8*	**T1**

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-2 Muscles Innervated by Brachial Plexus and Upper-Limb Nerves* (Continued)

NERVES	MUSCLES	ROOT							
Anterior interosseous nerve	Flexor digitorum pronfundus (I & II)	C2	C3	C4	C5	C6	*C7*	**C8**	T1
	Pronator quadratus	C2	C3	C4	C5	C6	*C7*	**C8**	T1
	Flexor pollicis longus	C2	C3	C4	C5	C6	*C7*	**C8**	T1
Ulnar nerve	Flexor digitorum profundus (III & IV)	C2	C3	C4	C5	C6	C7	**C8**	T1
	Flexor carpi ulnaris	C2	C3	C4	C5	C6	*C7*	**C8**	T1
	Adductor pollicis brevis (deep head)	C2	C3	C4	C5	C6	*C7*	*C8*	**T1**
	Abductor digiti minimi	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Interossei, volar (I–III), dorsal (I–IV)	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Opponens digit minimi	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Flexor digiti minimi	C2	C3	C4	C5	C6	C7	*C8*	**T1**
	Lumbricalis III, IV	C2	C3	C4	C5	C6	C7	*C8*	**T1**
Posterior primary rami	Cervical erector spinae	C2	C3	C4	**C5**	**C6**	**C7**	**C8**	**T1**

*The **boldface** and *italic* letters indicate **primary** and *secondary* innervation.

Table 1-3 Muscles Innervated by Lumbosacral Plexus and Lower-Limb Nerves*

NERVES	MUSCLES	ROOT						
Anterior primary rami								
Lumbosacral plexus								
Femoral nerve	Iliopsoas	**L2**	**L3**	L4	L5	S1	S2	S3
	Pectineus	**L2**	*L3*	L4	L5	S1	S2	S3
	Sartorius	**L2**	**L3**	**L4**	L5	S1	S2	S3
	Vastus intermedius	**L2**	**L3**	**L4**	L5	S1	S2	S3
	Rectus femoris	L2	**L3**	**L4**	L5	S1	S2	S3
	Vastus lateralis	L2	**L3**	**L4**	L5	S1	S2	S3
	Vastus medialis	L2	**L3**	**L4**	L5	S1	S2	S3
Obturator nerve	Gracilis	**L2**	**L3**	*L4*	L5	S1	S2	S3
	Obturator externus	*L2*	*L3*	**L4**	L5	S1	S2	S3
	Adductor longus, brevis, magnus	**L2**	**L3**	**L4**	L5	S1	S2	S3

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-3 Muscles Innervated by Lumbosacral Plexus and Lower-Limb Nerves* (Continued)

NERVES	MUSCLES	ROOT						
Superior gluteal nerve	Gluteus medius	L2	L3	**L4**	**L5**	**S1**	S2	S3
	Gluteus minimus	L2	L3	*L4*	**L5**	*S1*	S2	S3
	Tensor facie latae	L2	L3	*L4*	**L5**	*S1*	S2	S3
Inferior gluteal nerve	Gluteus maximus	L2	L3	L4	*L5*	**S1**	**S2**	S3
	Obturator internus	L2	L3	*L4*	*L5*	**S1**	*S2*	S3
	Gemelli—superior, inferior	L2	L3	*L4*	*L5*	*S1*	*S2*	S3
Sacral plexus								
Branches from plexus	Piriformis	L2	L3	L4	*L5*	**S1**	*S2*	S3
	Quadratus femoris	L2	L3	*L4*	*L5*	*S1*	S2	S3
Sciatic nerve								
Tibial division	Semitendinosus, s	L2	L3	L4	**L5**	**S1**	**S2**	S3
	Semimembranosus	L2	L3	L4	**L5**	**S1**	**S2**	S3
	Biceps femoris, long head	L2	L3	L4	*L5*	**S1**	*S2*	S3
Peroneal division	Biceps femoris, short head	L2	L3	L4	*L5*	**S1**	**S2**	S3
Common peroneal nerve								
Deep peroneal nerve	Tibialis anterior	L2	L3	**L4**	**L5**	S1	S2	S3
	Peroneus tertius	L2	L3	L4	*L5*	*S1*	S2	S3
	Extensor digitorum longus	L2	L3	L4	**L5**	**S1**	S2	S3
	Extensor digitorum brevis	L2	L3	L4	**L5**	**S1**	S2	S3
	Extensor hallucis longus	L2	L3	L4	L5	**S1**	S2	S3
Superficial peroneal nerve	Peroneus longus	L2	L3	L4	**L5**	**S1**	S2	S3
	Peroneus brevis	L2	L3	L4	**L5**	**S1**	S2	S3

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-3 Muscles Innervated by Lumbosacral Plexus and Lower-Limb Nerves* (Continued)

NERVES	MUSCLES	ROOT						
Tibial nerve	Tibialis posterior	L2	L3	**L4**	**L5**	S1	S2	S3
	Popliteus	L2	L3	L4	*L5*	*S1*	S2	S3
	Flexor digitorum longus	L2	L3	L4	**L5**	**S1**	*S2*	S3
	Flexor hallucis longus	L2	L3	L4	**L5**	**S1**	**S2**	S3
	Gastrocnemius, medial head	L2	L3	L4	L5	**S1**	*S2*	S3
	Gastrocnemius, lateral head	L2	L3	L4	L5	*S1*	**S2**	S3
	Soleus	L2	L3	L4	*L5*	**S1**	**S2**	S3
Medial plantar nerve	Abductor hallucis	L2	L3	L4	L5	**S1**	**S2**	S3
	Flexor digitorum brevis	L2	L3	L4	L5	*S1*	*S2*	S3
	Flexor hallucis brevis	L2	L3	L4	L5	*S1*	*S2*	S3
	Lumbrical I–II	L2	L3	L4	*L5*	*S1*	*S2*	S3
Lateral plantar nerve	Abductor digiti minimi	L2	L3	L4	L5	**S1**	**S2**	S3
	Flexor digiti minimi	L2	L3	L4	L5	*S1*	*S2*	*S3*
	Adductor hallucis	L2	L3	L4	L5	*S1*	*S2*	*S3*
	Dorsal interossei	L2	L3	L4	L5	*S1*	*S2*	*S3*
	Plantar interossei	L2	L3	L4	L5	*S1*	*S2*	*S3*
	Flexor digitorum accessories	L2	L3	L4	L5	S1	**S2**	*S3*
	Quadratus plantae	L2	L3	L4	L5	**S1**	**S2**	S3
	Lumbrical III–IV	L2	L3	L4	L5	*S1*	*S2*	*S3*
Posterior primary rami	Lumbosacral erector spinae	**L2**	**L3**	**L4**	**L5**	**S1**	**S2**	S3

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation.

B NORMAL VALUES FOR NERVE CONDUCTION STUDIES

Table 1-4 Normal Values for Motor Nerve Conduction Studies

NERVE (SITE OF RECORDING)	SITE OF STIMULATION*	LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	AMPLITUDE† (mV)	NERVE SEGMENT BETWEEN STIMULI	CONDUCTION VELOCITY (m/s)
Median nerve (Abductor pollicis brevis)	Palm	<2.4	<0.5	>3.5		
	Wrist	<4.2	<0.5	>3.5	Wrist–palm	>38
	Elbow	<8.8	<0.5	>3.5	Elbow–wrist	>48
	Axilla	<11.6	<0.5	>3.5	Axilla–elbow	>51
Ulnar nerve (Abductor digiti minimi)	Wrist	<3.4	<0.8	>2.8		
	Below elbow	<7.5	<0.8	>2.7	Below elbow–wrist	>49
	Above elbow	<9.6	<0.9	>2.7	Above elbow–below elbow	>50
	Axilla	<11.7	<1.2	>2.7	Axilla–above elbow	>53
Median/Ulnar nerve comparison	Wrist	<0.5	Abductor pollicis brevis (Median N.) vs. Adductor pollicis (Ulnar N.)			
	Wrist	<0.5	Lumbricalis II (Median N.) vs. Volar Iinterosseous I (Ulnar N.)			
Radial nerve (Extensor indicis proprius)	Forearm	<3.4		>3.5		
	Elbow				Elbow–forearm	>51
	Axilla				Axilla–elbow	>58
	Erb's point				Erb's point– axilla	>58
Peroneal nerve (Extensor digitrum brevis)	Ankle	<5.5	<1.8	>2.5		
	Below knee	<12.9	<2.0	>2.5	Below knee–ankle	>40
	Above knee	<14.9	<2.9	>2.5	Above knee–below knee	>40
Tibial nerve (Abductor hallucis)	Ankle	<6.0	<1.8	>2.9	Knee-ankle	>41
	Knee	<15.1	<2.0	>2.9		

(*continued*)

Table 1-4 Normal Values for Motor Nerve Conduction Studies* (Continued)

NERVE (SITE OF RECORDING)	SITE OF STIMULATION*	LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	AMPLITUDE† (mV)	NERVE SEGMENT BETWEEN STIMULI	CONDUCTION VELOCITY (m/s)
Femoral nerve (Quadriceps)	Groin	<4.6 (14 cm)				
Phrenic nerve (Diaphragm)	Sternocleido-mastoid	<8.0	<0.9	>0.4		

*Site of stimulation	Median nerve	Palm: Origin of the recurrent thenar nerve 3–4 cm distal to the wrist crease. Wrist: 3 cm proximal to the distal wrist crease. Elbow: Lateral to the brachial artery at the elbow crease. Axilla: Medial aspect of the arm at the armpit.
	Ulnar nerve	Wrist: 3 cm proximal to the distal wrist crease. Below elbow: 2–3 cm distal to the medial epicondyle. Above elbow: 2–3 cm proximal to the medial epicondyle.in Axilla: Medial aspect of the arm at the armpit.
	Radial nerve	Forearm: Lateral edge of the extensor carpi ulnaris, 8–10 cm proximal to the styloidprocess. Elbow: Between the brachioradialis and the tendon of the biceps, 6 cm proximal to the lateral epicondyle. Axilla: Between coracobrachialis and the medial edge of triceps.
	Tibial nerve	Ankle: Posterior to the medial malleolus. Knee: Midline of the posterior aspect of the knee.
	Peroneal nerve	Ankle: Dorsum of the foot near the ankle. Below knee: 3 cm distal to the fibula head. Above knee: 2 cm proximal to the fibula head.

†Baseline to peak. Also abnormal if <50% compared to healthy side

Table 1-5 Normal Values for Sensory Nerve Conduction Studies

NERVE (SITE OF RECORDING)	SITE OF STIMULATION*	LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	AMPLITUDE† (mV)	NERVE SEGMENT BETWEEN S TIMULI	CONDUCTION VELOCITY (m/s)
Median nerve (Index finger)					Palm–index finger	>47
	Palm	<1.9	<0.4	>20	Wrist-palm	>44
	Wrist	<3.5	<0.5		Elbow-wrist	
	Elbow	<7.9	<0.7			>53
Ulnar nerve (Little finger)					Wrist–little finger	>44
	Wrist	<3.1	<0.4	>18	Below elbow–wrist	>53
	Below elbow	<6.9	<0.5		Above elbow–below elbow	>55
	Above elbow	<8.7	<0.8			
Median/Ulnar nerve comparison	Wrist	<0.4	Lateral (Median nerve) vs. medial (Ulnar nerve) side of the ring finger			
Radial nerve (Snuff box)	Forearm			>7	Forearm–snuff box	>46
Lateral antebrachial cutaneous nerve (Forearm)	Elbow			>10	Elbow-forearm	>54
Medial antebrachial cutaneous nerve (Forearm)	Elbow			>6	Elbow-forearm	>53

* The **boldface** and *italic* letters indicate **primary** and *secondary* innervation, respectively.

(*continued*)

Table 1-5 Normal Values for Sensory Nerve Conduction Studies* (Continued)

NERVE (SITE OF RECORDING)	SITE OF STIMULATION*	LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	AMPLITUDE† (mV)	NERVE SEGMENT BETWEEN S TIMULI	CONDUCTION VELOCITY (m/s)
Superficial peroneal nerve (Medial to lateral malleolus)	Above ankle	<4.6 (14 cm)		>6	Above ankle–ankle	
Sural nerve (Lateral to lateral malleolus)	Above ankle posteriorly	<3.5		>10	Above ankle–ankle	>39

*Site of stimulation	Median nerve	Palm: Origin of the recurrent thenar nerve 3–4 cm distal to the distal wrist crease. Wrist: 3 cm proximal to the distal wrist crease. Elbow: Lateral to the brachial artery at the elbow crease.
	Ulnar nerve	Wrist: 3 cm proximal to the distal wrist crease. Below elbow: 2–3 cm distal to the medial epicondyle. Above elbow: 2–3 cm proximal to the medial epicondyle.
	Radial nerve	Forearm: 3–10 cm proximal to the snuff box against the lateral edge of radius.
	Lateral antebrachial cutaneous nerve	Elbow: Just lateral to the tendon of the biceps brachii with the active electrode placed 12 cm distally.
	Medial antebrachial cutaneous nerve	Elbow: Medial to the brachial artery, 4 cm above the elbow crease on line drawn from the ulnar styloid process to the point halfway between the medial epicondyle and the biceps brachii tendon with the active electrode placed 12 cm distally.
	Superficial peroneal nerve	Above ankle: Anterior edge of fibula, 10–12 cm proximal from the lateral malleolus.
	Sural nerve	Above ankle posteriorly: 7–14 cm above the lateral malleolus.

†Baseline to peak. Also abnormal if <50% compared to healthy side.

Table 1-6 Normal Values for Facial Nerve, and Blink, Masseter, and H Reflexes

NERVE (SITE OF RECORDING)	SITE OF STIMULATION	RESPONSE RECORDED	LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	AMPLITUDE* (mV)
Facial nerve (Nasalis)	Stylomastoid-foramen	Direct response	<4.1	<0.6	>0.6
Trigeminal nerve (Orbicularis oculi)	Supraorbital-foramen	Ipsilateral R1 Ipsilateral R2 Contralateral R2	<12.5 <40 <40	<1.2 <5 ms between ipsi and contra responses <7 ms between right- and left-sided stimulation	>0.2
Trigeminal nerve (Orbicularis oculi)	Glabella tap	Glabellar reflex	<16.7	<1.6	
Trigeminal nerve (Masseter)	Jaw tap	Masseter reflex	<9.0	<0.8	> 0.1
Tibial nerve (Soleus)	Behind the knee	H reflex	<35	<1.4	> 1.2

*Also abnormal if <50% compared to healthy side.

Table 1-7 Normal Values for F wave

NERVE (SITE OF RECORDING)	SITE OF STIMULATION*	LATENCY† (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	CENTRAL LATENCY (ms)	DIFFERENCE BETWEEN RIGHT AND LEFT (ms)	F-WAVE CONDUCTION VELOCITY (m/s)	F-WAVE PERSISTENCE (%)	F RATIO PROXIMAL AND DISTAL SEGMENT
Median nerve	Wrist	<31	<2.3	<27	<2.2	>56		0.82 – 1.14
(Abductor	Elbow	<27	<1.9	<18	<1.7	>56		
pollicis brevis)	Axilla	<24	<2.1	<14	<2.0			
Ulnar nerve	Wrist	<32	<2.7	<29	<2.0	>55	> 45	0.87 – 1.23
(Adductor digiti	Above elbow	<27	<1.6	<18	<1.8	> 55		
minimi)	Axilla	<24	<1.8	<13	<1.8			
Peroneal nerve	Ankle	<56	<3.5	<52	<3.1	> 43		0.87 – 1.23
(Extensor digitorum	Knee	<46	<3.2	<32	<3.0	> 46		
brevis)								
Tibial nerve	Ankle	<58	<3.5	<53	<3.6	> 44	> 87	0.87 – 1.33
(Abductor hallucis)	Knee	<48	<3.1	<34	<3.0	> 44		

*Site of stimulation	Median nerve	Wrist: 3 cm proximal to the distal wrist crease. Elbow: Lateral to the brachial artery at the elbow crease. Axilla: calculated as Fa = Fw + Mw – Ma,
	Ulnar nerve	Wrist: 3 cm proximal to the distal wrist crease. Above elbow: 3 cm proximal to the medial epicondyle. Axilla: calculated as Fa = Fw + Mw – Ma,
	Peroneal nerve	Ankle: Dorsum of the foot near the ankle. Knee: Just above the head of fibula.
	Tibial nerve	Ankle: Posterior to the medial malleolus. Knee: At the popliteal fossa.

†See height-latency nomogram for length adjusted upper limits of F-wave latencies.

C HEIGHT-LATENCY NOMOGRAMS FOR F WAVE

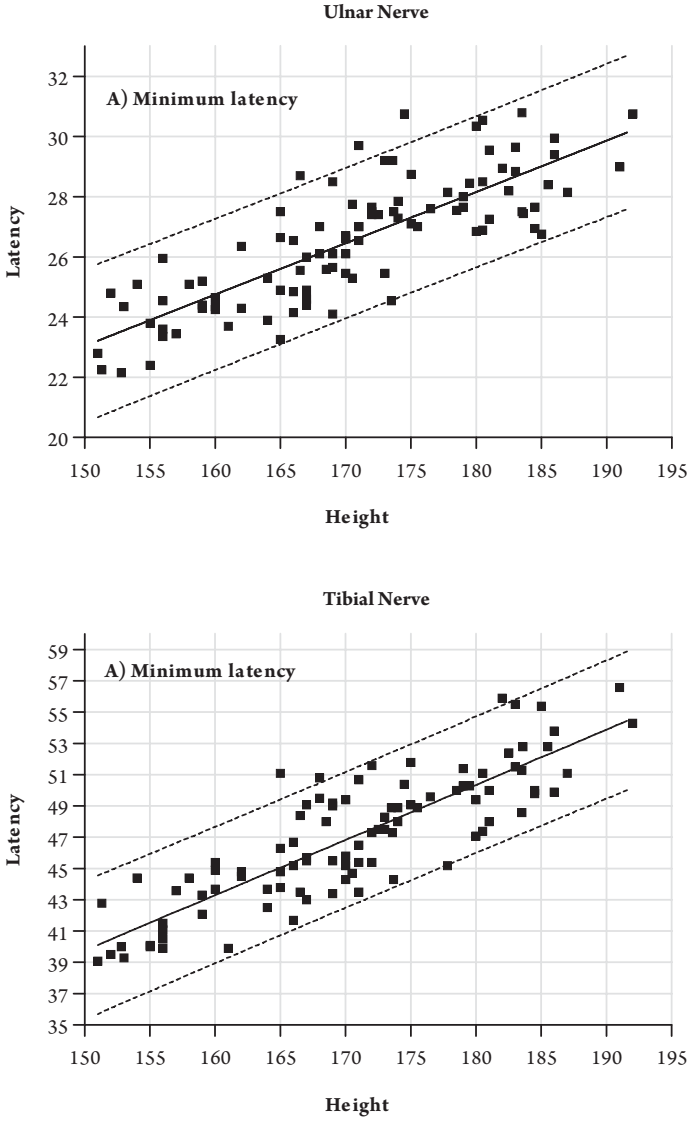

FIGURE 1-1 Height-Minimum F-wave Latency Nomogram.

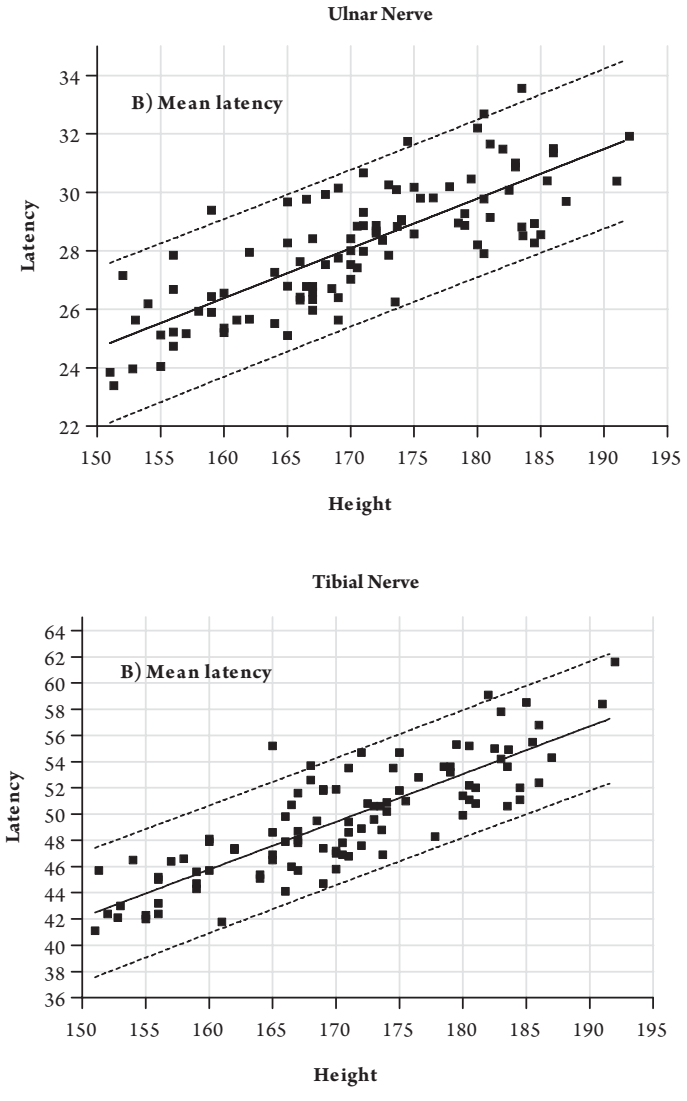

FIGURE 1-2 Height-Mean F-wave Latency Nomogram.

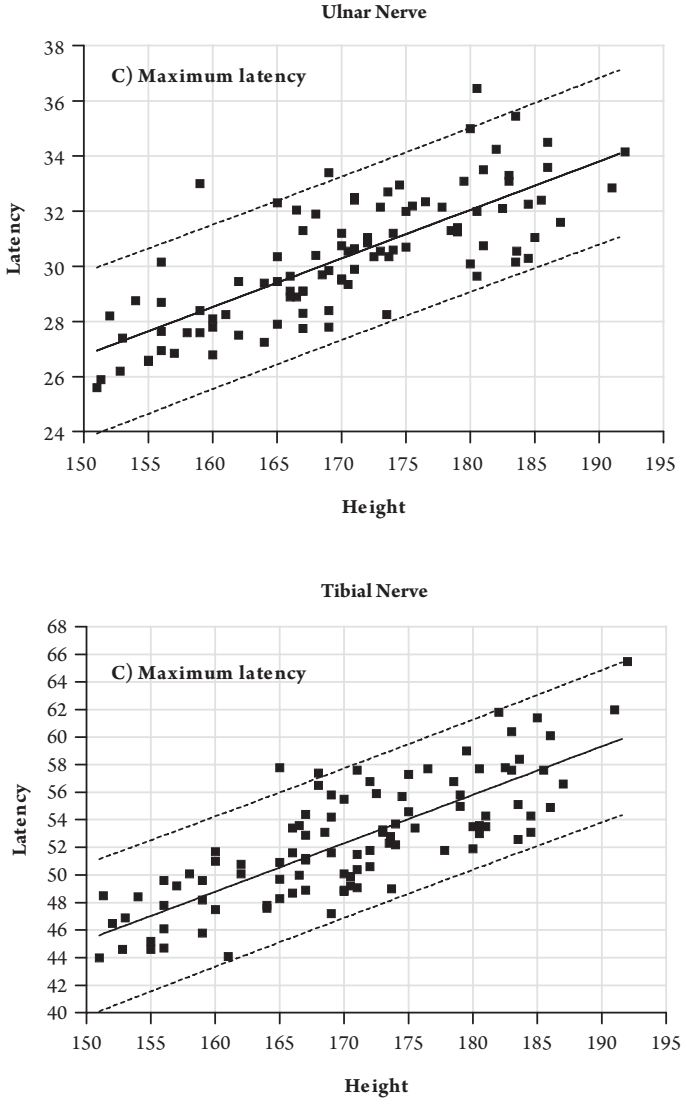

FIGURE 1-3 Height-Maximum F-wave Latency Nomogram.

II CONTENTS OF DVD

A OPERATONAL MANUAL

EMG Lecture with Live Sounds

HOW TO USE THE DVD-ROM

Windows_User

Nihon Kohden Co. reserves the copyright for the EMG Player program (EmgPlayerLE2.exe), a trademark of Nihon Kohden Co. This program is designed to play EMG files contained in this book. Nihon Kohden Co. has permitted its personal educational use only for owners of this book. Duplicating and distributing the EMG Player program without permission is prohibited by law.

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Use of the DVD-ROM assumes consent on the part of the user.

System Requirement to Run the DVD-ROM

WINDOWS OS

Microsoft Windows XP, Vista, 7, and 8

NOTE

The program may not work with the latest OS, Windows 8, depending on the PC environment. If so, please see the Section "What to Do If the Homepage Does Not Open".
Internet Explorer 7 or higher
Display resolution of 1024×768 or higher
Sound device and audio speaker

Macintosh OS

Internet browser (e.g., Safari)
Display resolution of 1280×720 or higher
Environment to play a MP4 format video with HD resolution of 1280×720 dots
Sound device and audio speaker

Windows PC

HOW TO USE THE DVD-ROM (WITH WINDOWS 7)

Insert the DVD-ROM to display the following screen (Fig. 1).
Click "Run run32dll.exe (icon of Jun Kimura)" to

Figure 1

open the next screen (Fig. 3).

NOTE
With Windows 8, insert the DVD to display the message in the upper right corner of screen and click it to open the next screen (Fig. 2).

Figure 2

Click "Run run32dll.exe (icon of Jun Kimura)" to open the next screen (Fig. 3).

NOTE

If the "AutoPlay" function is disabled, open the DVD-ROM and double-click the file "START_Win" in "Windows_User" folder.

Operation of EMG Lecture with LIVE SOUNDS

This software operates like any general Internet browser.

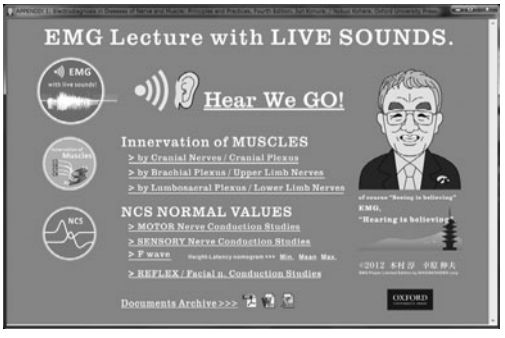


Figure 3

DVD-ROM contents include, in addition to EMG lectures, three tables on myotome, four tables on nerve conduction study (NCS) normal values, and three figures on height- F-wave latency nomograms (Nobrega et al, 2004). You can download any files from the "Documents Archive".

For EMG lectures, click the icon or "Hear We GO!" to open the "EMG findings" page. Then click the icon to open the "EMG description" page and click the icon again to select the item of interest to open the EMG Player (Fig. 4).

For myotome, NCS normal values, and height-F-wave latency nomograms, click the underlined item of interest or a symbol icon on the left of the screen.

How to Use the EMG Player

Click the play button PLAY on the toolbar on top of the screen to run the program, and click the close button to finish.

A real-time EMG trace is displayed with live sounds in the upper part of the screen, and compressed waveforms in the lower part.

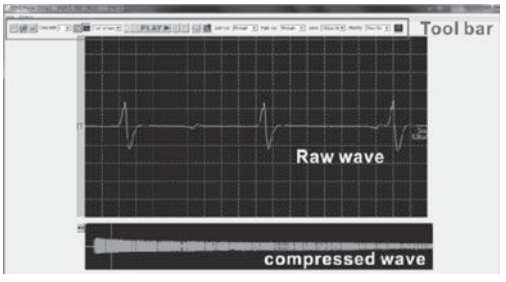


Figure 4

FUNCTION OF OTHER BUTTONS ON THE TOOLBAR

PAUSE button: Pause EMG play.

STOP button: Stop EMG play.

REPEAT button: Repeat EMG play.

VOLUME button: Adjust volume.

CASCADE button: Display the waveform in a cascade (raster) mode, showing the desired number of traces indicated in the pull-down menu.

Select the desired number in the pull-down menu to change sensitivity, filter setting, and sweep speed.

Low Cut through High Cut through Sens 200uV/di Monitor 10ms/div

Low Cut: Change the low-cut frequency.
High Cut: Change the high-cut frequency.
Sens: Change the sensitivity.
Monitor: Change the sweep speed (time scale) of the screen.

NOTE: Stop EMG play first, before changing the filter setting.

HOW TO USE TRIGGER MODE

Click icon to open "Trigger mode screen", which displays triggering waveforms on the right side (Fig. 5).

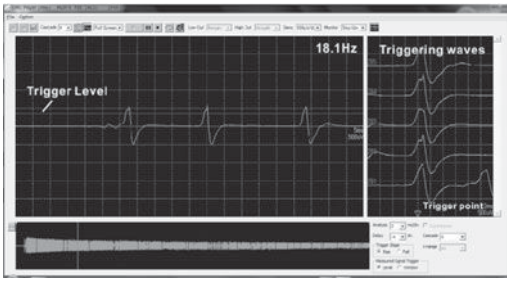


Figure 5

The main screen on the left shows the firing rate of discharge at the right corner on top and a green horizontal line which triggers the sweep as it crosses the rising slope of the waveform in the standard setting.
Drag this line up and down with a mouse to select a desired trigger level.
Trigger mode settings are found in the menu under trigger mode screen and includes the following (Fig. 6).

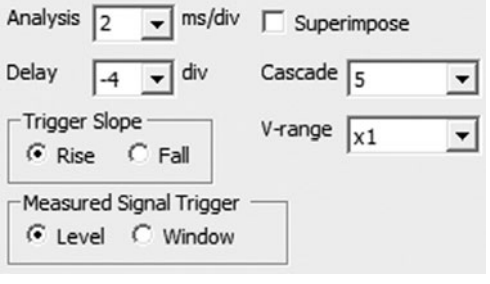


Figure 6

Analysis: Sweep speed of the triggered trace.
Delay: Interval between the onset of sweep and trigger point.
Trigger Slope
Rise: Triggers on crossing the rising slope of the waveform.
Fall: Triggers on crossing the falling slope of the waveform.
Measured Signal Trigger
Level: Triggers the sweep as the green line crossing the waveform.

Window: Triggers the sweep with a window formed by two horizontal lines when the bottom line but not the top line crosses the waveform. This type of triggering serves well in selecting one particular motor unit potential (MUP) in the presence of many others.
Superimpose: Superimpose triggering waveforms automatically at the end of analyses.
Cascade: Number of traces showing the triggering waveforms.
V-range: Amplifier sensitivity used to display triggering waveforms.

WHAT TO DO IF THE EMG PLAYER DOES NOT RUN

Open the DVD-ROM and the "EmgPlayer folder" in "Windows_User folder" and double-click "EmgPlayerLE2" to run the EMG Player.
Click a folder icon on top of the screen and select an EMG file to play.

WHAT TO DO IF THE HOMEPAGE DOES NOT OPEN

Use "Video type" contained in "Video_for_Windows" folder in the DVD-ROM.
Double-click "START_Win" in "Video_for_Windows" folder. EMG waveform is displayed with WMV format video with the HD resolution of 1280x720 dots.

NOTE

With Windows 8, which may not play the EMG video files, copy "Video_for_Windows" folder to your desktop from the DVD (following instruction on "How to Copy files to Another Media" section).

Macintosh PC

Open "Macintosh_User" folder in the DVD-ROM
Double-click "START_Mac.html".
The DVD-ROM contents include, in addition to EMG lectures, three tables on myotome, four tables on nerve conduction study (NCS) normal values, and three figures on height- F-wave latency nomograms (Nobrega et al, 2004). You can download any files from "Documents Archive".

For EMG lectures, click the  icon or "Hear We GO!" to open the "EMG findings". Then click the  icon to open the "EMG description" page and click the  icon again to select the item of interest. EMG sample is displayed in a MP4 format video with HD resolution of 1280x720 dots.

To display the tables for myotome, NCS normal values, and the figures for height- F-wave latency nomograms, click the under lined item of interest or the corresponding symbol icon on the left side of the screen.

HOW TO COPY FILES TO ANOTHER MEDIA

You can copy the contents of the DVD-ROM to the hard disk of a PC or a memory device such as USB as follows:

WITH WINDOWS OS

To use the EMG Player to play EMG files, copy "Windows_User" folder (which you can rename afterwards) to any memory device, open the copied folder, and double-click "START_Win".

To use Video to play EMG files, copy "Video_for_Windows" folder (which you can rename afterward) to any memory device, open the copied folder, and double-click "START_Win". EMG sample is displayed in a WMV format Video with HD resolution of 1280x720 dots.

WITH MACINTOSH OS

Copy "Macintosh_User" folder (which you can rename afterwards) to any memory device, open the copied folder, and double-click "START_Mac.html".

B DESCRIPTION OF EMG WAVES

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F01 Insertion-1	BB	Healthy subject	Insertional activity recorded from the biceps brachii (BB) in a healthy volunteer with the needle tip quickly moved five times into the muscle. Needle stimulation induces a short-lasting irregular discharge, which abates immediately with cessation of needle movement.	Typical pattern of normal insertional activity
F02 Insertion-2	BB	Myositis	Insertional activity recorded from the biceps brachii (BB) in a patient with myositis. Each needle insertion induces a myotonic discharge, which appears as a run of positive sharp waves lasting for at least 1 second with decreasing frequency. Myotonic discharges, though frequently observed in myositis, do not accompany clinical myotonia, which depends on a greater number of simultaneously discharging muscle fibers.	Myotonic discharge without clinical myotonia
F03 Insertion-3	TB	Chronic myositis	Insertional activity recorded from the triceps brachii (TB) in a patient with chronic myositis. In addition to fibrillation potentials, needle movement induces myotonic discharges not associated with clinical myotonia.	Myotonic discharge associated with fibrillation potential
F04 Insertion-4	BB	Hypothyroidism	An unusual type of insertional activity recorded from the biceps brachii (BB) in a patient with increased muscle membrane excitability probably related to hypothyroidism. Needle movements induce a sound resembling a bullet fired in a video game.	Insertional activity associated with hyperexcitable muscle membrane.

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F05 EP noise	TA	Healthy subject	Spontaneous activity recorded from the tibialis anterior (TA) in a healthy volunteer. Endplate (EP) noise appears with the tip of the needle near the motor point and disappears after a slight withdrawal of the needle. This represents a group of miniature endplate potentials recorded extracellularly simulating the sound of a seashell placed against the ear. This recording contains some high-frequency noise in the background.	EP noise without EP spike
F06 EP noise and EP spike-1	TA	Healthy subject	Spontaneous activity recorded from the tibialis anterior (TA) in a healthy volunteer. High-frequency endplate (EP) spikes characteristically discharge very irregularly often associated with a low-amplitude EP noise in the background. The initially negative biphasic spikes represent single muscle fiber potentials recorded by needle tip placed near the nerve terminals. The initially positive triphasic waveform may result if the shaft rather than the tip of the needle register the same discharge. In this recording, EP spikes, 2 ms in duration, exceed the measurement limit of 500 μV, indicating a close proximity between the tip of the recording electrode and the generator source.	EP noise and EP spike
F07 EP noise and EP spike-2	TA	Healthy subject	Spontaneous activity recorded from the tibialis anterior (TA) in a healthy volunteer. Endplate (EP) noise appears with the insertion of the needle into the muscle through the fascia, followed by a run of irregularly firing high-frequency EP spikes.	Typical appearance of EP noise followed by EP spike

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F08 EP noise and EP spike-3	BB	Healthy subject	Spontaneous activity recorded from the biceps brachii (BB) in a healthy volunteer. Endplate (EP) spikes appear with EP noise in the background.	Typical EP noise and EP spike recorded with the tip of the needle close to the source
F09 EP spike	EDC	Healthy subject	Spontaneous activity recorded from the extensor digitorum communis (EDC) in a healthy volunteer. High-frequency, irregular endplate (EP) spikes recorded in this tracing without the EP noise sound less crispy probably because the needle tip lies slightly away from the generator source.	EP spike without EP noise
F10 Myotonic discharge-1	EDC	Myotonic dystrophy	Insertional activity recorded from the extensor digitorum communis (EDC) in a patient with myotonic dystrophy. Myotonic discharge induced by needle movement shows a gradual increment and a decrement in frequency and amplitude. This activity involving different muscle fibers sequentially sounds like an accelerating and decelerating motor cycle.	Typical motor cycle sound of myotonic discharge
F11 Myotonic discharge-2	EDC	Myotonic dystrophy	Insertional activity recorded from the extensor digitorum communis (EDC) in a patient with myotonic dystrophy. In raster mode, negative spikes seen at the beginning, gradually turn into repeated positive spikes. Myotonic discharge with characteristic fluctuation in frequency sounds like an accelerating and decelerating motorcycle engine.	Typical motor cycle sound of myotonic discharge
F12 Myotonic discharge-3	EDC	Paramyotonia congenita	Insertional activity recorded from the extensor digitorum communis (EDC) in an asymptomatic patient with paramyotonia congenita. Some single motor unit potentials appear in addition to typical myotonic discharges, which represent repetitive firing of single muscle fibers induced by needle movements.	Myotonic discharge recorded in clinically unaffected muscle

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F13 Myotonic discharge-4	TB	Chronic myositis	Insertional activity recorded from the triceps brachii (TB) in a patient with chronic myositis. In addition to fibrillation potentials observed at the beginning and at the end, myotonic discharges follow needle movements. This finding, though nonspecific, commonly appears in myositis showing no clinical evidence of myotonia.	Myotonic discharge without clinical myotonia
F14 Myotonic discharge-5	TA	Acid maltase deficiency	Insertional activity recorded from the tibialis anterior (TA) in a 27-year-old woman with childhood acid maltase deficiency. Myotonic discharge appears immediately after needle insertion. This tracing, recorded outside the EMG lab, contains small, high-tone alternating current artifacts in the background. The patient, with no clinical evidence of myotonia, had respiratory muscle paralysis requiring a mechanical ventilator. She gradually improved by enzyme replacement therapy with α-glucosidase (Myozyme).	Myotonic discharge without clinical myotonia
F15 Myotonic discharge-6	TA	Acid maltase deficiency	Myotonic discharges triggered by voluntary contraction of the tibialis anterior (TA) in the same patient as F14. Positive waveforms seen at the beginning subsequently transform to negative spikes. Motor unit potentials, recorded at the beginning, show an increased number of polyphasic units and an early recruitment. Although nonspecific, recording myotonic discharges helps establish an early diagnosis of this disease, now treatable with enzyme replacement therapy.	Polyphasic MUP showing an early recruitment
F16 Myotonic discharge-7	EDC	Post-polio syndrome	Insertional activity recorded from the extensor digitorum communis (EDC) in a patient with polio sequelae. Myotonic discharge appears despite absence of clinical myotonia. This finding, though not seen as constantly as in myotonic disorders, characterizes same neurogenic disorders as a feature of denervation.	Myotonic discharge recorded in a denervated muscle

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F17 Fib and PW-1	EDC	ALS	Spontaneous activity recorded from the extensor digitorum communis (EDC) in a patient with amyotrophic lateral sclerosis (ALS). Fibrillation potentials and positive sharp waves, seen in ALS, indicate the loss of spinal motoneurons. Both activities usually show a regular firing pattern although they may also discharge at a progressively faster or slower frequency. Differences in waveform reflect the spacial relationship between the recording surface of the needle tip and the discharging muscle fibers. Occasional runs show irregular firing patterns and a shift from regular to irregular discharges.	Typical single muscle fiber discharge consisting of fibrillation potentials and positive sharp waves
F18 Fib and PW-2	TB	ALS	Spontaneous activity recorded from the triceps brachii (TA) in a patient with amyotrophic lateral sclerosis (ALS). Note two fibrillation potentials and one positive sharp wave discharging regularly. The firing rate of one of the fibrillation potentials gradually accelerates. The positive sharp waves recorded in this sample have a small spike in the middle, indicating a partial transition toward a fibrillation potential.	Transition of positive sharp waves to fibrillation potentials
F19 Fib and PW-3	BB	Compression neuropathy	Spontaneous activity recorded from the biceps brachii (BB) in a patient with brachial plexus compressive injuries sustained during a surgery 3 weeks earlier. The tracings show many fibrillation potentials and positive sharp waves, all firing regularly.	Typical spontaneous single muscle fiber discharges seen in a denervated muscle
F20 Fib and PW-4	ECR	Radial nerve palsy	Spontaneous activity recorded from the extensor carpi radialis (ECR) 3 months after sustaining a severe traumatic radial nerve palsy. In addition to a large number of fibrillation potentials and positive sharp waves, myotonic discharges appear in the middle of tracing, readily identifiable by the characteristic noise heard.	Good example of myotonic discharges mixed with spontaneous single muscle fiber discharges in a denervated muscle

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F21 Fib and PW-5	BB		Spontaneous activity recorded from the biceps brachii (BB) in a patient with dermatomyositis. The recording shows many low-amplitude, long-duration positive sharp waves with regularly recurring high-amplitude fibrillation potentials in the background. Despite the overall appearance and sound of irregular firing, detailed analysis reveals that individual single muscle fiber potentials discharge regularly as best seen in the raster mode. Fibrillation potentials and positive sharp waves constitute an essential finding in diagnosing active myositis. Their absence in a clinically weak muscle usually speaks against this possibility.	Low-amplitude positive sharp waves and high-amplitude fibrillation potentials, each firing regularly
F22 Fib and PW-6	RF	IBM	Spontaneous activity recorded from the rectus femoris (RF) at rest in a patient with a biopsy proven inclusion body myositis (IBM). The tracing shows typical fibrillation potentials and positive sharp waves, and in the latter half, a run of myotonic discharge.	Myotonic and spontaneous single muscle fiber discharges
F23 Fib and PW-7	TB	Chronic myositis	Spontaneous activity recorded from the triceps brachii (TB) in a patient with chronic myositis. Several fibrillation potentials appear, all firing regularly. With the needle electrode located close to the signal source, a single muscle fiber discharge can reach the order of millivolt in amplitude. In contrast, potentials recorded with the needle tip far from the signal source show a smaller amplitude and longer duration, making it difficult to clearly identify individual waveforms.	Fibrillation potentials recorded with the needle tip close to the source

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F24 Fib and PW-8	BB	Fukuyama muscular dystrophy	Spontaneous activity recorded from the biceps brachii (BB) during partial voluntary contraction in a patient with Fukuyama muscular dystrophy. Fibrillation potentials and positive sharp waves observed throughout the tracing indicate active degeneration of muscle fibers. Despite an attempt to record at rest, potentials induced by voluntary contraction appear at two points in the beginning of the recording.	Fibrillation potential and positive sharp waves
F25 Fib and PW-9	RF	IBM	Spontaneous activity recorded from the rectus femoris (RF) at rest in a patient with inclusion body myositis (IBM). This tracing shows a high-amplitude, irregularly firing doublet in addition to typical fibrillation potentials from two or three muscle fibers. The larger discharge probably represents an unstable single muscle fiber potential recorded close to the hypertrophic muscle fiber often reported in IBM. Note a distant MUP seen in the background.	A high amplitude spontaneous discharge probably recorded close to a hypertrophic muscle fiber, often seen in IBM
F26 Fib and PW-10	TB	Chronic myositis	Spontaneous activity recorded from the triceps brachii (TB) in a patient with chronic myositis. Positive sharp wave and negative spikes appear independently and consecutively at 19 Hz, without waxing and waning seen in myotonic discharge. Varying temporal relationship between the two suggests the origin from independent single muscle fibers rather than sequential activation observed in complex repetitive discharge (CRD).	Fibrillation potential and positive sharp waves firing independently at a similar frequency
F27 CRD-1	EDC	Cervical radiculopathy	Spontaneous activity recorded from the extensor digitorum communis (EDC) in a patient with cervical radiculopathy. Complex repetitive discharge (CRD) consists of a series of single muscle fiber discharge which repeats regularly, producing	Typical pattern of CRD showing sequential discharges of a group of single muscle fibers

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
			a sound resembling a machine gun (which I know only in movies). Repetitive potentials with such consistency result from ephaptic transmission among different hyperexcitable muscle fibers triggered by a spontaneous single muscle fiber discharge, which serves as pacemaker.	Typical pattern of CRD showing sequential discharges of a group of single muscle fibers
F28 CRD-2	TA	Familial chronic SMA	Spontaneous activity recorded from the tibialis anterior (TA) in a patient with familial chronic progressive spinal muscular atrophy. The first complex repetitive discharge (CRD) induced by the initial needle movement gradually turns into a simple waveform discharging at a regular interval before abrupt cessation. The second CRD maintains a consistent waveform for some period and then suddenly abates. Both have a frequency of about 70 Hz and thus might have originated from the same source. The CRD represents a number of muscle fibers forming a circuit, firing sequentially through ephaptic transmission.	Typical CRD beginning and ending abruptly
F29 CRD-3	BB	Cervical radiculopathy	Spontaneous activity recorded from the biceps brachii (BB) in a patient with cervical radiculopathy. Although a complex repetitive discharge (CRD) typically repeats the same pattern regularly, a close analysis of this tracing shows slight changes in the waveforms from one discharge to the next, probably indicating either instability of ephaptic transmission or a slight movement of the needle tip.	Unstable CRD, showing slight waveform change

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F30 Fasciculation-1	BB	ALS	Spontaneous activity recorded from the biceps brachii (BB) in a patient with amyotrophic lateral sclerosis (ALS). Unlike a voluntarily activated motor unit potential (MUP), which fires semi rhythmically, a fasciculation potential shows a low frequency and irregular firing pattern, making the two easily distinguishable. The discharges shown in this tracing has a dull sound as they originate at some distance from the recording tip of the needle.	Fasciculation potentials firing slowly and irregularly at distance
F31 Fasciculation-2	BB	ALS	Spontaneous activity recorded from the biceps brachii (BB) in a patient with amyotrophic lateral scoliosis (ALS). This tracing contains three types of fasciculation potentials each changing the waveform slightly and randomly with successive discharges: high- and low- frequency units and those appearing immediately after each large fasciculation. Although firing occurs irregularly, fasciculation potentials originating from the same or different motor units tend to form a cluster.	Fasciculation potentials firing in a cluster
F32 Fasciculation-3	BB	Bulbar ALS	Spontaneous activity recorded from the clinically unaffected biceps brachii (BB) in a 60-year-old woman with a bulbar ALS. Fasciculation potentials, considered crucial in the diagnosis of ALS, abound in this tracing despite the absence of fibrillation potentials or positive sharp waves.	Typical fasciculation potentials observed alone
F33 Fasciculation-4	EDC	Cramp fasciculation syndrome	Spontaneous activity recorded from the extensor digitorum communis (EDC) in a patient with the cramp fasciculation syndrome with normal muscle strength and a CK level. He had no abnormalities other than a 15-year history of recurrent cramps in the calf and generalized muscle spasms. A number of fasciculation	Fasciculation potentials associated with muscle cramps but no other abnormalities

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
			potentials appear irregularly at a relatively high frequency in the first half of the recording and at a lower frequency in the latter half.	
F34 Myokymia-1	FDI	Polyneuropathy	Spontaneous activity recorded from the first dorsal interosseous (FDI) in a patient with an idiopathic polyneuropathy. Myokymic discharges, otherwise known as grouped fasciculation potentials, consist of two to eight consecutive spontaneous single motor unit discharges, occurring repetitively. Such findings, commonly observed in post-radiation plexopathy, may also appear in demyelinating neuropathies.	Typical myokymic discharge seen in a demyelinating neuropathy
F35 Myokymia-2	FDI	Polyneuropathy	Spontaneous activity recoded from the same muscle as described in F34. The firing rate within each cluster reaches 200 Hz, resembling neuromyotonic discharges. A rapid change in the waveform seen in the middle of tracing suggests a slight movement of the recording needle electrode.	Myokymic discharge with a high firing rate reminiscent of neuromyotonic discharge
F36 Myokymia-3		Radial nerve palsy	Spontaneous activity recorded from the extensor digitorum communis (EDC) in a patient with an entrapment neuropathy. Different types of spontaneous discharges shown include fasciculation potentials and paired fasciculation potentials. The repetitive complex waveform seen in the middle of this tracing also represents a form of myokymic discharge. The potential lasting for at least 200 ms probably results from ephaptic transmission among a number of nerve or muscle fibers initially triggered by a fasciculation potential which serves as pacemaker.	Fasciculation potential, paired fasciculation potential, and myokymic discharge

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F37 Myokyimia-4		Alcoholic neuropathy	Spontaneous activity recorded from the rectus femoris (RF) in a patient with alcoholic neuropathy and clinical evidence of myokymia. Each of two myokymic discharges, one high and the other low in amplitude, consists of three or four consecutive discharges forming a unit, which then repeats every few seconds. The discharge frequency within a unit reaches 300 Hz. Then, the spikes become progressively smaller as they face the refractory period of the preceding discharge.	Myokymic discharge showing progressive amplitude reduction
F38 Myokymia and fasciculation-1		Kennedy's disease	Spontaneous activity recorded from the first dorsal interosseus (FDI) in a patient with Kennedy's disease. The recording shows fasciculation potentials, or spontaneous discharge of a motor unit, and myokymic discharges, or grouped fasciculation potentials. Recording also shows several doublets associated with contraction of FDI abducting the index finger.	Myokymic discharge as compared to fasciculation potential
F39 Myokymia and fasciculation-2		Isaac's syndrome	Spontaneous activity recorded from the gastrocnemius (GC) in a 37-year-old woman with clinical features of the Isaac's syndrome characterized by hypertrophy of the lower-limb muscles and extensive myokymia persisting during sleep. The recording shows fasciculation potentials and myokymic discharges. Despite the typical clinical presentation, laboratory studies failed to document anti K-channel antibodies usually seen in this disorder.	Typical myokymic discharges, the term sometimes used synonymously with a neuromyotonic discharge not seen in this tracing
F40 Neuromyotonia		Cervical radiculopathy	Insertional activity recorded from the biceps brachii (BB) in a patient with cervical radiculopathy. The tracing shows high-frequency repetitive discharges from a single motor unit at around 150 Hz without waxing and waning seen in myotonic discharge.	Neuromyotonic discharge seen in radiculopathy

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F41 MUP-1		Healthy subject	Motor unit potentials (MUPs) during voluntary contraction of the tibialis anterior (TA) in a healthy volunteer. The first MUP recorded produces a dull sound indicating its distant location. The rise time shortens with needle advancement, sharpening the sound and increasing the peak amplitude. This tracing shows a recording during the weakest muscle contraction to avoid the recruitment of other motor units, which interferes with MUP analysis.	The effect of needle placement, altering the distance to the discharging motor unit, which in turn, dictates the amplitude of MUP
F42 MUP-2		ALS	Motor unit potentials (MUP) recorded from the tibialis anterior (TA) during voluntary contraction in a patient with amyotrophic lateral sclerosis (ALS). Despite a substantial waveform change after each needle movement, all potentials recorded in this tracing originate from the same motor unit. Amplitude and waveform vary substantially depending on the location of the recording electrode. Placing the needle tip close to the signal source improves the analysis. The surviving motor units may discharge at 40–50 Hz to compensate for the loss in the number of spinal motoneurons.	High-amplitude MUP firing rapidly
F43 MUP-3		Healthy subject	Motor unit potentials (MUPs) recorded from the extensor digitorum communis (EDC) during voluntary contraction in a healthy volunteer. Applying greater force results in a gradual increase in the number of motor units recruited with eventual shift to an interference pattern induced by maximum contraction. Isometric contraction helps maintain the location of the needle tip despite gradually increasing force.	Normal recruitment showing a greater number of MUP with increasing force

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F44 MUP-4		Healthy subject	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) in a healthy volunteer. This tracing recorded during progressively stronger contraction shows a couple of motor units firing at a slow rate initially during a weak effort and more rapidly later before the recruitment of other units by greater voluntary force, eventually leading to a full interference pattern with a maximal effort.	Discharge pattern of a normal MUP during progressively stronger contraction
F45 MUP-5		ALS	Motor unit potentials (MUPs) recorded from the first dorsal interosseus (FDI) in a patient with amyotrophic lateral scoliosis (ALS). The MUP amplitude gradually decreases as the firing interval becomes irregular and returns to the original level after a few seconds of rest. This type of attenuation suggests depletion of acetylcholine (ACh) at the nerve terminal sometimes observed with repetitive nerve stimulation.	Attenuation of MUP with repetitive discharge reflecting ACh depletion at the nerve terminal
F46 MUP-6		ALS	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) during voluntary contraction in a patient with amyotrophic lateral scoliosis (ALS). Doublets, as seen in this recording, make a characteristic sound of double firing. The second of the two discharges has asmaller amplitude as it falls in the relative refractor period of the muscle fibers. A prolonged firing interval seen after each doublet indicates delayed depolarization of the spinal motoneurons, as often observed in ALS.	Doublets showing a smaller amplitude for the second as compared to the first discharge
F47 MUP-7		ALS	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) during voluntary contraction in a patient with amyotrophic lateral scoliosis (ALS). Most polyphasic potentials seen in this tracing show varying waveforms after each firing, indicating instability at the nerve terminal and neuromuscular junction observed in an early stage of regeneration.	Unstable polyphasic MUP indicating active degeneration and regeneration of motor fibers

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F48 MUP-8	PSM	ALS	Motor unit potentials (MUPs) recorded from the thoracic paraspinal muscle (PSM) during voluntary contraction in a patient with amyotrophic lateral scoliosis (ALS). The biphasic MUP with a relatively stable waveform indicates an intermediate stage of regeneration. In ALS, abnormalities seen in the thoracic PSM helps not only confirm the diagnosis but also evaluate the respiratory muscle function.	Relatively stable MUP indicating an intermediate stage of regeneration
F49 MUP-9	TB	ALS	Motor unit potentials (MUPs) recorded from the triceps brachii (TB) during voluntary contraction in a patient with amyotrophic lateral scoliosis (ALS). A maximum voluntary contraction immediately after the start of recording recruits only four high-amplitude potentials without completely filling the baseline. This type of reduced interference associated with rapid firing of remaining MUP denotes a substantial loss of the functional motor units.	A small number of high-amplitude MUP firing rapidly to compensate for the loss of motor units
F50 MUP-10	EDC	ALS	Motor unit potentials (MUPs) recorded from the extensor digitorum communis (EDC) during voluntary contraction in a patient with amyotrophic lateral scoliosis (ALS). Only one motor unit discharges rapidly during the maximum contraction, showing a veryreduced interference referred to as "picket fence" pattern. The baseline drift indicates activation of other motor units at a distance in addition to the surviving motor unit within the recording radius of the electrode. In the absence of normal recruitment, a compensatory increase in firing rate of existing motor units may reach 50 Hz.	Late recruitment with single motor unit firing rapidly forming "picket fence" pattern during a maximal contraction

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F51 MUP-11	PSM	Familial ALS	Motor unit potentials (MUPs) recorded from the paraspinal muscles (PSM) in a 38-year-old man with a familial ALS caused by FUS gene abnormality, which also affected one brother. Except for an early onset, the patient had the same clinical features as a sporadic case with the initial weakness affecting the lower limb. Severe trunk muscle weakness prevented unassisted rise from the supine position. A maximal contraction induces a single high-amplitude, long-duration MUP, which fires rapidly at 20 Hz to compensate for the lack of recruitment. This pattern, resembling a "picket fence" in appearance, indicates a severe loss of functional motor axons.	Typical finding for chronic denervation showing a large amplitude MUP firing rapidly to compensate for a late recruitment indicating the loss of functional units
F52 MUP-12	APB	Brachial plexus injury	Motor unit potentials (MUPs) recorded from the abductor pollicis brevis (APB) 4 months after a brachial plexus injury inflicted by a motor cycle accident. This tracing recorded during a weak muscle contraction shows a polyphasic MUP changing the waveform from one discharge to the next, best seen with the low cut filter elevated to 500 Hz and the sweep speed set at 1 ms/division. The finding suggests an early stage of regeneration characterized by incomplete myelination and unstable nerve terminals, showing an abnormally increased jitter and intermittent blocking	An abnormal MUP, showing waveform variability as a sign of instability of the regenerating nerve terminals
F53 MUP-13	FDI	Post-polio syndrome	Motor unit potentials (MUPs) recorded during voluntary contraction from the first dorsal interosseus (FDI) in a chronic polio patient. The tracing shows a stable and polyphasic MUP accompanied by satellite potentials.	Polyphasic MUP showing satellite potentials

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F54 MUP-14	RF	Post-polio syndrome	Motor unit potentials (MUPs) recorded from the rectus femoris (RF) during voluntary contraction in a patient with chronic polio myelitis. A simple-form MUP exceeding 10 mV in amplitude indicates a stable condition with completed regeneration of nerve fibers.	High-amplitude MUP
F55 MUP-15	FDI	Psychogenic weakness	Motor unit potentials (MUPs) recorded from the first dorsal interosseus (FDI) during voluntary contraction in a patient with psychogenic weakness. Apparent effort to contract the muscle gave rise to a tremulous movement without generating much force. The recording shows a grouped discharge, a pattern typically seen in a tremor, which may superficially mimic a polyphasic MUP. A maximal effort enhances the tendency to grouping without inducing a full interference pattern. This finding often indicates an insufficient central drive considered typical for hysterical weakness.	Irregular grouped firing of several motor units, forming a tremor discharge seen in hysterical weakness
F56 MUP-16	FDI	Becker MD	Motor unit potentials (MUPs) recorded from the first dorsal interosseus (FDI) during voluntary effort in a patient with Becker muscular dystrophy (MD). The recording obtained during a gradually increasing contraction force shows small, short-duration, polyphasic potentials. Note a typical finding of early recruitment making the baseline invisible even with a slight muscle contraction.	Early recruitment of small, short-duration, polyphasic MUP
F57 MUP-17	FDI	Becker MD	Motor unit potentials (MUPs) recorded from the same muscle as described in F56 during voluntary contraction. In myopathy, early recruitment of multiple motor units often precludes assessment of each individual MUP. The tracing shows both short- and long-duration polyphasic potentials and the abundance of a small MUP, probably derived from a single muscle fiber.	Small polyphasic MUP showing a typical early recruitment with minimal muscle contraction

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F58 MUP-18	BB	Mitochondrial encephalo-myopathy	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) during voluntary contraction in a patient with mitochondrial encephalomyopathy. An early recruitment during a slight muscle contraction readily leads to MUP overlap. The tracing contains long-duration polyphasic potentials as well as small potentials derived from a single muscle fiber. The polyphasic potentials seen during the weakest muscle contraction show an unstable waveform.	Early recruitment of small single fiber potential as well as unstable polyphasic units
F59 MUP-19	TB	Chronic myositis	Motor unit potentials (MUPs) recorded from the triceps brachii (TB) during voluntary contraction in a patient with chronic myositis. Spontaneous activities in the form of fibrillation potentials appear at the beginning of the recording. Subsequently, weak muscle contraction gives rise to a small MUP derived from a single muscle fiber, in addition to many polyphasic potentials, best observed in the raster mode. With the patient at rest, the tracing again shows only fibrillation potentials, which exceed 1 mV in amplitude, indicating the proximity of the needle to the signal source. Patients with active myositis typically show a combined EMG abnormality of a polyphasic MUP with early recruitment and spontaneous single muscle fiber discharge from muscle degeneration.	Typical findings in myositis consisting of spontaneous single muscle fiber discharge and early recruitment of a small MUP
F60 MUP-20	BB	Myositis	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) during voluntary contraction in a patient with myositis. This tracing recorded during a slight effort, reveals a number of short-duration, low-amplitude MUP indistinguishable from fibrillation potentials by waveform. Fibrillation potentials, however, maintain a regular firing pattern, whereas an MUP shows an increasing firing frequency with a greater force of muscle contraction.	Fibrillation potentials firing regularly and single muscle fiber MUP increasing the firing frequency with voluntary effort

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F61 MUP-21	RF	IBM	Motor unit potentials (MUPs) recorded from the rectus femoris (RF) during minimal muscle contraction in a patient with inclusion body myositis (IBM). The tracing shows a high-amplitude, short-duration MUP probably recorded with the needle tip very close to a single hypertrophic muscle fiber. The presence of other surviving muscle fibers in the vicinity within the recording radius gives rise to a fork-shaped MUP. A high-amplitude, short-duration MUP does not necessarily indicate a neuropathic process. Note a gain of 1 mV/division used for this recording.	A high-amplitude, short-duration, spiky MUP seen in IBM, probably originating from a hypertrophic single muscle fiber
F62 MUP-22	Deltoid	MG	Motor unit potentials (MUPs) recorded from the severely affected deltoid during voluntary contraction in a patient with generalized myasthenia gravis (MG). Although MUP waveform rarely changes in mild cases, an early recruitment of a short-duration MUP characterizes severe weakness, as exemplified in this tracing. This firing indicates a functional loss and secondary degeneration of the muscle fibers. In these cases, MUP waveform often varies from one discharge to the next, reflecting instability of neuromuscular transmission. This abnormality becomes more apparent if displayed with the low-frequency cutoff filter increased to 500 Hz, which, by removing low-frequency components, enhances fluctuation of high-frequency spikes.	Short duration MUP showing an early recruitment and varying waveform best seen with low-frequency cutoff filter increased to 500 Hz

(*continued*)

FILE	MUSCLE	DISEASE	DESCRIPTION	KEY WORD
F63 MUP-23	Deltoid	LEMS	Motor unit potentials (MUPs) recorded from the severely affected deltoid during voluntary contraction in a patient with Lambert-Eaton myasthenic syndrome (LEMS). All potentials originate from the same motor unit, despite the substantially varying waveform. All spike components may abate in some cases. These abnormalities become more apparent in a raster mode display using increased sensitivity and slow sweep speed. These motor units show frequent blocking and increased jitters if tested by single-fiber studies.	Unstable polyphasic MUP showing considerable waveform variability best seen in a raster mode
F64 MUP-24	BB	Myositis	Motor unit potentials (MUPs) recorded from the biceps brachii (BB) during voluntary contraction in a patient with myositis. The tracing shows an early recruitment of many small, long-duration potentials during a slight muscle contraction. An overlap of manypotentials makes it difficult to distinguish an individual MUP, which, therefore, must undergo scrutiny during a very minimal muscle contraction.	Small, long-duration MUP showing typical early recruitment

Appendix 2

Fundamentals of Electronics

1. INTRODUCTION

The electromyographer must have a basic knowledge of electronics to understand physiologic signals, instrumentation, and electrical safety. Familiarity with electronics will help in recognizing and correcting recording problems, selecting and operating new equipment, and applying new techniques in the clinical domain. This appendix briefly introduces the essential topics in electronics for application to electromyography. Interested readers should consult a good text on basic electronics or online resources for a more detailed discussion.[2,3,5,9]

2. ELECTRICAL CONCEPTS AND MEASURES

Charge

The fundamental electrical concept is charge. Natural occurrences like lightning or static cling demonstrate the effects of charge. Physics describes and accurately predicts the behavior of

"unit test charges" but does not provide an explanation or model for the source of the phenomenon. "Charge" is a name for observed effects in a theory that developed empirically.

The primary concept of **charge** is that two polarities of matter exist, called positive and negative. Negatively charged electrons revolve around a positively charged nucleus in all atoms. Other subatomic particles show positive or negative charge or a neutral state. No charge is smaller than the charge on one electron, and all measured amounts of charge are exact multiples of this smallest unit; so charge is quantized. Since all matter contains charges, the term "charge" generally refers to net charge imbalance. The unit for measuring charge, called a **coulomb**, equals the charge on about 6.25×10^{18} electrons. The symbol "Q" commonly represents the quantity of charge in equations.

Charged particles exert force on each other, called the electrostatic force, depending on the amount of charge and the distance between them. Charges of opposite polarity exert forces of attraction toward each other, analogous to gravitational attraction. Charges of like polarity exert equivalent forces of repulsion. The **electric field** in a region is a description of the force that would be exerted on a unit test charge at any point. Because of these forces, charges moving in relation to one another either absorb or release energy (work, in **joules**).

Voltage

It requires energy to lift a brick over your head. The mass of the brick moves away from the mass of the earth, storing the work of separation, called potential energy, in the earth-brick system. Similarly, separating a system of charges requires (positive or negative) energy, stored as the "electric potential." The energy required per unit charge has dimensions of joules per coulomb or **volts**. The difference in electric potential energy (for a unit test charge) between two points in space is called the **voltage,** or also the "**potential**."

Like mechanical potential, voltage is a measure of difference relative to some reference. Lifting bricks has immeasurable effect on the huge mass of the earth; so ground level is often the reference (zero) level for calculating potential energy. Similarly, the earth is a huge sink for the dispersion of charge and is frequently the reference (zero) level for measuring voltage. Voltage is also called electromotive force (EMF), which accounts for the symbol "E" in equations for voltage, but "V" is also commonly used.

Conceptualizations and measurements in electronics use voltage much more frequently than charge. Voltages encountered in common electronic circuits range from a few **microvolts** (10^{-6}) to a few thousand volts. In electrophysiology, measured potentials arise from the separation of charged atoms or molecules within the biochemical structures. Active transport of ions across a cell membrane exemplifies the expenditure of energy to separate charges, giving rise to a voltage difference.

Recall that energy = force × distance
(1 joule = 1 newton × 1 meter).

Current

Charge can move from one place to another by the motion of charged particles. Charge imbalance also propagates within conducting materials, perhaps like billiard balls in a row translate an impact. The latter mechanism transfers charge much faster than particle motion. **Current**, measured in amperes (also called amps), is the rate of charge flow. One **ampere** of current is the flow of one coulomb per second. Currents typically encountered in common electronic applications range from microamps to several amps.

Resistance

Regardless of how charge propagates through a material, its flow results in some conversion of electric energy into heat. One might think of it as charge-carrying particles colliding with other atoms. The terms *conductor*, *semiconductor*, and *insulator* refer to the ease with which current flows through a material. The loss of electric energy manifests as a decreasing potential in the direction of the current flow. The term *resistance* quantifies this effect. **Resistance** is the ratio of this voltage difference between two points to the current flow:

Resistance = Voltage/Current

from which derives the more familiar form of **Ohm's law**:

$$\text{Voltage} = (\text{Resistance}) \times (\text{Current})$$

and also:

$$\text{Current} = \text{Voltage} / \text{Resistance}$$

Using the symbol "R" for resistance, and the symbol "I" for current ("C" being reserved for capacitance), these forms of Ohm's law are often expressed as

$$R = E / I \quad E = I \times R \quad I = E / R$$

A good conductor has a relatively low value of resistance, and a good insulator has a relatively high value of resistance, the value judgment depending on the application. The resistance ratio may vary with temperature, voltage, or current, but often it is assumed to be constant, for simplicity. The units of resistance are called **ohms**:

$$1 \text{ Ohm} = 1 \text{ Volt} / 1 \text{ Amp}$$

Resistances typically involved in common electronic circuits range from almost zero ohms to several **megohms** (10^6 ohms). The unit **kilohms** (10^3 ohms) is also frequently used.

Power

Power is the time rate of energy flow. For steady conditions:

$$\text{Power} = \text{Energy} / \text{Time}$$
$$\text{or}$$
$$\text{Energy} = \text{Power} \times \text{Time}$$

The unit of power, a **watt**, equals 1 joule of energy per second. From the definition of voltage earlier, energy in a charge flow equals the voltage (difference) times the amount of charge. Because current is the time rate of charge flow, then:

$$\text{Power} = \text{Energy} / \text{Time}$$
$$= \text{Voltage} \times (\text{Charge} / \text{Time})$$
$$\text{Power} = \text{Voltage} \times \text{Current}$$

So the units of power also equal volts times amps, often abbreviated VA.

$$1 \text{ Watt} = 1 \text{ Volt} \times 1 \text{ Amp}$$

For example, if the headlights of an automobile draw 25 amps from the 12-volt battery, the total headlight power equals 300 watts.

Using Ohm's law, the power ("P") in a resistor is also calculated in the following forms:

$$P = E \times I = E^2 / R = I^2 \times R$$

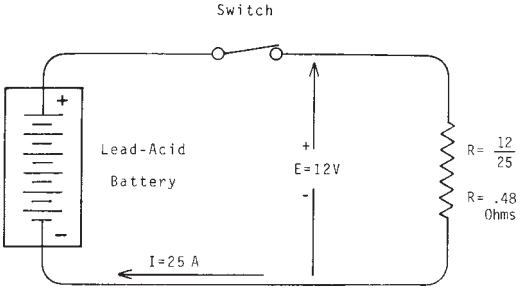
3. ELECTRIC CIRCUITS AND CIRCUIT LAW

Circuits and Schematics

Car headlights are an example of an **electric circuit**, an interconnection of components such that currents flow in one or more closed loops. Electrical systems take the form of circuits so that charge does not accumulate at any one point. Appendix Figure 2-1 shows the headlight circuit schematically.

A **schematic diagram** of an electrical circuit shows symbols for the various components and shows how they are interconnected. Most circuits of interest contain at least one source of energy, at least one component to dissipate energy (a load), conductors connecting the components together, and some means of controlling the flow of energy. Schematics model real circuits by a number of simplifying approximations.

The solid lines represent ideal (zero-resistance) conductors that interconnect the components. Ideal sources of energy are the constant-voltage source and the constant-current source. A battery is a fair approximation to an ideal voltage source. A fixed resistance models the load that the headlights represent.



APPENDIX FIGURE 2-1 Schematic diagram of a headlight circuit. The switch controls the current by opening and closing the conducting path. The zigzag line is a symbol for resistance.

Resistors in Parallel

Suppose more headlights were connected across the battery in the circuit of Appendix Figure 2-1. The schematic of the circuit could be drawn as in Appendix Figure 2-2. It would seem reasonable that the total current from the battery would equal the sum of the individual load currents. Indeed, at any circuit **node**, a point where two or more conductors connect, charge does not accumulate. This leads to **Kirchhoff's current law** for electric circuits:

> The sum of all currents into a node equals the sum of all currents leaving a node.

Resistances connected each end to each end, as in Appendix Figure 2-2, are in **parallel**. Each resistance has the same voltage across it. So the current in each resistor can be calculated by Ohm's law, giving the total current from the battery as:

$$I = (E / R1) + (E / R2)$$

which manipulates to

$$I / E = (1 / R1) + (1 / R2)$$

or

$$E/I = \frac{1}{(1/R1)+(1/R2)}$$

From Ohm's law, the above expression for E/I is the effective resistance of the whole circuit in Appendix Figure 2-2. In general, the equivalent resistance of "n" **resistors in parallel** equals:

$$R_{eq} = \frac{1}{(1/R1)+(1/R2)+\ldots+(1/Rn)}$$

Note that the equivalent resistance of two or more resistors in parallel is always less than any one of the individual resistors. If there are more paths along which current can flow, there is less equivalent resistance. Also, the total power in the circuit, the sum of the power in each individual resistance, equals the power calculated for the equivalent resistance.

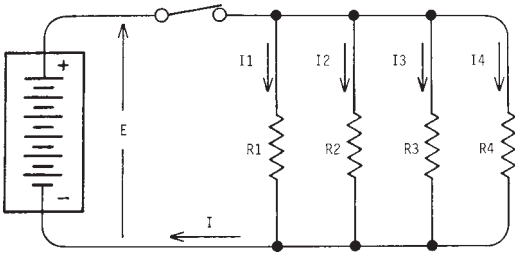
Resistors in Series

The circuit of Appendix Figure 2-3 shows several resistors connected to a battery in **series**. Series connection of two components means they have a node in common that does not connect anywhere else. By Kirchhoff's current law, mentioned earlier, the same current must flow in all components connected in series. **Kirchhoff's voltage law** for electric circuits states:

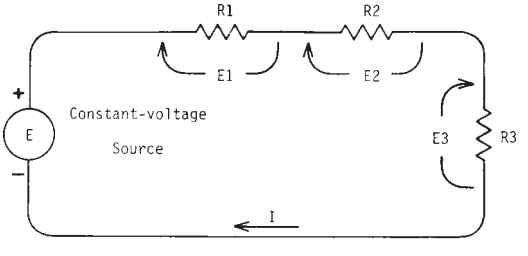
> Around any closed loop, the algebraic sum of the voltage differences between nodes equals zero.

This is analogous to a principle in physics that the potential energy of an object depends only on its height, and not on the path it followed to get there. Similarly, the voltage at any node does not depend on the circuit path followed for computing it.

To apply Kirchhoff's voltage law, one must establish a convention for the polarity of voltages in relation to the current. First, one assumes a direction for the loop current. Engineers often use the **"positive-current" convention**, that current entering a resistor makes that end of the resistor positive. Many electronics texts will use the **"negative-current" convention**, that



APPENDIX FIGURE 2-2 Resistances in parallel. A schematic of the headlight circuit with more lights.



APPENDIX FIGURE 2-3 Resistors in series. The direction of the current follows the positive-current convention, as it does in Appendix Figures 2-1 and 2-2.

current entering a resistor makes that end negative. The polarity of the convention is irrelevant as long as it is consistently applied to all components. Following either convention and using Kirchhoff's voltage law results in a correct magnitude for the current, with a negative value if the assumed direction was wrong. Applying the same convention with the correct currents will yield correct polarities for all component voltages.

To apply Kirchhoff's voltage law to the series circuit of Appendix Figure 2-3, one follows the direction of assumed current around the loop and adds the voltages algebraically. A voltage source has a fixed voltage across it regardless of the current magnitude or direction through it. From Appendix Figure 2-3 this process yields:

$$E = (I \times R1) + (I \times R2) = I \times (R1 + R2)$$

So for **resistors in series**:

$$R_{eq} = R1 + R2 + \ldots + Rn$$

Again, the total power in the circuit, the sum of the power in each resistor equals the power in the equivalent resistance.

Voltage Dividers

In the series circuit, the total voltage across the resistors equals the applied voltage from the battery. With the same current in all resistors, the voltage across each is proportional to its resistance. The applied voltage is "divided up" proportionately to the respective resistances. Taking the negative battery node in Appendix Figure 2-3 as the zero reference point, the voltage across R3 is given by:

$$V_{R3} = E \times R3 / (R1 + R2 + R3)$$

$$V_{R3} = E \times (\text{a constant} < 1)$$

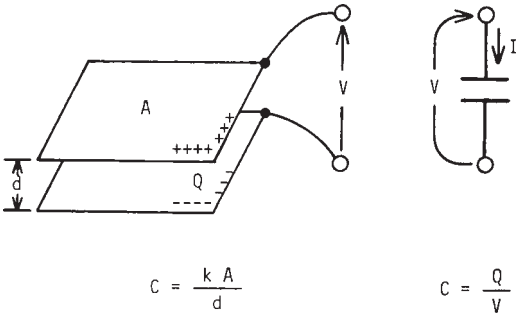
A fraction of the voltage applied to the series circuit of resistors appears across R3. This frequently used **voltage divider** arrangement provides a voltage output that is always a fixed fraction of the voltage input.

4. CAPACITANCE

When a nonconducting region of space separates two conducting regions, charge cannot flow through the nonconducting medium. Within the conducting regions, charge can flow freely and distribute, so there are no voltage gradients. If one conducting region has a charge different from the charge in the other, a voltage gradient or electric field exists across the insulating medium. For a steady charge difference, a fixed voltage difference is established between the conducting regions.

The physical properties of the nonconducting material and the geometry of the regions determine the amount of voltage for a given charge. The constant charge-to-voltage ratio is called the **capacitance**. Different insulating materials, like air, glass, or plastics, affect the capacitance, compared with that of a vacuum. The electric field polarizes atoms or molecules of the **dielectric** material. Their alignment with the field reduces the voltage for a given charge, increasing the capacitance ratio. Some materials yield several thousand times the capacitance of a vacuum, the ratio called the **dielectric constant**.

A **capacitor**, a two-terminal circuit element, provides a certain amount of capacitance between its terminals. While many geometries of construction are used, the capacitor is often conceptualized as two parallel, rectangular plates of metal separated by an insulator. As in Appendix Figure 2-4, the schematic symbol for a capacitor is two separated, parallel plates. The unit of capacitance, a **farad** (F), equals one coulomb per volt. This is a very large unit in most typical electronic work. A 1-farad parallel-plate capacitor with 1 mm air dielectric would have plates about 10.5



APPENDIX FIGURE 2-4 The parallel-plate capacitor and the schematic symbol for capacitance. Capacitance is proportional to the area of the plates and inversely proportional to the distance between them. The constant depends on the insulating material between the plates.

km^2. More common units of capacitance are the microfarad (uf = 10^{-6} F), nanofarad (nf = 10^{-9} F), and picofarad (pf = 10^{-12} F).

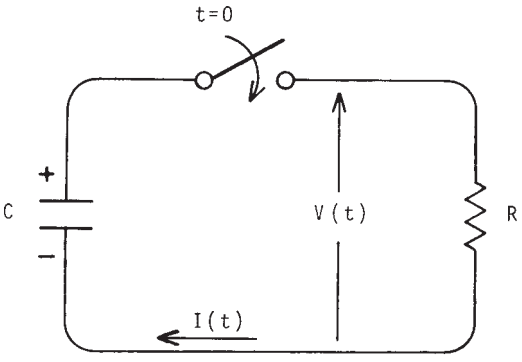
Connecting a capacitor across a voltage source causes a momentary surge of current while one plate acquires a positive charge and the other, a negative charge. When the voltage across the capacitor equals the voltage source, no current flows. When the voltage source is disconnected, the charges remain on the plates and the voltage remains across them. If connected to a resistor, the charged capacitor can supply current until its charges dissipate.

With a constant current into a capacitor, the charge and the voltage increase linearly with time. A current of 1 amp charges a 1-farad capacitor linearly to 1 volt in 1 second, a total charge of 1 coulomb. Since current is the time rate of charge, the rate of change (derivative) of voltage across a capacitor is proportional to its current. Put another way, the voltage across a capacitor is proportional to the integral of the current through it. This is a mathematical way to define the capacitive circuit element.

The property of having this voltage/current relationship, or the ability to store charge, is useful in many electronic circuits. A capacitance tends to oppose rapid changes of voltage across it, because that requires large currents. A certain amount of capacitance exists between any two insulated conductors, for example, between power lines on a pole and the earth. This **"stray" capacitance** must frequently be considered in electronic circuits. In the electrophysiology of excitable membranes, the capacitance of the membrane plays a considerable part. The very thin membrane, separating regions of fluid with different potential, forms a relatively large capacitance between the interior and the exterior of the cell: on the order of 1 uf/cm^2. This cell membrane capacitance plays a major role in the timing of cell depolarization and repolarization.

RC Time-Constant Circuit

Consider a charged capacitor suddenly connected in parallel with a resistor (see Appendix Fig. 2-5). At any instant, the current equals the voltage divided by the resistance. The charge on the capacitor will



APPENDIX FIGURE 2-5 Schematic of the RC discharge circuit. The switch closes at time t = 0.

dissipate through the resistor until the voltage and current both go to zero. From the definition of capacitance, the rate of voltage decline equals the rate of charge decline divided by the capacitance. So at any instant, the rate of voltage decline equals the current divided by the capacitance. As the current decreases, the rate of voltage decline decreases. The rate of discharge will be greatest initially and will also go to zero. Expressed mathematically:

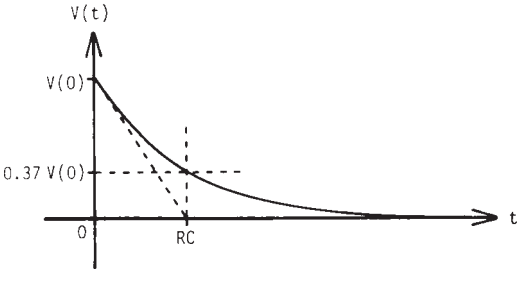
$$d[V(t)]/dt = I / C = [V(t) / R] / C = V(t) / RC$$

The solution of this differential equation for the voltage during discharge is an **exponential** function of time (shown in App. Fig. 2-6). Assuming the resistor is connected at t = 0:

$$V(t) = V(0)\, e^{-t/RC}$$

$$I(t) = V(t) / R \text{ so} \qquad I(t) = I(0)\, e^{-t/RC}$$

where the constant **"e"** (~2.7183…) is a special number such that: $d[e^t]/dt = e^t$



APPENDIX FIGURE 2-6 RC discharge voltage curve. After one time constant, the voltage is about 37% of its initial value.

The factor **RC**, resistance times capacitance, has units of **seconds** and is called the **time-constant** of the circuit, or of the exponential equation. The time-constant equals the time it would take the voltage or current to reach zero if the discharge maintained its initial rate. Instead, the rate declines, and the discharge theoretically takes an infinite time to reach zero, although, for practical purposes, it approaches zero in about five time-constants. At the end of any interval of one time-constant, the voltage is about 37% of its value at the beginning. Therefore, after five time-constants, the voltage will be less than 1% of its initial value.

Capacitors in Parallel

Consider two capacitors connected in parallel, as in Appendix Figure 2-7. The voltage across both capacitors must be the same. The total charge in the combination is the sum of the charges on each capacitor. So the equivalent capacitance of **capacitors in parallel**, the total charge divided by the voltage, equals the sum of the individual capacitances.

$$C_{eq} = C1 + C2\ \{+\ldots+ Cn\}$$

Capacitors in Series

Consider two capacitors connected in series, as in Appendix Figure 2-8. Any current in one capacitor must pass through the other, so the charges on each capacitor must be the same. This charge, Q, is the integral of current over all time up to the present, and so is also the charge in the equivalent capacitance. Dividing this charge by the total voltage across the combination yields the equivalent capacitance of **capacitors in series**:

$$C_{eq} = \frac{1}{(1/C1)+(1/C2)\{+\ldots+(1/Cn)\}}$$

The charge on a capacitor represents some stored energy, equal to the work expended to move the charge there. In the ideal (lossless) capacitor, this amount of energy is available for release to the rest of the electric circuit. It can be shown that the **energy stored in a capacitor** with capacitance "C," voltage "V," and charge "Q" is

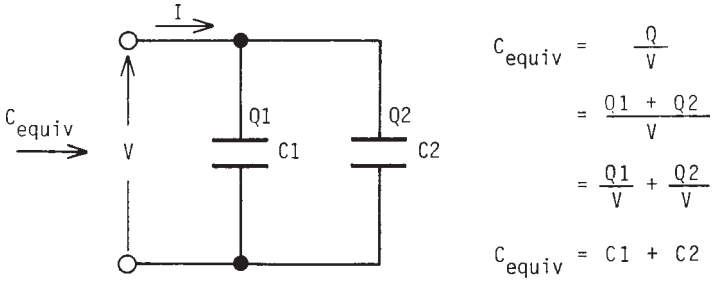
$$QV / 2 = CV^2 / 2.$$

5. INDUCTANCE

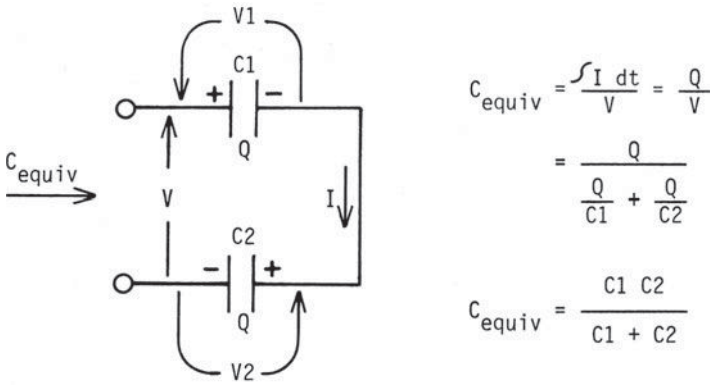
Magnetic Fields and Magnetism

A moving charge has an associated magnetic field. "Magnetic field" has no better theoretical explanation than "charge." Like charge, it has axiomatic descriptions in terms of observed forces and electrical interactions. Historically, the laws of magnetics arose empirically to form a consistent quantitative theory of the phenomena. Certain "**ferromagnetic**" metals and compounds display "permanent" magnetism due to the way the spinning charges, which are currents, of the atoms align themselves. Some fundamental mechanism, called **magnetism**, couples force between charged particles in motion. The **magnetic field** in a region is a description of the force that would be exerted on a unit magnetic dipole at any point.

So a flowing current has a magnetic field. Also, when a moving charge encounters a magnetic



APPENDIX FIGURE 2-7 Capacitors in parallel. The equivalent capacitance is the sum of the individual capacitances.



APPENDIX FIGURE 2-8 Capacitance in series. The equivalent capacitance is less than the smallest, as is the case with resistances in parallel.

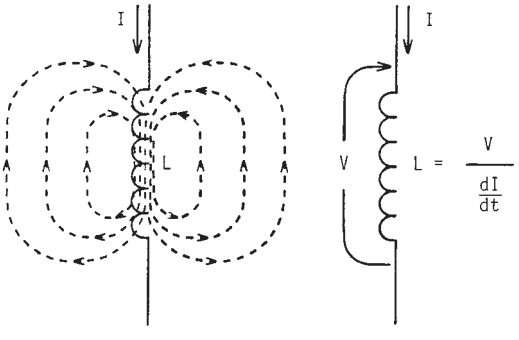
field from another source, it experiences a force. Certain geometries of current allow mathematically tractable magnetic field solutions—for example, current flowing in a line, as in a wire, or current flowing around a cylinder, as in a coil of wire. The magnetic field intensity at a point is directly proportional to the current. A steady current has a constant magnetic field. However, establishing this field stores energy in some mechanism; energy is absorbed if the current is increasing or released if the current is decreasing. We say energy is "stored in the magnetic field," or the magnetic field "collapses." Current and magnetic field energy have a relationship quantitatively like velocity and kinetic energy. Taking a mass from rest to some velocity absorbs energy, but no energy is required to maintain that velocity. An opposing force that reduces the velocity transfers energy into that force mechanism. The property of an electric circuit equivalent to the mass in this analogy is called **inductance**.

Magnetic Inductance

The name inductance comes from "induce." A time-varying magnetic field will induce current in a closed conducting loop. A varying current in one coil induces a voltage across the open ends of another coil in the same field. This is called **mutual inductance**. A changing magnetic field will also induce a current flow within any conducting material in the region of the field. Magnetic stimulation in electromyography relies on this principal to induce excitation current within the body fluid.

The increasing magnetic field of a coil with increasing current induces a voltage across the same coil, with a polarity that reflects the energy absorption. The decreasing magnetic field of a decreasing current induces a voltage across the coil, with a polarity that reflects energy return. This phenomenon is called **self-inductance**.

An **inductor** is a two-terminal circuit element providing a certain amount of inductance. Generally made from coiling some wire around a form or core, the two ends of the wire coil become the two terminals. A coiled wire is the schematic symbol for inductance, as in Appendix Figure 2-9. The common symbol for amount of inductance in equations is "L" (derivation unknown).



APPENDIX FIGURE 2-9 An inductance and its schematic symbol. Because of energy storage in its magnetic field, the voltage across an inductance is proportional to the rate of change of its current.

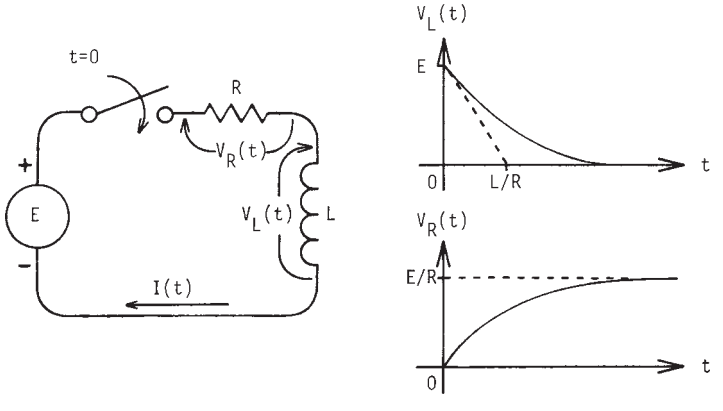
Coiling a wire increases the inductance to a useful level, although any conductor carrying current has some inductance. An ideal inductor has zero resistance between the terminals, and the inductance value is independent of current. In real inductors, the wire has some resistance, and the core material has different magnetic properties at different field strengths, making the inductance nonlinear. Inductors are less frequently seen in most electronic circuits than capacitors.

With zero resistance in an ideal inductor, the only voltage across its terminals is that induced by a changing magnetic field. If we assume no magnetic fields from any other circuits, the inductor voltage is directly proportional to its rate of current change. **Inductance**, the ratio of voltage over the rate of current change, has units of volts per amp-per-second or volt-seconds per amp, called henries. One **henry** of inductance has a 1-volt differential when its current has a gradient of 1 amp per second. This is a large unit in many applications (except power transformers), and the units of millihenry and microhenry are commonly used. A coil of 50 turns of wire on a nonmagnetic core 2 cm long and 1 cm^2 in area has an inductance of about 15 microhenries.

A coil in a vacuum has a certain intrinsic inductance for a given geometry. The same coil wound around various materials may have more or less inductance than in a vacuum, depending on how the atoms interact with a magnetic field and how well the material conducts induced currents. Like the dielectric constant in capacitors, the property called **magnetic permeability** changes the amount of energy stored for a given current. Nonconducting ferromagnetic materials have high permeability. Some materials have relative permeabilities of several thousand. Inductors wound on high-permeability cores have a useful property, their magnetic fields concentrated primarily within the core. However, the magnetic permeability of materials varies greatly with magnetic field strength; the core tends to "saturate" and lose permeability as the field strength increases. This makes the inductance vary with current and makes circuits using such an inductor nonlinear.

RL Time-Constant Circuit

As a circuit element, the ideal inductor has a voltage proportional to the derivative of its current, or a current proportional to the integral of its voltage. This voltage/current relationship is another way of defining an inductor as a circuit element. Inductance in a circuit tends to oppose rapid changes in current, because that requires large voltages. Consider a series circuit of a resistor and an inductor (App. Fig. 2-10) suddenly connected to voltage source (at t = 0). The sum of the resistor and inductor voltages equals the source, a constant. The inductor voltage equals the source voltage minus the current times the resistance. The inductor voltage also equals the derivative of the current times the inductance. Analogous to the capacitor discharge (see earlier), a differential equation describes the resulting current, an



APPENDIX FIGURE 2-10 RL time-constant circuit. The current in the inductor rises exponentially to its final value.

exponential rise to the final value. Expressing this mathematically:

$$V_L(t) = E - (I(t) \times R)$$

$$L \times d[I(t)]/dt = E - (I(t) \times R)$$

whose solution is:

$$I(t) = (E / R) \times (1 - e^{-tL/R})$$

where T = L/R, with units of seconds, is the **time-constant** of the circuit.

At first, the current is zero, and the full voltage appears across the inductor. The current in an inductance cannot change instantaneously. Then the current rises exponentially to its final value of E/R, while the inductor voltage goes to zero.

Inductors in Series and Parallel

Consider circuits that have two inductors in parallel or in series, under the condition that the two fields do not significantly overlap (not coupled). Two **inductors in series** have the same current, the same derivative of current, and the same polarity of voltage in relation to the current. Therefore, the voltage across the series combination is the sum of the voltages across each, and the equivalent inductance equals the sum of the individual inductances (the same relationship as resistors in series).

$$L_{eq} = V / [dI/dt] = [V1 + V2\ ] / [dI/dt]$$

$$L_{eq} = L1 + L2\ \{+ \ldots + Ln\}$$

By analysis similar to that used for resistors in parallel, with rate of current change instead of current, the equivalent inductance of **inductors in parallel** is given by:

$$L_{eq} = \frac{1}{(1/L1) + (1/L2)\{+ \ldots + (1/Ln)\}}$$

this is the same relationship as for resistors in parallel.

The magnetic field around an inductor carrying current represents some stored energy, equal to the work required to establish the field. In a lossless inductor, this same amount of energy is available for release to the rest of the electric circuit. It can be shown that the energy stored in inductance "L," with current "I," equals: $LI^2 / 2$.

Transformers

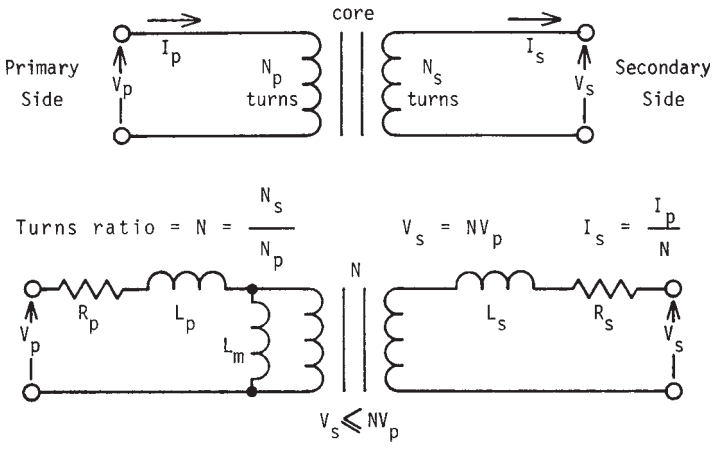
Two coils sufficiently close together that their magnetic fields occupy significant common space have mutual inductance between the separate coil circuits. A changing current in one coil induces a voltage in the other. The **transformer**, a common electronic circuit component, utilizes this effect. When both coils are wound on a highly permeable core, the energy coupling between the two becomes very efficient. Power transfers from one coil to the other with little loss. Transformers proportionately increase or decrease voltages or currents, and they couple energy from one circuit to another without a charge conducting path.

An ideal transformer, a four-terminal circuit element, multiplies the voltage across two of the terminals by a constant, the **turns-ratio**, to the other two terminals. Since power remains the same, the current is divided by the same constant. Two of the terminals are one coil, often called the "primary" winding, and the other two terminals are the "secondary" winding, with infinite resistance between the windings (Appendix Fig. 2-11).

Practical transformers have limitations of power loss, maximum power capability, and frequency of fluctuations. Real windings have some resistance in the wire. Core materials lose their effective permeability at higher frequencies of field fluctuation. Also, at very low frequencies, losses become greater than the energy transfer, and transformers become impractical. In the limit, a constant current in one coil does not induce any voltage in the other.

6. AC CIRCUITS

The term "AC," for **alternating current**, has two meanings in electronics. The literal meaning refers to voltages or currents which reverse in polarity at regular intervals, especially sinusoidal waveforms. The output of a rotating generator or alternator has a sinusoidal shape. A coil rotating in a fixed magnetic field generates voltage proportional to the sine of the angle between the coil plane and the field. This kind of **AC**, as shown in



APPENDIX FIGURE 20-11 Transformer symbols. The ideal transformer and a simple linear model of a real transformer.

Appendix Figure 2-12, is completely characterized by a frequency, amplitude, and a "phase." The **phase** specifies the time shift of the waveform, in degrees of angle (360 degrees = 1 cycle), relative to a reference sine wave of the same frequency.

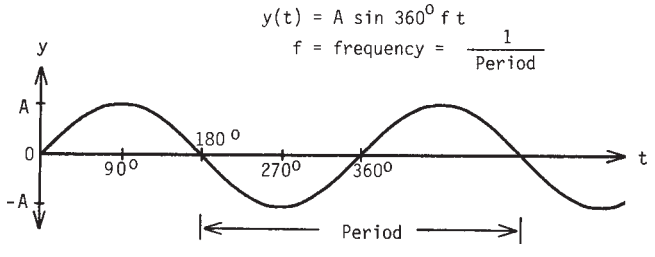
Another common meaning for "AC" in electronics is that portion of a fluctuating voltage or current with zero average value over a long time, as opposed to the "**DC**" (for direct current) **component**, which is the long-term average value. AC fluctuations could be complex, random, or nonperiodic. For example, the potential between a pair of skin electrodes has a non-zero average value attributable to metal/electrolyte interfaces. Subtracting this average value leaves the **AC component**, a varying potential that includes biopotentials, noise, and interference.

AC Circuit Laws

DC circuit theory, the circuit laws and calculations considered earlier, extends to circuits excited by AC sources. A sinusoidal source causes sinusoidal voltages and currents of the same frequency throughout any linear circuit. One can represent such values in the circuit by amplitude and phase information only. The common measure of AC amplitude, the "**RMS value**," stands for root-mean-square, the square root of the time average of the waveform squared. The RMS amplitude of a voltage or current equals the constant (DC) magnitude that has the same power, that is, the same heating effect in a resistor. Referring to an ordinary outlet as "110 volts" means that the AC potential has an RMS value of 110 volts. This sinusoidal voltage typically has a frequency of 60 cycles per second (called **Hertz**), with peak voltages of about +155 volts and –155 volts during the cycle.

Impedance and Reactance

In purely resistive AC circuits, the phase of all voltages and currents remains the same. One



APPENDIX FIGURE 2-12 The sine function.

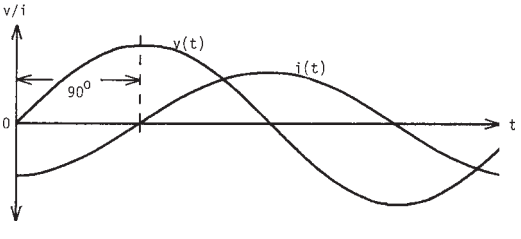
can solve for the AC values exactly as with DC circuits, by using RMS amplitudes. For example, in the headlight circuit of Appendix Figure 2-1, if the voltage source was 12 volts AC (RMS), then the current would be 25 amps AC (RMS), and the average power would still be 300 watts.

If the circuit contains capacitors or inductors, however, the analysis gets more complex. AC voltages or currents from sinusoidal sources have the same frequency but have different phases throughout the circuit. Thus, RMS amplitudes alone do not specify the AC values, and RMS values of different phases do not add or subtract directly.

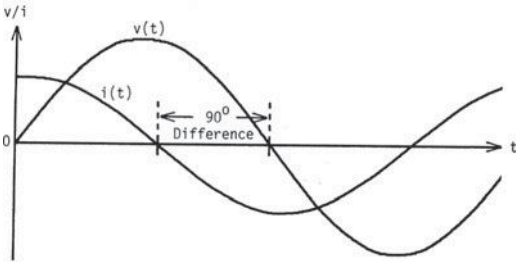
If a sinusoidal current passes through a capacitor, the AC voltage across the capacitor "lags" the current in phase by 90 degrees. When the current is crossing zero, reversing polarity, the voltage is at a peak, reversing slope. When the current is at a peak, the voltage is crossing zero, the point of maximum slope. One could also say the current "leads" the voltage by 90 degrees, as shown in Appendix Figure 2-13.

For an inductor the roles of voltage and current are reversed from earlier. The voltage leads the current, or the current lags the voltage, by 90 degrees, as shown in Appendix Figure 2-14.

For any component or combination of components in an AC circuit, the ratio of voltage to current is called the **impedance**, analogous to DC resistance in Ohm's law. Whereas resistance is a constant, impedance is a two-dimensional quantity, requiring the specification of magnitude and phase angle, both of which may vary with frequency. The impedance of a pure capacitor or inductor is called a **reactance**. An arbitrary impedance (any phase angle) can be divided into resistive and reactive components.



APPENDIX FIGURE 2-13 AC voltage and current in a capacitor. The voltage lags the current by 90 degrees.



APPENDIX FIGURE 2-14 AC voltage and current in an inductor. The voltage leads the current by 90 degrees.

The magnitude of inductive reactance increases with increasing frequency while the phase remains +90 degrees. A more rapid current variation through an inductor (at constant amplitude) induces a greater voltage across it. The **inductive reactance** of an inductance value "L" is:

$$L = 2 \times pi \times f \times L.$$

The magnitude of capacitive reactance decreases with increasing frequency while the phase remains –90 degrees. A more rapid voltage variation across a capacitor (at constant amplitude) requires greater current flow. The **capacitive reactance** of a capacitance value "C" is:

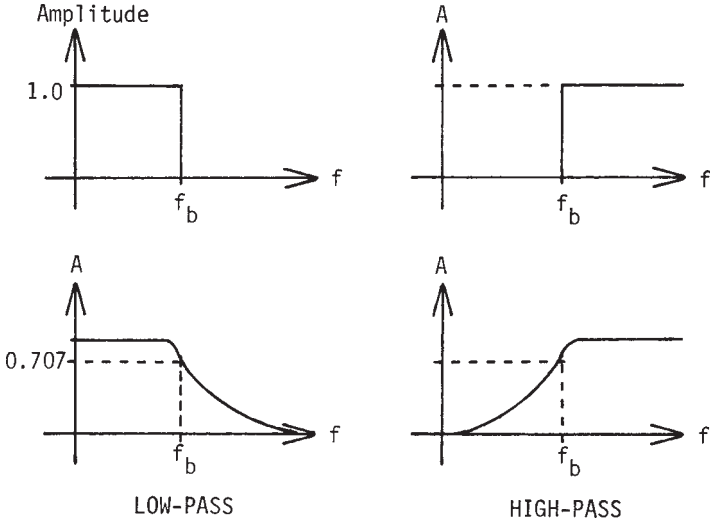
$$C = 1/(2 \times pi \times f \times C).$$

AC Power

An ideal reactance does not dissipate any energy. Energy may be stored or released, but none is lost. The instantaneous power in a capacitor or inductor, the instantaneous voltage times current, can be positive or negative, but the average power equals zero. Distributed resistance accounts for the power loss in real reactance.

7. FILTERS

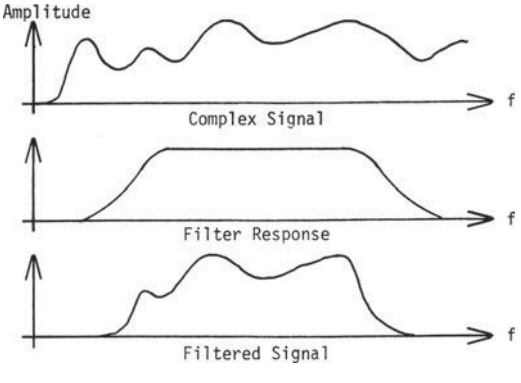
In electronics, a **filter** usually means a circuit that passes some bands of frequency while attenuating others. The effects of filters are often displayed in the "**frequency domain**" by graphing the output magnitude or the attenuation ratio versus frequency for constant-amplitude sine wave inputs. Examples of electronic filters are bass and treble



APPENDIX FIGURE 2-15 Ideal and practical filter response curves. (*A*) Low-pass. (*B*) High-pass.

tone controls or graphic equalizers in stereo music systems. The most common types of filters are low-pass (high-cut), high-pass (low-cut), band-pass (low- and high-cut), and notch (center-cut) filters. Appendix Figure 2-15 shows real and ideal response curves for high-pass and low-pass filters.

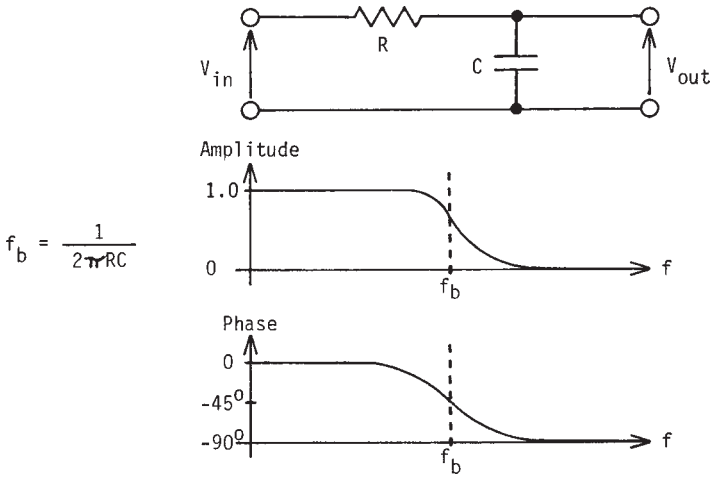
Complex signals composed of a spectrum of frequencies, such as a voice signal or a compound action potential, can often only be described as a graph of component magnitudes versus frequency. Multiplying such a graph times the attenuation curve of a filter, point by point in frequency, yields the frequency spectrum of the output signal passed through the filter, as shown in Appendix Figure 2-16.



APPENDIX FIGURE 2-16 Frequency-domain effects of band-pass filtering.

The simple RC networks of Appendix Figure 2-17A forms a **low-pass filter**. Appendix Figure 2-17B shows its attenuation curve. At very low frequencies the capacitor has high impedance and causes negligible attenuation. At very high frequencies the capacitor impedance approaches zero, as does the output magnitude. The transition from pass-band to stop-band occurs gradually, with no sudden discontinuities in real filters. The frequency where the attenuation ratio equals 0.707 (–3 dB) is called the "**break**" or "**corner**" **frequency**, where output power equals one-half the input power. This is also the frequency where the magnitude of the capacitive reactance equals the resistance, leading to the break frequency equation in Appendix Figure 2-17B. This comer frequency is generally taken as the cutoff point, making the pass band of the low-pass filter from DC (0 Hz) to the break frequency.

To specify a filter response curve completely, one must also specify the phase of the output relative to the sine wave input at each frequency. Appendix Figure 2-17C shows the phase response of the RC low-pass filter. Note that significant phase shift occurs at frequencies where the amplitude attenuation is still relatively insignificant. A negative (lagging) phase indicates a delay in the sine wave response and, indeed, in the time response to a transient signal. Low-pass filters increase the latency of fast peaks and limit



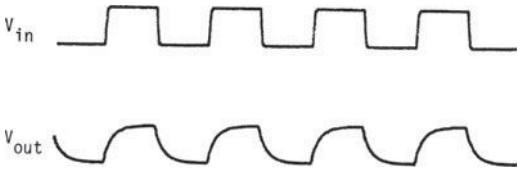
APPENDIX FIGURE 2-17 RC low-pass filter-network. (*A*) Schematic. (*B*) Attenuation curve. (*C*) Phase curve.

the speed of transition at the output, or the rise and fall times of a "square-wave" input. Appendix Figure 2-18 shows the effect of low-pass filtering on a calibrating signal.

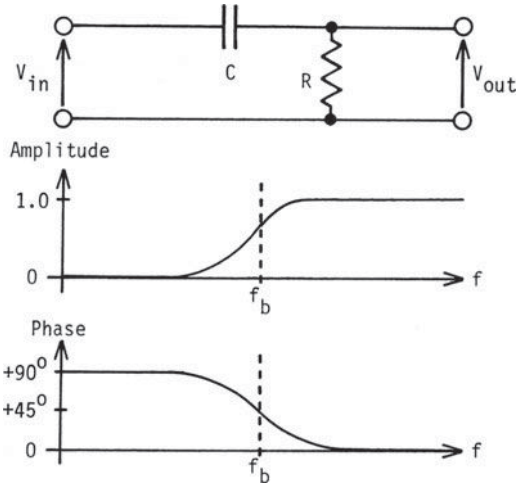
The RC network of Appendix Figure 2-19A forms a simple **high-pass filter**, with the attenuation curve shown in Appendix Figure 2-19B. At very high frequencies the capacitor has low impedance and causes negligible attenuation. At very low frequencies the capacitor impedance becomes very large, and the output amplitude approaches zero. The break frequency of this high-pass filter has the same value as the RC low-pass filter (see earlier).

The phase response of this high-pass filter, Appendix Figure 2-19C, has a phase lead of 45 degrees at the corner frequency, an effective negative delay for steady-state sine wave inputs. This apparent anticipation is indeed seen as reduced latency for transient signals with high-pass filtering, not that the circuit could create a negative delay, but because the attenuation of slowly varying components causes the response to peak earlier at reduced amplitude. High-pass filters suppress a slowly varying baseline shift and cause a drop in the response to square-wave signals, such as the calibration signal in Appendix Figure 2-20.

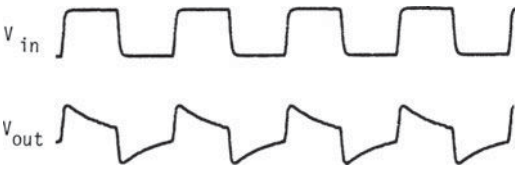
These simple RC high- and low-pass filters, called **first order**, have an attenuation slope in the stop band proportional to frequency; attenuation doubles at each octave of frequency. Higher order filters can have more abrupt descent into the stop band but also have greater phase shift in



APPENDIX FIGURE 2-18 Time-domain effects of low-pass filtering. Note the slowing of abrupt transitions in the square-wave (calibrating) signal, creating a delay.



APPENDIX FIGURE 2-19 RC high-pass filter network. (*A*) Schematic. (*B*) Attenuation curve. (*C*) Phase curve.

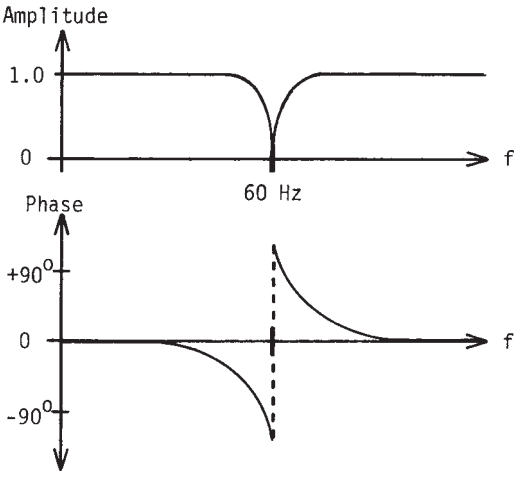


APPENDIX FIGURE 2-20 Effect of high-pass filter on square-wave (calibrating) signal.

the pass band and sharper phase transitions near the comer frequency. Higher order or multistage filters can have complex, biphasic responses to sharp transitions or spikes, which may mimic or mask physiologic responses.

Band-pass filters are low-pass and high-pass filters combined, with overlapping pass bands in the center. With a wide pass band, the two corner frequencies far apart, frequencies in the middle have little attenuation or phase distortion. As the two corners become close together, making a narrow pass band, phase shifts become significant and complex in the pass band, causing distortion. Sharp LC band-pass filters are used at radio frequencies for tuning. Amplifiers for EMG and other electrophysiology use wide band-pass filters, with adjustable low- and high-frequency cutoffs, to eliminate baseline shifts, undesirable components, and excessive noise. [4,6,8]

Notch filters pass all frequencies except a small band. The common notch filter encountered in electrophysiology is the "60-Hz filter," generally optional to reduce power line interference. Appendix Figure 2-21 shows a typical 60-Hz notch filter amplitude and phase response. While good filters have extremely narrow amplitude notches, the phase distortion can be significant over a much broader band. In electromyography, the use of notch filters should be limited to cases where no recording would be obtained otherwise, and the resulting measurements qualified in that light. [7]



APPENDIX FIGURE 2-21 Amplitude and phase curves for 60-Hz notch filter.

8. SOLID-STATE DEVICES

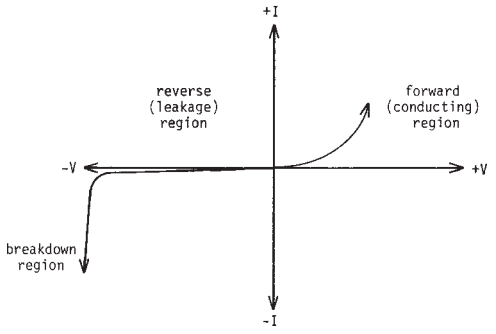
Active and Passive Circuit Elements

Passive devices, resistors, capacitors, inductors, and transformers have a constant proportionality between the voltage and current at their terminals, at least within a range of linearity, and they add no power to a circuit. An **active device** has voltage/current relationships that can vary in response to some circuit parameter, and they can add power to the circuit.

Diodes

An ideal **diode**, a two-terminal nonlinear device, has zero resistance ("**short circuit**") for current flowing in one direction and infinite resistance ("**open circuit**") for current flowing in the other direction. Therefore, one terminal is distinguished from the other. Real diodes have some resistance to current in the "forward" direction, nonlinear with current; and they have leakage current and breakdown voltage in the "reverse" direction. The name "diode" carries over from the days of vacuum tubes, when a tube with two electrodes created this effect. Today, most diodes are made in the solid state, in crystals of semiconducting material like silicon or germanium, doped in different regions with other elements to alter their conduction properties.

Graphs of current versus voltage, **V/I curves**, visually describe the characteristics of nonlinear devices. Appendix Figure 2-22 shows the V/I curve of a semiconductor diode. In the forward direction, the current is essentially an exponential function of voltage. In the reverse direction,



APPENDIX FIGURE 2-22 V/I curve of a semiconductor diode.

a small leakage current flows unless the reverse voltage becomes sufficient to cause breakdown of the diode.

Diodes find frequent use in electronic circuits to restrict current flow to predominantly one direction. Applied to an AC source, this creates a unidirectional supply which can be filtered and regulated to become a DC source. This conversion of AC power into DC power is called **rectification**. Diodes can switch currents between different circuit paths; and they can implement simple logic functions. Special diodes also find use as light emitters (LEDs), light detectors, voltage regulators, temperature sensors, and voltage-variable capacitors.

Transistors

The name "**transistor**" was a contraction of "transfer resistor," referring to a model whereby a small current in one loop modulated the resistance, and therefore a larger current, in another loop. This effect enables the transistor to amplify the input current.

Transistors are made in crystals of pure semiconducting elements, usually silicon, by diffusing other elements into different regions of the crystalline structure. In "**bipolar**" transistors, a small input current facilitates current flow in the output circuit, and thus the input current variations can be multiplied several hundred times in the output circuit. "**Field-effect**" transistors (FETs) employ a different mechanism. The input voltage creates an electric field, which modulates the transistor conductivity in the output circuit, allowing large output currents to be controlled with very little input current (or power). Complementary metal oxide silicon **(CMOS)** transistors are a type of FET, with the input insulated by silicon dioxide (glass).

Transistors replaced vacuum tube amplifiers because of their smaller size and much greater power efficiency. Many electronic applications, such as calculators and computers, were very impractical or impossible with vacuum tube circuits, but they became practical, reliable, and inexpensive with transistors.

Integrated Circuits

Integrated circuits contain many transistors, diodes, resistors, and capacitors in a single silicon crystal with interconnections to form complex circuits. Using processes with very small geometries, hundreds of thousands of such components are integrated on **chips** several millimeters square. Functions available as integrated circuits include logic blocks, amplifiers, microprocessors, memory blocks, speech synthesizers, and filters.

Circuit integration has many advantages. Complex functions occupy a small space, with few external interconnections. Less stray capacitance allows lower power levels and higher speeds. This results in greater reliability at a lower cost and repair by replacement. A host of standard integrated circuits solve many design problems with a building-block approach. Integrated circuit technology continues to evolve in speed and complexity.

9. DIGITAL ELECTRONICS

Digital and Analog Circuits

An electrical circuit used for **analog** purposes means that a voltage or current is proportional to some measurement that varies in a continuous (smooth) fashion. Transducers provide analog electrical signals from various physical phenomena such as pressure, oxygen concentration, light, temperature, muscle force, and so forth. Biopotentials are analog electrical fluctuations proportional to electrochemical activities.

An electrical circuit ascribed to **digital** purposes has a discrete number of "states" represented by voltages or currents within a certain range. For example, a wire from a switch to monitor the position of a microwave oven door could have a potential in the range of 0 to 2 volts with the door closed, and in the range of 3 to 5 volts with the door open. The circuit design should keep the "door state" signal within the specified limits over all reasonable conditions of variability, such as temperature, supply voltage, and manufacturing tolerances. The range of 2 to 3 volts would be an indeterminate band indicating abnormal operation or failure.

From this one can see that a "digital" voltage represents much less information than an "analog" voltage, but the digital voltage conveys its information with much greater reliability and accuracy.

The most commonly used digital circuits have just two states, variously named on/off, true/false, high/low, or active/inactive. A digital system could assign three or more states to an electrical quantity, but that would reduce reliability and increase complexity. Instead, to convey more information, more digital circuits are used simultaneously. The major advantage of a digital system is its immunity to electrical noise, interference, and component tolerances. The major disadvantage of digital circuits is that they limit information to a discrete number of choices.

Many applications lend themselves well to digital representations by nature. Integer arithmetic involves numbers as a series of digits; each digit has a discrete number of values. Many operations of machines or processes occur as a number of states. A common furnace thermostat is a good example of a digital circuit, because the furnace fire is either on or off to regulate temperature, not proportionally controlled. Digital circuits can perform the mathematical "logic" involved in many control procedures: "IF the door is open, THEN disable all control buttons, AND IF the microwave power is on, THEN stop it."

Mathematical Logic

Boolean algebra, the mathematics of variables having only two states, is often called **logic**, when considering the states as "true" or "false." Using voltages to represent these states, digital circuits can perform Boolean operations on variables. A **combinational logic** system has variables derived only from operations on the current states of other variables. **Sequential logic** involves variables depending also on the past states of variables. Introducing the concept of past states requires the system to have memory and a sense of time passage, a clock.

The basic operations of combinational logic, AND, OR, and NOT, together form more complex operations. The **AND operator** on two variables says:

> If A is true and B is true, only then (A AND B) is true.

The **OR operator** on two variables says:

> If A is true or B is true (or both), only then (A OR B) is true.

The **NOT operator** inverts one variable:

> If A is true, then (NOT A) is false;
> If A is false, then (NOT A) is true.

A combination of these gives the **EXCLUSIVE-OR (XOR) operation**:

> If A is true or B is true, but not both, only then (A XOR B) is true.
>
> (A XOR B) = (A OR B) AND [(NOT A) OR (NOT B)]

Large systems of combinational and sequential circuits can implement very complex logic functions, such as a digital watch or a computer.

Binary Number System

Our decimal number system uses one of ten characters (0 to 9) in a digit place and as many digit places as necessary to represent a number. Equally valid are other number systems with more or fewer characters in the digit set. The **binary number** system has only two characters, 0 and 1, and thus requires many more digits to represent a

number than the decimal system. Each digit place of a binary representation is called a **bit**, from the contraction of "binary digit."

Computer systems do counting and arithmetic in the binary system because of the reliability of on/off digital circuits. This use of binary is usually transparent to the user. Data are input and output in decimal, freeing the user from any need to understand other number systems. It is useful to know some of the powers of two, as these quantities often come up in computer use.

BITS	NO. OF COMBINATIONS	NAME
8	256	Byte
10	1024	Kilobyte
16	65,536	Word
20	1,048,576	Megabyte
30	1,073,741,824	Gigabyte
40	1,099,511,627,776	Terabyte

Converting between Analog and Digital Representations

Converting an analog voltage into a digital representation requires a device called an **A-to-D converter**, some analog and digital circuits, which generate a binary number proportional to the value of the analog input voltage. The digital representation includes only a finite number of discrete values according to the number of bits implemented. Dividing the analog input range by the number of digital combinations gives the 1-bit resolution of the converter, the **digitizing error** of the process. A furnace thermostat makes an A-to-D conversion of the room temperature into a 1-bit (on/off) control signal, centered about the set point. An audio CD contains the data from music digitized with 20-bit conversions. Biopotential averaging equipment may make 10-bit to 16-bit conversions of amplified electrode signals. This digital value represents the amplitude of the biopotential at one instant in time. Repeating the conversions at sufficiently rapid rates allows the waveform over a limited interval to be approximated by an array of digital values. Digital circuits can then store and manipulate the waveform as a set of numbers.[1]

The A-to-D conversion process requires some amount of time, setting the minimum time between samples, and thereby maximum frequency resolution, of the analog waveform. The sampling speed determines the memory requirements to store an analog signal as a set of sample values, or the maximum interval one can store in a given amount of memory.

D-to-A conversion, converting a digital representation into a proportional analog voltage, results in only a discrete number of steps in the "analog" output, of course. Examples of D-to-A conversion include driving an analog monitor display, generating stored or synthesized sounds, or setting the stimulus intensity by means of software.

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Appendix 3

Historical Review

1. INTRODUCTION

Electrophysiology began toward the end of the 18th century with Galvani's discovery of animal electricity and has since progressed steadily during the past two centuries. Electrophysiologic assessments of muscle and nerve are now considered indispensable in the practice of neurology, physiatrics, and other related clinical disciplines. The historical growth of this medical field may be divided arbitrarily into four relatively distinct but overlapping eras. They represent (1) early developments, (2) classical electrodiagnosis, (3) electromyography and nerve stimulation techniques, and (4) recent developments.

During the first period, ending around the mid-19th century, the existence of bioelectricity was firmly established by Galvani and others. The basic concepts of electricity were also founded during this period by a series of scientific achievements of Volta and his pupils. The progress in these two branches of science complemented each other despite the initial controversy that arose over the existence of animal electricity. A number of studies in the last half of the 19th century established the relationship between the duration of stimulation and current strength in eliciting muscle contractions. This led to the development of classic electrodiagnosis, the study of muscle response to electrical stimulation as a diagnostic test. The method gained popularity during the first half of this century as the recording apparatus was improved from the capillary electrometer to the string galvanometer. Modern techniques began with the invention of the cathode ray oscilloscope in 1922 and the concentric needle electrode a few years later. Aided by these technical advances, electromyography became a clinically useful tool. The nerve stimulation technique was then introduced, first for studies of neuromuscular transmission and later for assessments of conduction velocity. Since then, there has been wide application of these techniques, which are now considered conventional. More recently, an increasing number of newer electrophysiologic tests emerged for evaluation of anatomic regions not accessible by the traditional methods. These include studies of human reflexes and other late potentials, recordings of somatosensory and motor evoked potentials, and single-fiber electromyography.

2. EARLY DEVELOPMENTS

Ancient physicians used electrical discharges from the black torpedo fish for the treatment of headaches and arthritis. It was not until the turn of the 17th century that the word *electric* was first used by William Gilbert[54] in his book *De Magnete*. Static discharges were also well known after the

invention of the Leyden jar by Musshenbroek in 1745. In the same year, Kratzenstein first induced muscle contraction by static electricity. The next year he wrote the first paper on the use of electricity in medical therapy.[80] Many similar studies followed toward the end of the 18th century, each describing muscle contraction induced by electrical stimulation. It was Galvani who laid the foundation for clinical electrophysiology. After a series of experiments on muscle contraction in frog legs, he introduced the idea that electricity was generated by nervous tissue. This observation was first published in 1791 in his now famous article "De viribus electricitatis in motu musculari commentarius," which appeared in the Proceedings of the Bologna Academy.[48] His concept of animal electricity was received with considerable skepticism during his time. Controversy arose chiefly from Volta's belief that the two plates of different metals were responsible for the electricity observed in Galvani's experiments.[127] Fowler[46] agreed with Volta that dissimilar metals and the muscle had to be connected to generate frog current. Later, Galvani was able to produce muscle contraction by draping the free end of the nerve across the muscle without the use of metals. This finding was reproduced by Humboldt in 1797[74] and Matteucci in 1844.[102] In the meantime, Volta's conviction that animal electricity was in reality the effect of a very weak artificial current induced by application of two different metals led to the development of the Voltanic pile in 1799. He also noted that muscle contracted only at the closing and opening of the circuit. Although Galvani's view on intrinsic electrical current in frog legs was correct, Volta's new invention was so dramatic and convincing that his view of electricity of metallic origin prevailed. This is understandable, because the Voltanic pile produced all the phenomena attributed to animal electricity by Galvani.[128] Indeed, Galvani's experiment was all but forgotten until much later, when Nobili[109] and Matteucci[101] reported electrical activity from muscle in 1830 and 1842, respectively.

In 1822, Magendie[96] who is credited for distinguishing between motor and sensory nerves, tried to insert a needle into the nerve for electrical stimulation, a practice soon abandoned because of the patient's discomfort! Sarlandiere in 1825[118] was the first to introduce electropuncture for direct electrical activation of muscle. One of Volta's pupils, Marianini[98] found in 1829 that ascending (negative) current elicited muscle contraction more effectively than descending current. Nobili in 1830,[109] recognized different stages of excitability, based on the degree of muscle contraction after turning on and off the electrical current supplied by a battery. Later, Erb[42] used this concept clinically in the assessment of abnormal excitabilities of disordered muscles.

According to Licht[92] Ampere introduced the concept of current flow after witnessing Oersted's demonstration that a battery, through metallic wire extended from the two poles, acted on a magnetic needle at a distance. In 1831, Henry found the augmenting action of a long coil of wire on direct current; and in the same year Faraday described alternating current induced in a coil of wire by another coil that was periodically charged. In 1833, Duchenne de Boulogne found that a muscle could be stimulated electrically from the skin surface with the use of cloth-covered electrodes. He was also the first to use Faradic current for stimulation.[33]

Carlo Matteucci[101,102] of Pisa demonstrated that stimulation of the nerve proximal to the application of a ligature or section failed to elicit muscle contraction. In his 1838 experiment, published a few years later, he placed the sciatic nerve still connected to the leg muscles on the thigh muscles dissected from the other leg.[101] In this preparation, contraction of the thigh muscles induced movements of the other leg, provided that its sciatic nerve was not insulated from bared muscle. Hence, he detected electrical activity of contracting muscle for the first time using a neuromuscular preparation, the only means available in those days. Inspired by the work of Matteucci, DuBois-Reymond [31] registered action potentials generated in the muscle.[105] In 1851, he identified the action potential of voluntarily contracting arm muscles, using jars of liquid as electrodes.[32] This was perhaps the beginning of electromyography.[106]

In 1850, Helmholtz[63] succeeded in measuring the conduction velocity of the nerve impulse in the frog by mechanically recording the muscle twitch. Using the same procedure, a conduction

velocity of 61.0 ± 5.1 m/s was found in the human median nerve.[64] He also determined the conduction rate in sensory nerve of man to be 60 m/s by measuring the difference in reaction time. In 1878, Hermann[65, 66] stimulated the brachial plexus in the axilla and recorded a response from the surface of the forearm, which he called action potential. Burdon Sanderson[15] was the first to show in 1895 that this wave of excitation preceded the mechanical response.

3. CLASSICAL ELECTRODIAGNOSIS

Duchenne[34] found that electrical simulation activated certain localized areas of muscle more easily than others. Remak[113] discovered that these points represented entry zones of the muscular nerves. In 1866, Ziemssen[135] carefully mapped out the whole skin surface of the body in agonal patients and proved by dissection immediately after death that the motor points were indeed entrances of the nerve into the muscle. Krause,[81] known for the skin corpuscle that now bears his name, suggested that nerve impulses terminated at the motor points. Kuhne[84] coined the name *endplates* for the nerve endings of striated muscle.

In 1869, Meyer[104] provided a comprehensive discussion on electrical stimulation of the muscle. He also found that galvanic current activated the paralytic limb from cerebral disease more easily than the normal limb. In contrast, more current was necessary if paralysis was caused by lesions of the spinal (peripheral) nerve. Baierlachera[3] had noted that diseased muscle responded better to continuous galvanic current than interrupted faradic current. Neumann[108] however, was the first to recognize that it was the duration that determined the effectiveness of current. Erb also noted failure of the paralyzed muscle to contract in response to frequently interrupted stimuli, and he called this phenomenon the reaction of degeneration.[42] His quantitative studies revealed a certain relationship between muscle contraction and current strength. Based on this principle, he assessed excitability of the muscle in various disorders and found marked irritability in tetany. In 1882, he introduced a formula of polar contraction in normal subjects and its reversal in some disease states, thus establishing the foundation for classical electrodiagnosis.

DuBois-Reymond believed that change in current, rather than the absolute value of current strength, determined muscle response. This view prevailed until the end of the 19th century despite mounting evidence to the contrary, showing a relationship between current intensity and duration in eliciting muscle contraction. This finding paved the way for determination of the strength-duration curve in laboratory animals.[90] Hoorweg[72] further challenged the concept of DuBois-Reymond by stating that nerve excitation occurred as a function of stimulus time and intensity, a view vigorously supported by Lapicque.[90] Waller and Watteville[130] also suggested a duration–intensity relationship for optimal stimulation in 1883.

Toward the end of the 19th century, a few investigators recognized abnormal localization of motor points in degenerated muscles.[30,53] Lewis Jones[91] pointed out that the phenomenon of "displaced motor point" simply represented abnormal sensitivity in regions distinct from the motor point. In 1907, Bordet reported that during passage of a sustained current the critical excitatory level changed less rapidly in the denervated muscle than in normal muscle.[114] This observation led to measurements of accommodation and the galvanic-tetanic ratio, electrodiagnostic tests used widely until recent years.

D'Arsonval's [20] use of a reflecting coil improved the galvanometer built by Sturgeon in 1836. Lippmann[95] introduced the capillary electrometer in 1872. In the meantime, Weiss[134] first attempted to produce a rectangular stimulus pulse, with a device called ballistic rheotome. Lapicques[89,90] developed a more accurate apparatus with a circuit breaker operated by gravity in 1907. Using this instrument, he defined rheobase as the minimal continuous current intensity required for muscle excitation and chronaxie as the minimal current duration required at an intensity twice the rheobase.[90] Lewis Jones[91] constructed a battery of condensers (capacitors) for diagnostic purposes. Using this apparatus, Bourguignons[8] was the first to study chronaxie in man. Plotting strength duration curves for the first time in man, Adrian[1] reported a fairly constant time course in

healthy muscles. He also noted a predictable shift in the regenerating muscle during different phases of recovery after degeneration. A constant current stimulator designed by Bauwens[5] improved the accuracy in determining the strength-duration curve.

4. ELECTROMYOGRAPHY AND NERVE STIMULATION TECHNIQUES

Bernstein[6] introduced the term *action potential*, but Schiff[120] was the first to observe oscillation (fasciculation) of denervated muscle after section of the hypoglossal nerve in 1851. This spontaneous movement ceased if the muscle became atrophic or the nerve regenerated. Fibrillation meant a tremor of denervated muscle in experimental animals, according to Rogowicz[116] and Ricker.[115] In the first electromyography after DuBois-Reymond, Piper[111] recorded voluntary activity of muscles using a string galvanometer. He believed that the muscle activity discharges at a constant frequency independent of the force generated. For him, this reflected the rhythm of neural impulses, although others considered the rate of firing to be inherent in the muscle.[49,50] Using the capillary electrometer, Buchanan[12] arrived at the opposite conclusion: that the frequency of the electromyogram shifted substantially during different degrees of contraction. She stated that the study of the interference pattern could not elucidate the mechanism of neural innervation. At the turn of the century. Langley and Kato[88] and Langley[87] studied fibrillation in muscular dystrophy.

The study of muscle action potentials progressed rapidly after the development of sensitive recording apparatus. Braun[9] invented the cathode-ray tube. Later, Einthoven[40] designed the string galvanometer with a fiber of quartz. In 1920, Forbes and Thacher[45] were the first to use the electron tube to amplify the action potential and a string galvanometer to record it. Gasser and Erlanger[51] introduced one of the most important advances in technology, the cathode-ray oscilloscope, which eliminated the mechanical limitation of galvanometers.[52] Their book, *Electrical Signs of Nervous Activity*, laid the foundation of modern clinical electrophysiology.[43]

In 1925, Liddell and Sherrington[93] proposed the concept of the motor unit. Shortly thereafter, Proebster[112] performed the first clinical electromyography in neurogenic weakness, recording spontaneous potentials in brachial plexus injury and long-standing poliomyelitis. Another major advancement came when Adrian and Bronk[2] introduced the concentric needle electrode in 1929. The use of this electrode made it possible for the first time to record from single motor units. Adrian also initiated the use of a loudspeaker so that electromyographers could use not only visual but also acoustic cues. Motor unit potentials were studied by Denny-Brown[25] in the same year and later by Eccles and Sherrington,[38] Clark,[17] and Hoefer and Putnam.[69]

Invention of the differential amplifier by Matthews in 1934[103] made the recording of small muscle potentials possible, because it minimized electrical interference from other sources. Lindsley[94] noted unusual fluctuation of motor units in a patient with myasthenia gravis. Further work on denervation potentials came from Brown,[11] who tested the effect of acetylcholine on the denervated muscles. Using a bipolar electrode, Denny-Brown and Pennybacker[27] differentiated fibrillation potentials from fasciculation potentials in 1938, a finding later substantiated by Eccles,[37] who used a refined method. In 1941, Denny-Brown and Nevin[26] recorded myotonic discharges. In the same year, Buchthal and Clemmesen[14] confirmed the electromyographic findings of atrophic muscles.

During the two world wars, the large number of battlefield peripheral nerve injuries increased the need for electrical testing. An accelerated growth of electronic devices such as radar and oscilloscopes enhanced this tendency. At the same time, polio epidemics demanded development of procedures to accurately determine the presence and extent of nerve injury and the status of regeneration. Many fundamental contributions to electromyography and nerve conduction studies came from this combination of circumstances.

Using standardized clinical testing, Weddell, Feinstein, and Pattle[132,133] noted the appearance of spontaneous discharges 18 to 20 days after denervation. Watkins, Brazier, and Schwab[131] recorded similar activities in poliomyelitis from the skin surface at various sites. The following

year, Hoefer and Guttman[68] recorded paraspinal denervation using a surface electrode. They reported that such abnormalities, detected longitudinally, sometimes help localize the level of spinal cord lesions. Around the same time, Jasper and Notman[76] introduced the monopolar electrode, and Jasper, Johnston, and Geddes[75] built a portable apparatus for electromyography. Further clinical applications of the needle examination were reported in poliomyelitis by Huddleston and Golseth,[73] in lower motor neuron by Golseth and Huddleston,[57] and in nerve root compression by Shea, Woods, and Werden.[121] In 1955, Marinacci[99] published the first book of electromyography since Piper, and Buchthal[13] contributed a monograph two years later.

Jolly[78] described abnormal fatigability of the orbicularis oculi muscle to intermittent, direct-current stimulation in myasthenic patients. Harvey and Masland[62] were the first to quantitate this clinical observation by stimulating the nerve repetitively and recording the muscle action potentials. This technique was also applied to the study of myasthenic syndromes.[36] It became an important part of our electrodiagnostic armamentarium after standardization by Lambert[86] and Desmedt.[29]

Piper[110] and Munnich[107] first recorded the muscle action potential instead of the muscle twitch for determination of motor nerve conduction. Inspired by Sherrington's work[122] on the stretch reflex, Hoffmann[70,71] demonstrated the monosynaptic reflex in humans by stimulating the tibial nerve and recording the muscle action potential from the soleus. Based on latency measures of the H reflex, Schäffer[119] calculated a velocity of 60 to 65 m/s for the human sensory nerve. Interest in nerve injury and repair during the war prompted basic scientists to study conduction velocity of regenerating nerves in experimental animals.[44,117] Harvey and Kufflerr[60] and Harvey, Kuffler, and Tredway [61] studied peripheral neuritis in humans, stimulating the nerve and recording muscle action potentials. It was Hodes, Larrabee, and German[67] who first calculated the conduction velocity, stimulating the nerve at different levels in neurologic patients. Around the same time, Kugelberg[82] used nerve stimulation to study the effect of ischemia on nerve excitability. Cobb and Marshall,[18] extending this work, demonstrated slowed impulse propagation in the ischemic nerve.

Eichler[39] was the first to report percutaneous recording of nerve action potentials in response to electrical stimulation of the median and ulnar nerves in 1937. The averaging technique of sensory nerve conduction studies emerged as a by-product when Dawson[21] was attempting to record cortical potentials by stimulating peripheral nerves in patients with myoclonus. He used photographic superimposition[47] of a number of faint traces to improve the resolution of the recorded response. Dawson and Scott[24] needed the same technique to assess the growth of the sensory action potential of the peripheral nerve with increasing stimulus strength to prove the origin of their cortical potential.[55] Dawson[22,23] subsequently resorted to digital nerve stimulation to differentiate sensory potentials from antidromic impulses in motor fibers. Although some felt that latency measures sufficed,[16] calculation of nerve conduction velocity became an integral part of electrodiagnostic assessment in the 1960s.

These initial studies, started independently in the United States and Europe, soon spread to many countries, resulting in the common use of the whole field of electromyography and nerve conduction measurements. Important contributions came from Magladery and McDougal,[97] Wagman and Lesse,[129] Gilliatt and Wilson,[56] Lambert,[85] Simpson,[123] Buchthal,[13] Thomas, Sears, and Gilliatt,[126] Johnson and Olsen,[77] Kato,[79] Thomas and Lambert,[125] and Desmedt,[28] to name only a few. The First International Congress of Electromyography, held at Pavia, Italy, in 1961, signaled the rapidly growing worldwide interest in this then relatively new branch of medicine.

5. RECENT DEVELOPMENTS

Conventional methods of nerve conduction study mainly dealt with diseases affecting the distal portion of the peripheral nerve in the four extremities and seldom contributed to the investigation of the remainder of the nervous system. Several neurophysiologic techniques have emerged as diagnostic tests in evaluating the function of these less accessible anatomic regions. These include

studies of human reflexes and other late responses. Of these, the most extensively investigated have been the H reflex of Hoffmann,[70,71] the F wave of Magladery and McDougal,[97] and the blink reflex of Kugelberg.[83]

Somatosensory evoked potentials provided another electrophysiologic means for study of the central nervous system.[19,28,59] The technique of signal averaging initially helped develop the methods for peripheral sensory conduction and much later those for cerebral evoked potential. The wide availability of minicomputers and averagers has since accelerated the clinical application of this technique in the assessment of the central nervous system. As stated earlier, this development is of historical interest because Dawson[21] originally used photographic superimposition, a forerunner of electrical averaging, in the study of somatosensory cerebral potentials. With the advent of electrical[100] and magnetic coil stimulators[4] capable of noninvasive excitation of the brain or spinal cord, it is now feasible to study the central motor pathways as well.

Introduction of single-fiber electromyography has made it possible to study electrophysiologic characteristics of individual muscle fibers.[41] This stands in contrast to the conventional use of coaxial or monopolar recording needles for assessment of the motor unit, the smallest functional element of muscle contraction. Stålberg and others have since refined the technique for research application and clinical use.[124] Some other newer techniques, although directly related to electromyography and nerve conduction studies, have not yet found their way into the clinical laboratory. These include the in-vitro technique of sural nerve conduction studies[35] and electroneurography[58] and threshold tracking.[7]

This outline includes most of the major events that have taken place in the history of clinical electrophysiology of muscle and nerve. Inclusion of additional details, although tempting because of a number of intriguing anecdotes, fall outside the scope of this book. Interested readers should consult previous publications on this subject by Mottelay,[106] Marinacci,[99] Licht,[92] Gilliatt,[55] and Brazier.[10]

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Appendix 4

AAEM Glossary of Terms in Electrodiagnostic Medicine

Compiled by the AAEM Nomenclature Committee

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CONTENTS

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FOREWORD

In 1980, a committee of distinguished members of the American Association of Electromyography and Electrodiagnosis (AAEE) published the first comprehensive collection of terms used in the practice of what was then referred to by the generic name of electromyography. A second such committee, responding to advances and changes in the field, produced a revised glossary in 1987. Many changes, including the name of the organization to the American Association of Electrodiagnostic Medicine (AAEM), have occurred since that time. Some of the changes have been advances in the science of the field, but others have occurred in response to the changing face of medical practice at the turn of the century. For example, we have recognized that our area of special knowledge and skill in medicine is better described as the practice of *electrodiagnostic medicine* rather than the more narrowly defined term *electromyography.* Such changes are not just cosmetic, but they reflect a clearer sense of what makes the activities of the membership of the AAEM unique in the world of medicine. In response to the many changes that have occurred since 1987, a new Nomenclature Committee was formed in 1994 to revise and update the glossary. This document reflects the hard work of that committee. From the work of the committee, it has become clear that the specialty of electrodiagnostic medicine is a growing and changing field. More than 150 new terms have been added, and 15 terms were deleted from the previous glossary. By the time this glossary is in print, additional new terms will likely have come into common usage. It is hoped that this glossary will serve as a stimulus to further growth into the future.

AAEM Nomenclature Committee 1994–2001

Lawrence H. Phillips, II, MD, Chair (1997–2001)
William J. Litchy, MD, Chair (1994–1997)
Raymond G. Auger, MD (1994–2001)
Ernest M. Baran, MD, MSBME (1997–2001)
Francis J. Bonner Jr., MD (1995–1996)
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Daniel Dumitru, MD, PhD (1994–2001)
Björn Falck, MD, PhD (1994–2001)
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Mark Hallett, MD (1995–2001)
Charles K. Jablecki, MD (1994–2001)
Dale J. Lange, MD (1996–2001)
Janice M. Massey, MD (1994–1996)
Lawrence R. Robinson, MD (1994–2001)
Margaret A. Turk, MD (1994–1996)
Jacqueline J. Wertsch, MD (1994–2001)
Asa J. Wilbourn, MD (1995–2001)

SECTION I:
ALPHABETIC LIST OF TERMS WITH DEFINITIONS

[*]**A wave** A *compound muscle action potential* that follows the *M wave*, evoked consistently from a muscle by submaximal electric stimuli and frequently abolished by *supramaximal stimuli.* Its *amplitude* is similar to that of an *F wave*, but the *latency* is more constant. Usually occurs before the F wave, but may occur afterwards. Thought to be due to extra *discharges* in the nerve, *ephapses*, or axonal branching. This term is preferred over *axon reflex*, *axon wave*, or *axon response.* Compare with the *F wave.*

absolute refractory period See *refractory period.*

accommodation In neuronal physiology, a rise in the *threshold* transmembrane *depolarization* required to initiate a *spike*, when depolarization is slow or a subthreshold depolarization is maintained. In the older literature, the observation that the final intensity of current applied in a slowly rising fashion to stimulate a nerve was greater than the intensity of a pulse of current required to stimulate the same nerve. The latter may largely be an *artifact* of the nerve sheath and bears little relation to true accommodation as measured intracellularly.

accommodation curve See *strength-duration curve.*

acoustic myography The recording and analysis of sounds produced by contracting muscle. The muscle *contraction* may be produced by stimulation of the nerve supply to the muscle or by volitional *activation* of the muscle.

action potential (AP) The brief regenerative electric *potential* that propagates along a single axon or muscle fiber membrane. An all-or-none phenomenon; whenever the *stimulus* is at or above *threshold*, the action potential generated has a constant size and configuration. See also *compound action potential*, *motor unit action potential.*

activation 1) In physiology, a general term for the initiation of a process. 2) The process of *motor unit action potential* firing. The force of muscle *contraction* is determined by the number of *motor units* and their *firing rate.*

activation procedure A technique used to detect defects of neuromuscular transmission during *repetitive nerve stimulation* testing. Most commonly a sustained voluntary *contraction* is performed to elicit *facilitation* or *postactivation depression.* See also *tetanic contraction.*

active electrode Synonymous with *exploring electrode*. See *recording electrode*.

acute inflammatory neuropathy An acute, monophasic *polyneuropathy.* Characterized by a time course of progression to maximum deficit within 4 weeks of onset of symptoms. Most common clinical presentation is an ascending sensory-motor *neuropathy.* Electrodiagnostic studies most commonly reveal evidence for *demyelination*, but *axonal degeneration* also occurs. Distinguish from *chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).* See also *Guillain-Barré syndrome.*

adaptation A decline in the *frequency* of the *spike discharge* as typically recorded from sensory axons in response to a maintained *stimulus.*

ADEMG Abbreviation for *automatic decomposition electromyography*.

AEP Abbreviation for *auditory evoked potential*.

afterdischarge 1) The continuation of *action potentials* in a neuron, axon, or muscle fiber following the termination of an applied *stimulus.* 2) The continuation of firing of *muscle action potentials* after cessation of voluntary *activation*, for example in *myotonia.*

afterpotential The membrane *potential* between the end of the *spike* and the time when the membrane potential is restored to its resting value. The membrane during this period may be depolarized or hyperpolarized at different times.

akinesia Lack or marked *delay* of intended movement, often observed in patients with

[*]The items with asterisks have an illustration in Section II.

Parkinson's disease. Often used synonymously with *bradykinesia.*

amplitude With reference to an *action potential,* the maximum *voltage* difference between two points, usually *baseline*-to-peak or peak-to-peak. By convention, the amplitude of *potentials* which have an initial negative deflection from the baseline, such as the *compound muscle action potential* and the *antidromic sensory nerve action potential,* are measured from baseline to the most negative peak. In contrast, the amplitude of a *compound sensory nerve action potential, motor unit potential, fibrillation potential, positive sharp wave, fasciculation potential,* and most other action potentials is measured from the most positive peak to the most negative peak.

amplitude decay The percent change in the *amplitude* of the *M wave* or the *compound sensory nerve action potential* between two different stimulation points along the nerve. Decay = 100^{*} (amplitude$_{distal}$ – amplitude$_{proximal}$) / amplitude$_{distal}$. Useful in the evaluation of *conduction block.* Abnormal decay without increased *temporal dispersion* may indicate a conduction block.

anodal block A local block of nerve conduction caused by membrane *hyperpolarization* under a stimulating *anode.* Does not occur in routine clinical studies, since it is possible for the anode to routinely result in nerve *depolarization* if sufficient current intensities are used.

anode The positive terminal of an electric current source. See *stimulating electrode.*

antidromic Propagation of a nerve impulse in the direction opposite to physiologic conduction; e.g., conduction along *motor nerve* fibers away from the muscle and conduction along sensory fibers away from the spinal cord. Contrast with *orthodromic.*

AP Abbreviation for *action potential.*

artifact (also artefact) A *voltage* change generated by a biologic or nonbiologic source other than the ones of interest. The *stimulus artifact* (or *shock artifact*) represents cutaneous spread of stimulating current to the *recording electrode* and the *delay* in return to *baseline* which is dependent on the ability of filters to respond to high voltage. Stimulus artifacts may precede or overlap the activity of interest. *Movement artifact* refers to a change in the recorded activity caused by movement of the recording electrodes.

asterixis A quick involuntary movement caused by a brief lapse in tonic muscle *activation.* It can be appreciated only during voluntary movement. Is usually irregular but can be rhythmic and confused with action *tremor.*

ataxia Clumsiness of movement. Specific features include dysmetria (incorrect distance moved) and dysdiadochokinesis (irregularity of attempted rhythmic movements). Most commonly due to a disorder of the cerebellum or proprioceptive sensory system. Referred to, respectively, as cerebellar ataxia or sensory ataxia.

auditory evoked potential (AEP) Electric *waveforms* of biologic origin elicited in response to sound stimuli. Classified by their *latency* as short-latency *brainstem auditory evoked potential (BAEP)* with a latency of up to 10 ms, middle-latency with a latency of 10 to 50 ms, and long-latency with a latency of over 50 ms. See *brainstem auditory evoked potential.*

automatic decomposition EMG (ADEMG) Computerized method for extracting individual *motor unit action potentials* from an *interference pattern.*

averager See *signal averager.*

averaging A method for extracting time-locked *potentials* from random background *noise* by sequentially adding traces and dividing by the total number of traces.

axon reflex Use of term discouraged as it is incorrect. No *reflex* is thought to be involved. See preferred term, *A wave.*

axon response See preferred term, *A wave.*

axon wave See *A wave.*

axonal degeneration Degeneration of the segment of a nerve distal to the cell body with preferential distal pathology.

axonotmesis Nerve injury characterized by axon and myelin sheath disruption with supporting connective tissue preservation, resulting in *axonal degeneration* distal to the injury site. Compare *neurapraxia, neurotmesis.*

backaveraging *Averaging* a signal which occurs in a time epoch preceding a triggering event. Often used to extract a time-locked EEG signal preceding voluntary or involuntary movement, usually triggered by the onset of the *EMG* activity of the movement. An example is the *Bereitschaftspotential.*

backfiring *Discharge* of an *antidromically* activated motor neuron.

BAEP Abbreviation for *brainstem auditory evoked potential.*

BAER Abbreviation for *brainstem auditory evoked response.* See preferred term, *brainstem auditory evoked potential.*

baseline 1) The *potential* recorded from a biologic system while the system is at rest. 2) A flat trace on the recording instrument; an equivalent term, *isoelectric line,* may be used.

benign fasciculation potential A *firing pattern* of *fasciculation potentials* occurring in association with a clinical syndrome of *fasciculations* in an individual with a nonprogressive neuromuscular disorder. Use of term discouraged.

BER Abbreviation *for brainstem auditory evoked responses.* See preferred term, *brainstem auditory evoked potentials.*

Bereitschaftspotential (BP) A component of the *movement-related cortical potential.* The slowly rising negativity in the EEG preceding voluntary movement. The German term means "readiness potential." Has two *phases* called BP1 and BP2 or BP and NS' (negative slope). See *backaveraging.*

biphasic action potential An *action potential* with one *baseline* crossing, producing two *phases.*

biphasic end-plate activity See *end-plate activity (biphasic).*

*__bipolar needle electrode__ *Recording electrode* that measures *voltage* between two insulated wires cemented side-by-side in a steel cannula. The bare tips of the electrodes are flush with the level of the cannula which may serve as a ground.

bipolar stimulating electrode See *stimulating electrode.*

bizarre high-frequency discharge See preferred term, *complex repetitive discharge.*

bizarre repetitive discharge See preferred term, *complex repetitive discharge.*

bizarre repetitive potential See preferred term, *complex repetitive discharge.*

blink reflex See *blink responses.*

*__blink responses__ *Compound muscle action potentials* evoked from orbicularis oculi muscles as a result of brief electric or mechanical *stimuli* applied to the cutaneous area innervated by the supraorbital (or less commonly, the infraorbital) branch of the trigeminal nerve. Typically, there is an early compound muscle action potential (*R1 wave*) ipsilateral to the stimulation site with a *latency* of about 10 ms and a bilateral late compound muscle action potential (*R2 wave*) with a latency of approximately 30 ms. Generally, only the R2 wave is associated with a visible *contraction* of the muscle. The configuration, *amplitude, duration,* and latency of the two components, along with the sites of recording and stimulation, should be specified. The R1 and R2 waves are oligosynaptic and polysynaptic brainstem *reflexes,* respectively. Together they are called the *blink reflex.* The afferent arc is provided by the sensory branches of the trigeminal nerve and the efferent arc is provided by facial nerve motor fibers.

blocking Term used in *single fiber electromyography* to describe dropout of one or more components of the *potential* during sequential firings. If more than one component drops out simultaneously, it is described as concomitant blocking. Usually seen when *jitter* values exceed 80 to 100 μs. A sign of abnormal neuromuscular transmission, which may be due to primary *neuromuscular transmission disorders,* such as *myasthenia gravis* and other myasthenic syndromes. Also seen as a result of degeneration and reinnervation in *neuropathies* or *myopathies.* Concomitant blocking may be generated by a split muscle fiber or failure of conduction at an axon branch serving several muscle fibers.

BP Abbreviation for *Bereitschaftspotential.*

brachial plexus An anatomical structure which is formed by the spinal roots from C5 to T1,

*The items with asterisks have an illustration in Section II.

traverses the shoulder region, and culminates in the named peripheral nerves in the arm. It is composed of roots, trunks, divisions, cords, and terminal nerves.

bradykinesia Slowness of movement, often observed in patients with Parkinson's disease. Often used synonymously with *akinesia.*

*__brainstem auditory evoked potential (BAEP)__ Electric *waveforms* of biologic origin elicited in response to sound stimuli. Normally consists of a sequence of up to seven waves, designated I to VII, which occur during the first 10 ms after the onset of the *stimulus* and have positive polarity at the vertex of the head.

brainstem auditory evoked response (BAER, BER) See preferred term, *brainstem auditory evoked potentials.*

BSAP Abbreviation for brief, small, abundant potentials. (See *BSAPP*). Use of term is discouraged.

BSAPP Abbreviation for brief, small, abundant, polyphasic *potentials.* Used to describe a *recruitment pattern* of brief *duration*, small *amplitude*, overly abundant, polyphasic *motor unit action potentials*, with respect to the amount of force generated; usually a minimal *contraction.* Use of term discouraged. Quantitative measurements of motor unit action potential duration, amplitude, numbers of *phases*, and *recruitment frequency* are preferred. See *motor unit action potential.*

carpal tunnel syndrome A *mononeuropathy* affecting the median nerve at the wrist. As the nerve passes through the carpal tunnel, a space bounded dorsally by the bones of the wrist, laterally by the forearm flexor tendons, and volarly by the transverse carpal ligament, it is subject to compression by any of these structures. Repetitive hand and wrist movement is thought to contribute to the compression.

C reflex An abnormal *reflex response* representing the electrophysiologic correlate of sensory evoked *myoclonus.* The term "C" was chosen to indicate that the reflex might be mediated in the cerebral cortex. This is sometimes, but not always, true.

c/s (also cps) Abbreviation for *cycles per second.* See preferred term, *Hertz (Hz).*

cathode The negative terminal of an electric current source. See *stimulating electrode.*

center frequency The mean or median *frequency* of a *waveform* decomposed by *frequency analysis.* Employed in the study of muscle *fatigue.*

central electromyography Use of electrodiagnostic recording techniques to study *reflexes* and the control of movement by the spinal cord and brain. See *electrodiagnosis.*

central motor conduction The time taken for conduction of *action potentials* in the central nervous system from motor cortex to alpha motoneurons in the spinal cord or brainstem. Calculated from the *latencies* of the *motor evoked potentials* produced by *transcranial magnetic stimulation* or *transcranial electrical stimulation*, subtracting the time for peripheral conduction.

chorea Clinical term used to describe irregular, random, brief, abrupt, involuntary movements of the head or limbs due to a disorder of the basal ganglia. Most commonly observed in patients with Huntington's disease and Sydenham's chorea.

chronaxie (also chronaxy) See *strength-duration curve.*

chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) A *polyneuropathy* or *polyradiculoneuropathy* characterized by generalized *demyelination* of the peripheral nervous system. In most cases there is also a component of *axonal degeneration.* Some cases are associated with a monoclonal gammopathy of undetermined significance (MGUS). Distinguish from *acute inflammatory neuropathy.*

clinical electromyography Term used commonly to describe the scientific methods of recording and analysis of biologic electrical *potentials* from human peripheral nerve and muscle. See preferred term, *electrodiagnostic medicine.*

CMAP Abbreviation for *compound muscle action potential.*

coaxial needle electrode See synonym, *concentric needle electrode.*

*The items with asterisks have an illustration in Section II.

collision When used with reference to *nerve conduction studies*, the interaction of two *action potentials* propagated toward each other from opposite directions on the same nerve fiber so that the *refractory periods* of the two potentials prevent propagation past each other.

complex motor unit action potential A *motor unit action potential* that is polyphasic or serrated. See preferred terms, *polyphasic action potential* or *serrated action potential.*

*__complex repetitive discharge__ A type of *spontaneous* activity. Consists of a regularly repeating series of complex polyphasic or serrated *potentials* that begin abruptly after *needle electrode* movement or spontaneously. The potentials have a uniform shape, *amplitude*, and *discharge frequency* ranging from 5 to 100 *Hz.* The discharge typically terminates abruptly. May be seen in both myopathic and neurogenic disorders, usually chronic. Thought to be due to ephaptic excitation of adjacent muscle fibers in a cyclic fashion. This term is preferred to *bizarre high frequency discharge, bizarre repetitive discharge, bizarre repetitive potential, pseudomyotonic discharge*, and *synchronized fibrillation.* See also *ephapse* and *ephaptic transmission.*

compound action potential A *potential* or *waveform* resulting from the summation of multiple individual axon or *muscle fiber action potentials*. See *compound mixed nerve action potential, compound motor nerve action potential, compound nerve action potential, compound sensory nerve action potential*, and *compound muscle action potential*.

compound mixed nerve action potential A *compound nerve action potential* recorded from a *mixed nerve* when an electric *stimulus* is applied to a segment of the nerve that contains both afferent and efferent fibers. The *amplitude, latency, duration,* and *phases* should be noted.

compound motor nerve action potential (compound motor NAP) A *compound nerve action potential* recorded from efferent fibers of a *motor nerve* or a motor branch of a *mixed nerve.* Elicited by stimulation of a motor nerve, a motor branch of a mixed nerve, or a ventral nerve root. The *amplitude, latency, duration,* and number of *phases* should be noted. Distinguish from *compound muscle action potential.*

compound muscle action potential (CMAP) The summation of nearly synchronous *muscle fiber action potentials* recorded from a muscle, commonly produced by stimulation of the nerve supplying the muscle either directly or indirectly. *Baseline*-to-peak *amplitude, duration,* and *latency* of the negative *phase* should be noted, along with details of the method of stimulation and recording. Use of specific named *potentials* is recommended, e.g., *M wave, F wave, H wave, T wave, A wave,* and *R1 or R2 wave (blink responses).*

compound nerve action potential (compound NAP) The summation of nearly synchronous *nerve fiber action potentials* recorded from a nerve trunk, commonly produced by stimulation of the nerve directly or indirectly. Details of the method of stimulation and recording should be specified, together with the fiber type (*sensory, motor,* or *mixed nerve*).

*__compound sensory nerve action potential (compound SNAP)__ A *compound nerve action potential* recorded from the afferent fibers of a *sensory nerve*, a sensory branch of a *mixed nerve,* or in response to stimulation of a sensory nerve or a dorsal nerve root. May also be elicited when an adequate *stimulus* is applied synchronously to sensory receptors. The *amplitude, latency, duration,* and configuration should be noted. Generally, the amplitude is measured as the maximum peak-to-peak *voltage* when there is an initial positive deflection or from *baseline*-to-peak when there is an initial negative deflection. The latency is measured as either the time to the initial deflection or the negative peak, and the duration as the interval from the first deflection of the *waveform* from the baseline to its final return to the baseline. Also referred to by the less preferred terms *sensory response, sensory potential,* or *SNAP.*

*__concentric needle electrode__ *Recording electrode* that measures an electric *potential* difference between a centrally insulated wire and the cannula of the needle through which it runs.

*The items with asterisks have an illustration in Section II.

conditioning stimulus See *paired stimuli.*

conduction block Failure of an *action potential* to propagate past a particular point in the nervous system whereas conduction is possible below the point of the block. Documented by demonstration of a reduction in the area of a *compound muscle action potential* greater than that normally seen with stimulation at two different points on a nerve trunk; anatomic variations of nerve pathways and technical factors related to nerve stimulation must be excluded as the cause of the reduction in area.

conduction distance The length of nerve or muscle over which conduction is determined, customarily measured in centimeters or millimeters.

conduction time See *conduction velocity.*

conduction velocity (CV) Speed of propagation of an *action potential* along a nerve or muscle fiber. The nerve fibers studied (motor, sensory, autonomic, or *mixed nerve*) should be specified. For a nerve trunk, the maximum conduction velocity is calculated from the *latency* of the *evoked potential* (muscle or nerve) at maximal or supramaximal intensity of stimulation at two different points. The distance between the two points (*conduction distance*) is divided by the difference between the corresponding latencies (*conduction time*). The calculated result is the conduction velocity of the fastest fibers and is usually expressed as meters per second (m/s). As commonly used, refers to the *maximum conduction velocity.* By specialized techniques, the conduction velocity of other fibers can also be determined and should be specified, e.g., *minimum conduction velocity.*

congenital myasthenia A heterogeneous group of genetic disorders of the neuromuscular junction manifest by muscle weakness and *fatigue.*

contraction A voluntary or involuntary reversible muscle shortening that may or may not be accompanied by *action potentials* from muscle. Contrast the term *contracture.*

contraction fasciculation Clinical term for visible twitching of a muscle with weak voluntary or postural *contraction* which has the appearance of a *fasciculation.* More likely to occur in neuromuscular disorders in which the *motor unit* territory is enlarged and the tissue covering the muscle is thin, but may also be observed in normal individuals.

contracture 1) Fixed resistance to stretch of a shortened muscle due to fibrous connective tissue changes and loss of sarcomeres in the muscle. Limited movement of a joint may be due to muscle contracture or to fibrous connective tissue changes in the joint. Contrast with *contraction*, which is a rapidly reversible painless shortening of the muscle. 2) The prolonged, painful, electrically silent, and involuntary state of temporary muscle shortening seen in some *myopathies* (e.g., muscle phosphorylase deficiency).

coupled discharge See preferred term, *satellite potential.*

cps (also c/s) Abbreviation for *cycles per second.* See preferred term, *Hertz (Hz).*

*__cramp discharge__ Involuntary repetitive firing of *motor unit action potentials* at a high *frequency* (up to 150 *Hz*) in a large area of a muscle usually associated with painful muscle *contraction.* Both *discharge frequency* and number of motor unit action potentials activated increase gradually during development, and both subside gradually with cessation. See *muscle cramp.*

crossed leg palsy Synonym for *peroneal neuropathy at the knee.*

cross talk 1) A general term for abnormal communication between excitable membranes. See *ephapse* and *ephaptic transmission.* 2) Term used in *kinesiologic EMG* for signals picked up from adjacent muscles.

cubital tunnel syndrome A *mononeuropathy* involving the ulnar nerve in the region of the elbow. An *entrapment neuropathy* caused by compression of the nerve as it passes through the aponeurosis (the cubital tunnel) of the two heads of the flexor carpi ulnaris approximately 1.5 to 3.5 cm distal to the medial epicondyle of the elbow. The mechanism of entrapment is presumably

*The items with asterisks have an illustration in Section II.

narrowing of the cubital tunnel during elbow flexion. See also *tardy ulnar palsy* and *ulnar neuropathy at the elbow.*

cutaneous reflex A *reflex* produced by cutaneous stimulation. There are several *phases* to cutaneous reflexes, and, if the muscle has a background *contraction*, the phases can be seen to be inhibitory as well as excitatory.

CV Abbreviation for *conduction velocity.*

cycles per second (c/s, cps) Unit of *frequency.* See preferred term *hertz* (*Hz*).

decomposition EMG Synonym for *automatic decomposition EMG.*

decremental response See preferred term, *decrementing response.*

*__decrementing response__ A reproducible decline in the *amplitude* and/or area of the *M wave* of successive *responses* to *repetitive nerve stimulation.* The rate of stimulation and the total number of stimuli should be specified. Decrementing responses with disorders of neuromuscular transmission are most reliably seen with slow rates (2 to 5 *Hz*) of nerve stimulation. A decrementing response with *repetitive nerve stimulation* commonly occurs in disorders of neuromuscular transmission but can also be seen in some *neuropathies*, *myopathies*, and *motor neuron disease.* An *artifact* resembling a decrementing response can result from movement of the *stimulating* or *recording electrodes* during *repetitive nerve stimulation* (see *pseudodecrement*). Contrast with *incrementing response.*

delay 1) The time between the beginning of the horizontal sweep of the oscilloscope and the onset of an applied *stimulus.* 2) A synonym for an information storage device (*delay line*) used to display events occurring before a trigger signal.

delay line An information storage device used to display events which occur before a trigger signal. A method for displaying a *waveform* at the same point on a sweep from a free-running *electromyogram.*

demyelination Disease process affecting the myelin sheath of central or peripheral nerve fibers, manifested by *conduction velocity* slowing, *conduction block*, or both.

denervation potential Sometimes used as a synonym for *fibrillation potential.* Use of this term is discouraged, since fibrillation potentials can occur in the absence of denervation. See preferred term, *fibrillation potential.*

depolarization A change in the existing membrane *potential* to a less negative value. Depolarizing an excitable cell from its resting level to *threshold* typically generates an *action potential.*

depolarization block Failure of an excitable cell to respond to a *stimulus* due to pre-existing *depolarization* of the cell membrane.

depth electrodes *Electrodes* which are inserted into the substance of the brain for electrophysiological recording. Most often inserted using stereotactic techniques.

dermatomal somatosensory evoked potential (DSEP) Scalp recorded *waveforms* generated from repeated stimulation of a specific dermatome. Different from typical *somatosensory evoked potentials* which are recorded in response to stimulation of a named peripheral nerve.

discharge The firing of one or more excitable elements (neurons, axons, or muscle fibers); as conventionally used, refers to all-or-none *potentials* only. Synonymous with *action potential.*

discharge frequency The rate at which a *potential* discharges repetitively. When potentials occur in groups, the rate of recurrence of the group and rate of repetition of the individual components in the groups should be specified. See also *firing rate.*

discrete activity See *interference pattern.*

distal latency The interval between the delivery of a *stimulus* to the most distal point of stimulation on a nerve and the onset of a *response.* A measure of the conduction properties of the distal most portion of motor or sensory nerves. See *motor latency* and *sensory latency.*

double discharge Two sequential firings of a *motor unit action potential* of the same form and nearly the same *amplitude*, occurring consistently in the same relationship to one another at intervals of 2 to 20 ms. See also *multiple discharge*, *triple discharge.*

*The items with asterisks have an illustration in Section II.

doublet Synonym for the preferred term, *double discharge.*

DSEP Abbreviation for *dermatomal somatosensory evoked potential.*

duration The time during which something exists or acts. 1) The interval from the beginning of the first deflection from the *baseline* to its final return to the baseline of an *action potential* or *waveform*, unless otherwise specified. If only part of the waveform is measured, the points of the measurement should be specified. For example, the duration of the *M wave* may be measured as the negative *phase* duration and refers to the interval from the deflection of the first negative phase from the baseline to its return to the baseline. 2) The interval of the applied current or *voltage* of a single electric *stimulus.* 3) The interval from the beginning to the end of a series of recurring stimuli or action potentials.

dynamic EMG See *kinesiologic EMG*.

dyskinesia An abnormal involuntary movement of a *choreic* or *dystonic* type. The term is nonspecific and is often used in association with a modifier that describes its etiology, e.g., tardive dyskinesia or L-DOPA dyskinesia.

dystonia A disorder characterized by involuntary movements caused by sustained muscle *contraction*, producing prolonged movements or abnormal postures.

E-1 Synonymous with *input terminal 1*. See *recording electrode.*

E-2 Synonymous with *input terminal 2*. See *recording electrode*.

E:I ratio In autonomic testing, the ratio of the longest electrocardiographic R-R interval during expiration to the shortest during inspiration. Primarily a measure of parasympathetic control of heart rate.

early recruitment A *recruitment pattern* which occurs in association with a reduction in the number of muscle fibers per *motor unit* or when the force generated by the fibers is reduced. At low levels of muscle *contraction* more *motor unit action potentials* are recorded than expected, and a *full interference pattern* may be recorded at relatively low levels of muscle contraction. Most often encountered in *myopathy.*

earth electrode Synonymous with *ground electrode.*

EDX Abbreviation for *electrodiagnosis.* Can also be used for electrodiagnostic and *electrodiagnostic medicine.*

electric inactivity See preferred term, *electric silence.*

electric silence The absence of measurable electric activity due to biologic or nonbiologic sources. The sensitivity and signal-to-*noise* level of the recording system should be specified.

electrocorticography Electrophysiologic recording directly from the surface of the brain. In the intra-operative setting, recordings are made of ongoing spontaneous electroencephalogram activity, or *potentials* evoked by stimulation of peripheral sensory pathways.

electrode A conducting device used to record an electric *potential* (*recording electrode*) or to deliver an electric current (*stimulating electrode*). In addition to the *ground electrode* used in clinical recordings, two electrodes are always required either to record an electric potential or to deliver a *stimulus.* See *ground electrode*, *recording electrode*, and *stimulating electrode.* Also see specific *needle electrode* configurations: *monopolar*, *unipolar*, *concentric*, *bifilar recording*, *bipolar stimulating*, *multilead*, *single fiber*, and *macro-EMG needle electrodes.*

electrodiagnosis (EDX) The scientific methods of recording and analyzing biologic electrical *potentials* from the central, peripheral, and autonomic nervous systems and muscles. See also *clinical electromyography*, *electromyography*, *electroneurography*, *electroneuromyography*, *evoked potentials*, *electrodiagnostic medicine*, *electrodiagnostic medicine consultation*, and *electrodiagnostic medicine consultant.*

electrodiagnostic medicine A specific area of medical practice in which a physician integrates information obtained from the clinical history, observations from physical examination, and scientific data acquired

by recording electrical *potentials* from the nervous system and muscle to diagnose, or diagnose and treat diseases of the central, peripheral, and autonomic nervous systems, neuromuscular junctions, and muscle. See also *electrodiagnosis*, *electrodiagnostic medicine consultation*, and *electrodiagnostic medicine consultant.*

electrodiagnostic medicine consultant A physician specially trained to obtain a medical history, perform a physical examination, and to record and analyze data acquired by recording electrical *potentials* from the nervous system and muscle to diagnose and/or treat diseases of the central, peripheral, and autonomic nervous systems, neuromuscular junction, and muscle. See also *electrodiagnosis*, *electrodiagnostic medicine*, and *electrodiagnostic medicine consultation.*

electrodiagnostic medicine consultation The medical evaluation in which a specially trained physician (*electrodiagnostic medicine consultant*) obtains a medical history, performs a physical examination, and integrates scientific data acquired by recording electrical *potentials* from the nervous system and muscle to diagnose and/or treat diseases of the central, peripheral, and autonomic nervous systems, neuromuscular junction, and muscle. See also *electrodiagnosis*, *electrodiagnostic medicine*, and *electrodiagnostic medicine consultant.*

electromyogram The record obtained by *electromyography.*

electromyograph Equipment used to activate, record, process, and display electrical *potentials* for the purpose of evaluating the function of the central, peripheral, and autonomic nervous systems, neuromuscular junction, and muscles.

electromyographer See preferred term, *electrodiagnostic medicine consultant.*

electromyography (EMG) Strictly defined, the recording and study of *insertion*, *spontaneous*, and *voluntary activity* of muscle with a *recording electrode* (either a *needle electrode* for invasive *EMG* or a *surface electrode* for kinesiologic studies). The term is also commonly used to refer to an *electrodiagnostic medicine consultation*, but its use in this context is discouraged.

electroneurography (ENG) The recording and study of the *action potentials* of peripheral nerve. Synonymous with *nerve conduction studies.*

electroneuromyography (ENMG) The combined studies of electromyography and electroneurography. Synonymous with clinical electromyography. See preferred term *electrodiagnostic medicine consultation.*

EMG Abbreviation for *electromyography.*

*__end-plate activity__ Spontaneous electric activity recorded with a *needle electrode* close to muscle end plates. These *potentials* may have several different morphologies.

1. Monophasic: Low-*amplitude* (10 to 20 μV), short-*duration* (0.5 to 1.0 ms), negative potentials occurring in a dense, steady pattern, the exact *frequency* of which cannot be defined. These nonpropagated potentials are probably *miniature end-plate potentials* recorded extracellularly. Referred to as *end-plate noise* or *sea-shell sound (sea shell roar or noise).*
2. Biphasic: Moderate-amplitude (100 to 300 μV), short-duration (2 to 4 ms), initially negative *spike* potentials occurring irregularly in short bursts with a high frequency (50 to 100 *Hz*). These propagated potentials are generated by muscle fibers excited by activity in nerve terminals. These potentials have been referred to as biphasic spike potentials, *end-plate spikes*, and, incorrectly, *nerve potentials.* May also have a biphasic initially positive morphology.
3. Triphasic: Similar to biphasic potentials, but the *waveforms* have three *phases* with an initial positive deflection. Fire in an irregular fashion; contrast with *fibrillation potential.*

end-plate noise See *end-plate activity (monophasic).*

end-plate potential (EPP) The graded nonpropagated membrane potential induced in the postsynaptic membrane of a muscle fiber by release of acetyl-choline from the

*The items with asterisks have an illustration in Section II.

presynaptic axon terminal in response to an *action potential.*

end-plate spike See *end-plate activity (biphasic).*

end-plate zone The region in a muscle where neuromuscular junctions are concentrated.

ENG Abbreviation for *electroneurography.*

ENMG Abbreviation for *electroneuromyography.*

entrapment neuropathy A *mononeuropathy* caused by compression of a nerve as it passes through an area of anatomical narrowing.

ephapse A point of abnormal communication where an *action potential* in one muscle fiber or axon can cause *depolarization* of an adjacent muscle fiber or axon to generate an action potential.

ephaptic transmission The generation of a *nerve fiber action potential* from one muscle fiber or axon to another through an *ephapse.* Postulated to be the basis for *complex repetitive discharges, myokymic discharges,* and *hemifacial spasm.*

EPSP Abbreviation for *excitatory postsynaptic potential.*

Erb's point The site at the anterolateral base of the neck where percutaneous nerve stimulation activates the axons comprising the upper trunk of the *brachial plexus.*

Erb's point stimulation Percutaneous *supraclavicular nerve stimulation* during which the upper trunk of the *brachial plexus* is activated. See the more general and preferred term, *supraclavicular nerve stimulation.*

evoked potential Electric *waveform* elicited by and temporally related to a *stimulus,* most commonly an electric stimulus delivered to a sensory receptor or nerve, or applied directly to a discrete area of the brain, spinal cord, or muscle. See *auditory evoked potential, brainstem auditory evoked potential, spinal evoked potential, somatosensory evoked potential, visual evoked potential, compound muscle action potential,* and *compound sensory nerve action potential.*

evoked potential studies Recording and analysis of electric *waveforms* of biologic origin elicited in response to electrical, magnetic, or physiological *stimuli.* Stimuli are applied to specific motor or sensory receptors, and the resulting waveforms are recorded along their anatomic pathways in the peripheral and central nervous system. A single motor or sensory modality is typically tested in a study, and the modality studied is used to define the type of study performed. See *auditory evoked potentials, brainstem auditory evoked potentials, visual evoked potentials,* and *somatosensory evoked potentials.*

evoked response Tautology. Use of term discouraged. See preferred term, *evoked potential.*

excitability Capacity to be activated by or react to a *stimulus.*

excitatory postsynaptic potential (EPSP) A local, graded *depolarization* of a neuron in response to *activation* by a nerve terminal. Contrast with *inhibitory postsynaptic potential.*

exploring electrode Synonymous with *active electrode.* See *recording electrode.*

F reflex An incorrect term for *F wave.*

F response Synonymous with *F wave.* See preferred term, *F wave.*

*__F wave__ An *action potential* evoked intermittently from a muscle by a supramaximal electric *stimulus* to the nerve due to *antidromic activation* of *motor neurons.* When compared with the maximal *amplitude* of the *M wave,* it is smaller (1 to 5% of the M wave) and has a variable configuration. Its *latency* is longer than the M wave and is variable. It can be evoked in many muscles of the upper and lower extremities, and the latency is longer with more distal sites of stimulation. Named "F" wave by Magladery and McDougal in 1950, because it was first recorded from foot muscles. Compare with the *H wave* and the *A wave.* One of the *late responses.*

facial neuropathy Clinical diagnosis of facial weakness or paralysis due to pathology affecting the seventh cranial nerve (facial nerve). Bell's palsy refers to a facial *neuropathy* due to inflammation of the facial nerve.

*__facilitation__ An increase in an electrically measured *response* following identical *stimuli.* Occurs in a variety of circumstances: 1) Improvement of neuromuscular transmission resulting in *activation* of previously inactive

*The items with asterisks have an illustration in Section II.

muscle fibers. May be identified in several ways: *Incrementing response*–a reproducible increase in the *amplitude* and area of successive *M waves* during *repetitive nerve stimulation. Postactivation* or *posttetanic facilitation*–Nerve stimulation studies performed within a few seconds after a brief period (2 to 60 s) of nerve stimulation producing *tetanus* or after a strong voluntary *contraction* may show changes in the configuration of the M wave(s) compared to the results of identical studies of the rested muscle as follows: a) *repair of the decrement*–A diminution of the *decrementing response* with slow rates (2 to 5 *Hz*) of repetitive nerve stimulation; b) increment after exercise– an increase in the amplitude and area of the M wave elicited by a single supramaximal stimulus. Distinguish from *pseudofacilitation*, which occurs in normal individuals in response to repetitive nerve stimulation at high rates (20 to 50 Hz) or after strong volitional contraction. It probably reflects a reduction in the *temporal dispersion* of the summation of a constant number of *muscle fiber action potentials* and is characterized by an increase in the amplitude of the successive M waves with a corresponding decrease in their *duration.* There is no net change in the area of the negative *phase* of successive M waves. 2) An increase in the amplitude of the *motor evoked potential* as a result of background muscle activation.

far-field A region of electrical *potential* where the isopotential *voltage* lines associated with a current source change slowly over a short distance. Some use the term far-field potential to designate a potential that does not change in *latency*, *amplitude*, or polarity over infinite distances; alternative designations include "boundary potential" and "junctional potential." The terms *near-field* and *far-field* are arbitrary designations as there are no agreed-upon criteria defining where the near-field ends and the far-field begins. Compare with *near-field.*

fasciculation The random, spontaneous twitching of a group of muscle fibers belonging to a single *motor unit.* The twitch may produce movement of the overlying skin (if in limb or trunk muscles) or mucous membrane (if in the tongue). If the motor unit is sufficiently large, an associated joint movement may be observed. The electric activity associated with the twitch is termed a *fasciculation potential.* See also *myokymia.* Historically, the term *fibrillation* was used incorrectly to describe fine twitching of muscle fibers visible through the skin or mucous membranes. This usage is no longer accepted.

*__fasciculation potential__ The electric activity associated with a *fasciculation* which has the configuration of a *motor unit activation potential* but which occurs spontaneously. Most commonly occur sporadically and are termed "single fasciculation potentials." Occasionally the potentials occur as a *grouped discharge* and are termed a "brief *repetitive discharge.*" The repetitive firing of adjacent fasciculation potentials, when numerous, may produce an undulating movement of muscle (see *myokymia*). Use of the terms *benign fasciculation* and *malignant fasciculation* is discouraged. Instead, the configuration of the *potentials*, peak-to-peak *amplitude*, *duration*, number of *phases*, stability of configuration, and *frequency* of occurrence, should be specified.

fatigue A state of depressed responsiveness resulting from activity. Muscle fatigue is a reduction in *contraction* force following repeated voluntary contraction or electric stimulation.

fiber density 1) Anatomically, a measure of the number of muscle or nerve fibers per unit area. 2) In *single fiber electromyography*, the mean number of *muscle fiber action potentials* fulfilling *amplitude* and *rise time* criteria belonging to one *motor unit* within the recording area of a *single fiber needle electrode* encountered during a systematic search in a weakly, voluntarily contracting muscle. See also *single fiber electromyography*, *single fiber needle electrode.*

fibrillation The spontaneous *contractions* of individual muscle fibers which are not visible through the skin. This term has been used loosely in *electromyography* for the preferred term, *fibrillation potential.*

*The items with asterisks have an illustration in Section II.

*__fibrillation potential__ The *action potential* of a single muscle fiber occurring spontaneously or after movement of a *needle electrode.* Usually fires at a constant rate. Consists of biphasic or triphasic *spikes* of short *duration* (usually less than 5 ms) with an initial positive *phase* and a peak-to-peak *amplitude* of less than 1 mV. May also have a biphasic, initially negative phase when recorded at the site of initiation. It has an associated high-pitched regular sound described as "rain on a tin roof." In addition to this classic form, *positive sharp waves* may also be recorded from fibrillating muscle fibers when the potential arises from an area immediately adjacent to the needle electrode.

firing pattern Qualitative and quantitative descriptions of the sequence of *discharge* of electric *waveforms* recorded from muscle or nerve.

firing rate *Frequency* of repetition of a *potential.* The relationship of the frequency to the occurrence of other potentials and the force of muscle *contraction* may be described. See also *discharge frequency.*

flexor reflex A *reflex* produced by a noxious cutaneous *stimulus,* or a train of electrical stimuli, that activates the flexor muscles of a limb and thus acts to withdraw it from the stimulus. In humans, it is well-characterized only in the lower extremity.

frequency Number of complete cycles of a repetitive *waveform* in 1 second. Measured in *hertz* (*Hz*) or *cycles per second* (*cps* or c/s).

frequency analysis Determination of the range of *frequencies* composing a *waveform*, with a measurement of the absolute or relative *amplitude* of each component frequency.

full interference pattern See *interference pattern.*

*__full wave rectified EMG__ The absolute value of a *raw EMG* signal. Involves inverting all the *waveforms* below the *isopotential line* and displaying them with opposite polarity above the line. A technique used to analyze *kinesiologic EMG* signals.

functional refractory period See *refractory period.*

G1, G2 Abbreviation for *grid 1* and *grid 2.*

generator In *volume conduction* theory, the source of electrical activity, such as an *action potential.* See *far-field* and *near-field.*

"giant" motor unit action potential Use of term discouraged. Refers to a *motor unit action potential* with a peak-to-peak *amplitude* and *duration* much greater than the range found in corresponding muscles in normal subjects of similar age. Quantitative measurements of amplitude and duration are preferable.

giant somatosensory evoked potential Enlarged *somatosensory evoked potentials* seen as a characteristic of cortical *reflex myoclonus* and reflecting cortical hyperexcitability.

grid 1 Synonymous with *G1*, *input terminal 1 (E-1)*, or *active or exploring electrode*. Use of the term *G1* is discouraged. See *recording electrode*.

grid 2 Synonymous with *G2*, *input terminal 2 (E-2)*, or *reference electrode*. Use of the term *Grid 2* is discouraged. See *recording electrode*.

ground electrode A connection from the patient to earth. Used as a common return for an electric circuit and as an arbitrary zero *potential* reference point.

grouped discharge Term used historically to describe three phenomena: (1) irregular, voluntary grouping of *motor unit action potentials* as seen in a tremulous muscular *contraction,* (2) involuntary grouping of motor unit action potentials as seen in *myokymia,* (3) general term to describe repeated firing of motor unit action potentials. See preferred term, *repetitive discharge.*

Guillain-Barré syndrome Eponym for *acute inflammatory neuropathy.* Also referred to as Landry-Guillain-Barré syndrome or Landry-Guillain-Barré-Strohl syndrome.

H reflex Abbreviation for Hoffmann reflex. See *H wave.*

H response See preferred term, *H wave.*

*__H wave__ A *compound muscle action potential* with a consistent *latency* recorded from muscles after stimulation of the nerve. Regularly found in adults only in a limited group of physiologic extensors, particularly the calf muscles. Compared to the *M wave* of the same muscle, has a longer latency and thus is one of the *late responses* (see *A* and *F wave*).

*The items with asterisks have an illustration in Section II.

Most reliably elicited with a *stimulus* of long *duration* (500 to 1000 μs). A stimulus intensity sufficient to elicit a maximal amplitude M wave reduces or abolishes the H wave. Thought to be due to a spinal *reflex,* with electric stimulation of afferent fibers in the *mixed nerve* and *activation* of motor neurons to the muscle mainly through a monosynaptic connection in the spinal cord. The latency is longer with more distal sites of stimulation. The reflex and *wave* are named in honor of Hoffman's description (1918). Compare the *F wave* and *A wave.*

habituation Decrease in size of a *reflex motor response* to an afferent *stimulus* when the latter is repeated, especially at regular and recurring short intervals.

hemifacial spasm Clinical condition characterized by frequent, repetitive, unilateral, involuntary *contractions* of the facial muscles. Electrodiagnostic studies demonstrate brief *discharges* of groups of *motor unit action potentials* occurring simultaneously in several facial muscles. Occasionally high *frequency* discharges occur.

hertz (Hz) Unit of *frequency.* Synonymous with *cycles per second.*

Hoffmann reflex See *H wave.*

hyperekplexia Clinical condition characterized by exaggerated *startle reflexes.* Startle reflexes can be exaggerated by being more extreme than expected (larger *amplitude* or more widespread) or by lack of normal *habituation* to repeated similar *stimuli.* Can be either genetic or acquired.

hyperpolarization A change in the existing membrane *potential* to a more negative value.

hypertonia See *tone.*

hypotonia See *tone.*

Hz Abbreviation for *hertz.*

impulse blocking See *blocking.*

inching A *nerve conduction study* technique consisting of applying stimuli at multiple short distance increments along the course of a nerve. This technique is used to localize an area of focal slowing or *conduction block.*

incomplete activation *Motor unit action potentials* firing, on requested maximal effort, in decreased numbers at their normal physiological rates, within the basal firing range of 5 to 10 *Hz.* Causes include *upper motor neuron syndrome,* pain on muscle *contraction,* hysteria/conversion reaction, and malingering. Contrast with *reduced recruitment.*

increased insertion activity See *insertion activity.*

increment after exercise See *facilitation.*

incremental response See preferred term, *incrementing response.*

*__incrementing response__ A reproducible increase in *amplitude* and/or area of successive *M waves* to *repetitive nerve stimulation.* The rate of stimulation and the number of *stimuli* should be specified. Commonly seen in two situations. First, in normal subjects the configuration of the M wave may change in response to repetitive nerve stimulation so that the amplitude progressively increases as the *duration* decreases, leaving the area of the M wave unchanged. This phenomenon is termed *pseudofacilitation.* Second, in *neuromuscular transmission disorders,* the configuration of the M wave may change with repetitive nerve stimulation so that the amplitude and the area of the M wave progressively increase. This phenomenon is termed *facilitation.* Contrast with *decrementing response.*

indifferent electrode Synonymous with *reference electrode.* Use of term discouraged. See *recording electrode.*

infraclavicular plexus Segments of the *brachial plexus* inferior to the divisions; includes the three cords and the terminal peripheral nerves. This clinically descriptive term is based on the fact that the clavicle overlies the divisions of the brachial plexus when the arm is in the anatomic position next to the body.

inhibitory postsynaptic potential (IPSP) A local graded *hyperpolarization* of a neuron in response to *activation* at a synapse by a nerve terminal. Contrast with *excitatory postsynaptic potential.*

injury potential 1) The *potential* difference between a normal region of the surface of a

*The items with asterisks have an illustration in Section II.

nerve or muscle and a membrane region that has been injured; also called a "demarcation," or "killed end" potential. Approximates the potential across the membrane because the injured surface has nearly the same potential as the interior of the cell. 2) In *electrodiagnostic medicine,* the term is also used to refer to the electrical activity associated with *needle electrode* insertion into muscle. See preferred terms *fibrillation potential, insertion activity,* and *positive sharp wave.*

input terminal 1 The input terminal of a differential amplifier at which negativity, relative to the other input terminal, produces an upward deflection. Synonymous with *active* or *exploring electrode, E-1* or less preferred term, *grid 1.* See *recording electrode.*

input terminal 2 The input of a differential amplifier at which negativity, relative to the other input terminal, produces a downward deflection. Synonymous with *reference electrode, E-2* or less preferred term, *grid 2.* See *recording electrode.*

*__insertion activity__ Electric activity caused by insertion or movement of a *needle electrode* within a muscle. The amount of the activity may be described as normal, reduced, or increased (prolonged), with a description of the *waveform* and repetition rate. See also *fibrillation potential* and *positive sharp wave.*

integrated EMG Mathematical integration of the *full wave rectified EMG* signal. Reflects the cumulative EMG activity of a muscle over time. See also *linear envelope EMG.*

interdischarge interval Time between consecutive *discharges* of the same *potential.* Measurements should be made between the corresponding points on each *waveform.*

interference Unwanted electric activity recorded from the surrounding environment.

*__interference pattern__ Electric activity recorded from a muscle with a *needle electrode* during maximal voluntary effort. A full interference pattern implies that no individual *motor unit action potentials* can be clearly identified. A reduced interference pattern (intermediate pattern) is one in which some of the individual motor unit action potentials may be identified while others cannot due to superimposition of *waveforms.* The term *discrete activity* is used to describe the electric activity recorded when each of several different motor unit action potentials can be identified in an ongoing recording due to limited superimposition of waveforms. The term *single unit pattern* is used to describe a single motor unit action potential, firing at a rapid rate (should be specified) during maximum voluntary effort. The force of *contraction* associated with the interference pattern should be specified. See also *early recruitment, recruitment pattern, reduced recruitment pattern.*

interference pattern analysis Quantitative analysis of the *interference pattern.* This can be done either in the *frequency* domain using fast Fourier transformation (FFT) or in the time domain. Can be done using a fixed load (e.g., 2 kg), at a given proportional strength (e.g., 30% of maximum), or at random strengths. The following are measured in the time domain: a) the number of *turns* per second and b) the *amplitude,* defined as the mean amplitude between peaks.

intermediate interference pattern See *interference pattern.*

international 10–20 system A system of *electrode* placement on the scalp in which electrodes are placed either 10% or 20% of the total distance on a line on the skull between the nasion and inion in the sagittal plane and between the right and left preauricular points in the coronal plane.

interpeak interval Difference between the peak *latencies* of two components of a *waveform.*

interpotential interval Time between two different *potentials.* Measurement should be made between the corresponding parts of each *waveform.*

intraoperative monitoring The use of electrophysiological stimulating and recording techniques in an operating room setting. The term is usually applied to techniques which are used to detect injury to nervous tissue during surgery or to guide the surgical procedure.

involuntary activity *Motor unit action potentials* that are not under volitional control. The

*The items with asterisks have an illustration in Section II.

condition under which they occur should be described, e.g., spontaneous or *reflex* potentials. If elicited by a *stimulus*, its nature should be described. Contrast with *spontaneous activity.*

IPSP Abbreviation for *inhibitory postsynaptic potential.*

irregular potential See preferred term, *serrated action potential.*

isoelectric line In electrophysiologic recording, the display of zero *potential* difference between the two input terminals of the recording apparatus. See *baseline.*

iterative discharge See preferred term, *repetitive discharge.*

jiggle Shape variability of *motor unit action potentials* recorded with a conventional *EMG needle electrode.* A small amount occurs normally. In conditions of disturbed neuromuscular transmission, including early reinnervation and myasthenic disorders, the variability can be sufficiently large to be easily detectable by eye. Quantitative methods for estimating this variability are not yet widely available.

*__jitter__ The variability of consecutive *discharges* of the *interpotential interval* between two *muscle fiber action potentials* belonging to the same *motor unit.* Usually expressed quantitatively as the mean value of the difference between the interpotential intervals of successive discharges (the *mean consecutive difference, MCD*). Under certain conditions, it is expressed as the mean value of the difference between interpotential intervals arranged in the order of decreasing interdischarge intervals (the *mean sorted difference, MSD*). See *single fiber electromyography.*

Jolly Test A technique named for Friedrich Jolly, who applied an electric current to excite a *motor nerve* repetitively while recording the force of muscle *contraction.* Use of the term is discouraged. Inappropriately used to describe the technique of *repetitive nerve stimulation.*

kinematics Technique for description of body movement without regard to the underlying forces. See *kinesiologic EMG.*

kinesiologic EMG The muscle electrical activity recorded during movement. Gives information about the timing of muscle activity and its relative intensity. Either *surface electrodes* or intramuscular fine *wire electrodes* are used. Synonymous with *dynamic EMG.*

kinesiology The study of movement. See *kinesiologic EMG.*

kinetics The internal and external forces affecting the moving body. See *kinesiologic EMG.*

late component (of a motor unit action potential) See preferred term, *satellite potential.*

late response A general term used to describe an *evoked potential* in motor *nerve conduction studies* having a longer *latency* than the *M wave.* Examples include *A wave, F wave,* and *H wave.*

latency Interval between a *stimulus* and a *response.* The *onset latency* is the interval between the onset of a stimulus and the onset of the *evoked potential.* The *peak latency* is the interval between the onset of a stimulus and a specified peak of the evoked potential.

latency of activation The time required for an electric *stimulus* to depolarize a nerve fiber (or bundle of fibers as in a nerve trunk) beyond *threshold* and to initiate an *action potential* in the fiber(s). This time is usually of the order of 0.1 ms or less. An equivalent term, now rarely used, is the "utilization time."

latent period See preferred term, *latency.*

linear envelope EMG Moving average of the *full wave rectified EMG.* Obtained by low pass filtering the full wave rectified EMG. See also *integrated EMG.*

linked potential See preferred term, *satellite potential.*

lipoatrophy Pathologic loss of subcutaneous fat and connective tissues overlying muscle which mimics the clinical appearance of atrophy of the underlying muscle.

long-latency reflex A *reflex* with many synapses (polysynaptic) or a long pathway (long-loop) so that the time to its occurrence is greater than the time of occurrence of *short-latency reflexes.* See also *long-loop reflex.*

long-loop reflex A *reflex* thought to have a circuit that extends above the spinal segment of the sensory input and motor output.

*The items with asterisks have an illustration in Section II.

May involve the cerebral cortex. Should be differentiated from reflexes arising from stimulation and recording within a single or adjacent spinal segments (i.e., a segmental reflex). See also *long-latency reflex.*

M response See preferred term, *M wave.*

*__M wave__ A *compound muscle action potential* evoked from a muscle by an electric *stimulus* to its *motor nerve.* By convention, the M wave elicited by a supramaximal *stimulus* is used for motor *nerve conduction studies.* Ideally, the *recording electrodes* should be placed so that the initial deflection of the *evoked potential* from the *baseline* is negative. Common measurements include *latency*, *amplitude*, and *duration.* Also referred to as the *motor response.* Normally, the configuration is biphasic and stable with repeated stimuli at slow rates (1 to 5 *Hz*). See *repetitive nerve stimulation.*

macro motor unit action potential The average electric activity of that part of an anatomic *motor unit* that is within the recording range of a *macro-EMG electrode.* Characterized by consistent appearance when the small recording surface of the macro-EMG electrode is positioned to record *action potentials* from one muscle fiber. The following characteristics can be specified quantitatively: (1) maximal peak-to-peak *amplitude*, (2) area contained under the *waveform*, (3) number of *phases.*

macro MUAP Abbreviation for *macro motor unit action potential.*

*__macroelectromyography (macro-EMG)__ General term referring to the technique and conditions that approximate recording of all *muscle fiber action potentials* arising from the same *motor unit.* See *macro motor unit action potential.*

macro-EMG Abbreviation for *macroelectromyography.*

*__macro-EMG needle electrode__ A modified *single fiber electromyography* electrode insulated to within 15 mm from the tip and with a small recording surface (25 μm in diameter) 7.5 mm from the tip.

malignant fasciculation Used to describe large, polyphasic *fasciculation potentials* firing at a slow rate. This pattern has been seen in progressive *motor neuron disease*, but the relationship is not exclusive. Use of this term is discouraged. See *fasciculation potential.*

maximal stimulus See *stimulus.*

maximum conduction velocity See *conduction velocity.*

MCD Abbreviation for *mean consecutive difference*. See *jitter*.

mean consecutive difference (MCD) See *jitter.*

mean sorted difference (MSD) See *jitter.*

membrane instability Tendency of a cell membrane to depolarize spontaneously in response to mechanical irritation or following voluntary *activation.* May be used to describe the occurrence of spontaneous single *muscle fiber action potentials* such as *fibrillation potentials* during *needle electrode* examination.

MEP Abbreviation for *motor evoked potential.*

MEPP Abbreviation for *miniature end-plate potential.*

microneurography The technique of recording peripheral nerve *action potentials* in humans by means of intraneural *electrodes.*

miniature end-plate potential (MEPP) The postsynaptic muscle fiber *potentials* produced through the spontaneous release of individual acetylcholine quanta from the presynaptic axon terminal. As recorded with *monopolar* or *concentric needle electrodes* inserted in the end-plate region, MEPPs are monophasic, negative, short *duration* (less than 5 ms), and generally less than 20 μV in *amplitude.*

minimum conduction velocity The *nerve conduction velocity* measured from slowly conducting nerve fibers. Special techniques are needed to produce this measurement in *motor* or *sensory nerves.*

mixed nerve A nerve composed of both motor and sensory axons.

MNCV Abbreviation for *motor nerve conduction velocity*. See *conduction velocity*.

mononeuritis multiplex A disorder characterized by axonal injury and/or *demyelination* affecting nerve fibers in multiple nerves (multiple *mononeuropathies*). Usually occurs in an asymmetric anatomic

*The items with asterisks have an illustration in Section II.

distribution and in a temporal sequence which is not patterned or symmetric.

mononeuropathy multiplex A disorder characterized by axonal injury and/or *demyelination* affecting nerve fibers exclusively along the course of one named nerve.

monophasic action potential An *action potential* with the *waveform* entirely on one side of the *baseline.*

monophasic end-plate activity See *end-plate activity (monophasic).*

*__monopolar needle electrode__ A solid wire *electrode* coated with Teflon™, except at the tip. Despite the term *monopolar*, a separate surface or subcutaneous reference electrode is required for recording electric signals. May also be used as a *cathode* in *nerve conduction studies* with another electrode serving as an *anode.*

motor evoked potential (MEP) A compound muscle action potential produced by either *transcranial magnetic stimulation* or *transcranial electrical stimulation*.

motor latency Interval between the onset of a *stimulus* and the onset of the resultant *compound muscle action potential (M wave).* The term may be qualified, as proximal motor latency or *distal motor latency*, depending on the relative position of the stimulus.

motor nerve A nerve containing axons which innervate extrafusal and intrafusal muscle fibers. These nerves also contain sensory afferent fibers from muscle and other deep structures.

motor nerve conduction velocity (MNCV) The speed of propagation of *action potentials* along a *motor nerve.* See *conduction velocity.*

motor neuron disease A clinical condition characterized by degeneration of *motor nerve* cells in the brain, brain stem, and spinal cord. The location of degeneration determines the clinical presentation. Primary lateral sclerosis occurs when degeneration affects mainly corticospinal tract motor fibers. Spinal muscular atrophy occurs when degeneration affects lower motor neurons. Amyotrophic lateral sclerosis occurs when degeneration affects both corticospinal tracts and lower motor neurons.

motor point The site over a muscle where its *contraction* may be elicited by a minimal intensity short *duration* electric *stimulus.*

motor response 1) The *compound muscle action potential* (*M wave*) recorded over a muscle in response to stimulation of the nerve to the muscle. 2) The muscle twitch or *contraction* elicited by stimulation of the nerve to a muscle. 3) The muscle twitch elicited by the *muscle stretch reflex.*

motor unit The anatomic element consisting of an anterior horn cell, its axon, the neuromuscular junctions, and all of the muscle fibers innervated by the axon.

*__motor unit action potential (MUAP)__ The *compound action potential* of a single *motor unit* whose muscle fibers lie within the recording range of an *electrode.* With voluntary muscle *contraction*, it is characterized by its consistent appearance and relationship to the force of the contraction. The following measures may be specified, quantitatively if possible, after the *recording electrode* is placed randomly within the muscle:

1. Configuration
   a. *Amplitude*, peak-to-peak (μV or mV).
   b. *Duration*, total (ms).
   c. Number of *phases* (monophasic, biphasic, triphasic, tetraphasic, polyphasic).
   d. Polarity of each phase (negative, positive).
   e. Number of *turns.*
   f. Variation of shape (*jiggle*), if any, with consecutive *discharges.*
   g. Presence of satellite (linked) potentials, if any.
   h. *Spike* duration, including satellites.
2. *Recruitment* characteristics
   a. *Threshold* of *activation* (first recruited, low threshold, high threshold).
   b. *Onset frequency.*
   c. *Recruitment frequency* (*Hz*) *or recruitment interval* (ms) of individual potentials.

Descriptive terms implying diagnostic significance are not recommended, e.g., *myopathic*, *neuropathic*, *regeneration*, *nascent*,

*The items with asterisks have an illustration in Section II.

giant, *BSAP*, and *BSAPP*. See *polyphasic action potential*, *serrated action potential*.

motor unit fraction See *scanning EMG*.

motor unit number counting See the preferred term *motor unit number estimate (MUNE)*.

motor unit number estimate (MUNE) A quantitative technique for determining the number of functioning *motor units* in a muscle. A variety of methods, including *spike*-triggered *averaging*, incremental *motor nerve* stimulation, *F-wave* measurement, or a Poisson statistical technique can be used. Synonyms can include *motor unit number estimation* and *motor unit number estimating*.

motor unit number estimating (MUNE) See *motor unit number estimate (MUNE)*.

motor unit number estimation (MUNE) See *motor unit number estimate (MUNE)*.

motor unit potential (MUP) See synonym, *motor unit action potential*.

motor unit territory The area of a muscle cross-section within which the muscle fibers belonging to an individual *motor unit* are distributed.

movement artifact See *artifact*.

movement-related cortical potential Electroencephalogram activity associated with (before and after) a voluntary movement. There are several components including the *Bereitschaftspotential* before the movement and the motor potential at about the time of the movement. See also *Bereitschaftspotential*.

MSD Abbreviation for *mean sorted difference*. See *jitter*.

MUAP Abbreviation for *motor unit action potential*.

multi MUP analysis A *template matching*, *decomposition EMG* method used for *MUAP* analysis.

multielectrode See *multilead electrode*.

multifocal motor neuropathy A disease characterized by selective focal block of *motor nerve* conduction in multiple nerves. Motor *nerve conduction studies* may permit identification and localization of the segments of nerve affected by the underlying pathology.

multilead electrode Three or more insulated wires inserted through apertures in a common metal cannula with their bared tips flush with the cannula's outer circumference. The arrangement of the bare tips relative to the axis of the cannula and the distance between each tip should be specified. See *electrode*.

multiple discharge Four or more *motor unit action potentials* of the same form and nearly the same *amplitude* occurring consistently in the same relationship to one another and generated by the same axon. See *double* and *triple discharge*.

multiplet See *multiple discharge*.

MUNE Abbreviation *for motor unit number estimate*, *motor unit number estimation*, and *motor unit number estimating*.

MUP Abbreviation for *motor unit potential*. See preferred term, *motor unit action potential*.

muscle action potential Term commonly used to refer to a *compound muscle action potential*.

muscle atrophy Decrease in size of a muscle that may be due to disease of nerve or muscle, or to disuse.

muscle cramp An involuntary, painful muscle *contraction* associated with electrical activity. *Cramp discharges* are most common, but other types of *repetitive discharges* can also be seen.

muscle fiber action potential *Action potential* recorded from a single muscle fiber.

muscle fiber conduction velocity The speed of propagation of a single *muscle fiber action potential*, usually expressed as meters per second. Usually less than most *nerve conduction velocities*, varies with the rate of *discharge* of the muscle fiber, and requires special techniques for measurement.

muscle hypertrophy Increase in the size of a muscle due to an increase in the size of the muscle fibers or replacement or displacement of muscle fibers by other tissues. The latter is also referred to by the term *pseudohypertrophy*, because the muscle is enlarged but weak. Muscle fibers increase in size as a physiologic *response* to repetitive and forceful voluntary *contraction* or as a pathologic response to involuntary electric activity in a muscle, for example, *myotonic discharges* or *complex repetitive discharges*.

*The items with asterisks have an illustration in Section II.

muscle stretch reflex *Activation* of a muscle which follows stretch of the muscle, e.g., by percussion of a muscle tendon. See *stretch reflex, T wave.*

muscle tone See *tone.*

myasthenia gravis A disease characterized by muscle weakness which increases with repetitive muscle *activation.* Most commonly, an autoimmune disease caused by the presence of antibodies to the acetylcholine receptors at the neuromuscular junction.

myoclonus A quick jerk of a body part produced by a brief muscle *contraction* typically originating from activity in the central nervous system. Based on the anatomic location of the pathology, may be classified as spinal, segmental, brainstem, or cortical.

myoedema Focal muscle *contraction* produced by muscle percussion. Not associated with propagated electric activity. May be seen in hypothyroidism (myxedema) and chronic malnutrition.

myokymia Continuous quivering or undulating movement of surface and overlying skin and mucous membrane associated with spontaneous, *repetitive discharge* of *motor unit action potentials.* See *myokymic discharge, fasciculation,* and *fasciculation potential.*

*__myokymic discharge__ A form of *involuntary activity* in which *motor unit action potentials* fire repetitively and may be associated with clinical *myokymia.* Two firing patterns have been described: (1) Commonly, the *discharge* is a brief, repetitive firing of single motor unit action potentials for a short period (up to a few seconds) at a uniform rate (2 to 60 *Hz*) followed by a short period (up to a few seconds) of silence, with repetition of the same sequence for a particular potential at regular intervals. (2) Rarely, the potential recurs continuously at a fairly uniform *firing rate* (1 to 5 Hz). Myokymic discharges are a subclass of *grouped discharges* and *repetitive discharges.* See also *ephapse* and *ephaptic transmission.*

myopathic motor unit potential Low *amplitude,* short *duration,* polyphasic *motor unit action potentials.* Use of term discouraged. It incorrectly implies specific diagnostic significance of a motor unit action potential configuration. See *motor unit action potential.*

myopathic recruitment Used to describe an increase in the number and *firing rate* of *motor unit action potentials* compared with normal for the strength of muscle *contraction.* Use of term discouraged.

myopathy Disorder affecting the structure and/or function of muscle fibers. Etiologies include hereditary, congenital, mitochondrial, inflammatory, metabolic, infectious, neoplastic, vascular, and traumatic diseases. Most, but not all, of these disorders show abnormalities on needle *electromyography.*

myotonia Delayed relaxation of a muscle after voluntary *contraction* or percussion. Associated with propagated electric activity, such as *myotonic discharges, complex repetitive discharges,* or *neuromyotonic discharges.*

*__myotonic discharge__ *Repetitive discharge* which occurs at rates of 20 to 80 *Hz.* There are two types: 1) biphasic (positive-negative) *spike potentials* less than 5 ms in *duration* resembling *fibrillation potentials.* 2) *positive waves* of 5 to 20 ms duration resembling *positive sharp waves.* Both potential forms are recorded after *needle electrode* insertion, after voluntary muscle *contraction* or after muscle percussion, and are due to independent, repetitive discharges of single muscle fibers. The *amplitude* and *frequency* of the potentials must both wax and wane. This change produces a characteristic musical sound in the audio output of the *electromyograph* due to the corresponding change in pitch, which has been likened to the sound of a "dive bomber." Contrast with *waning discharge.*

myotonic potential See preferred term, *myotonic discharge.*

NAP Abbreviation for *nerve action potential*. See *compound nerve action potential.*

nascent motor unit potential From the Latin nascens, "to be born." Refers to very low *amplitude,* short *duration,* highly polyphasic *motor unit action potentials* observed during early states of reinnervation. Use of term is discouraged, as it incorrectly implies

*The items with asterisks have an illustration in Section II.

diagnostic significance of a motor unit action potential configuration. See *motor unit action potential.*

NCS Abbreviation for *nerve conduction study*.

NCV Abbreviation for *nerve conduction velocity*. See *conduction velocity*.

near-field A region of electrical activity where the isopotential *voltage* lines associated with a current source change rapidly over a short distance. The terms near-field and *far-field* are arbitrary designations, as there are no agreed-upon criteria defining where the near-field ends and the far-field begins. Compare with *far-field.*

*__needle electrode__ An electrical device used for recording or stimulating that is positioned near the tissue of interest by penetration of the skin. See specific electrodes: *bifilar (bipolar) needle recording electrode*, *concentric needle electrode*, *macro-EMG needle electrode*, *monopolar needle electrode*, *multilead electrode*, *single fiber needle electrode*, and *stimulating electrode.*

nerve action potential (NAP) Strictly defined, refers to an *action potential* recorded from a single nerve fiber. The term is commonly used to refer to the *compound nerve action potential.* See *compound nerve action potential.*

nerve conduction study (NCS) Recording and analysis of electric *waveforms* of biologic origin elicited in response to electric or physiologic *stimuli.* The waveforms are *compound sensory nerve action potentials*, *compound muscle action potentials*, or *mixed nerve action potentials.* The compound muscle action potentials are generally referred to by letters which have historical origin: *M wave*, *F wave*, *H wave*, *T wave*, *A wave*, and *R1*, *R2 waves.* It is possible under standardized conditions to establish normal ranges for *amplitude*, *duration*, and *latency* of the waveforms and to calculate the maximum *conduction velocity* of *sensory* and *motor nerves.* The term generally refers to studies of waveforms generated in the peripheral nervous system, whereas *evoked potential studies* refers to studies of waveforms generated in both the peripheral and central nervous systems. Synonymous with *electroneurography.*

nerve conduction velocity (NCV) The speed of *action potential* propagation along a nerve fiber or nerve trunk. Generally assumed to refer to the maximum speed of propagation unless otherwise specified. See *conduction velocity.*

nerve fiber action potential *Action potential* recorded from a single axon.

nerve potential Equivalent to *nerve action potential.* Also commonly, but inaccurately, used to refer to the biphasic form of *end-plate activity* observed during *needle electrode* examination of muscle. The latter use is incorrect, because muscle fibers, not nerve fibers, are the source of these *potentials.*

nerve trunk action potential See preferred term, *compound nerve action potential.*

neurapraxia Clinical term used to describe the reversible motor and sensory deficits produced by focal compressive or traction lesions of large myelinated nerve fibers. It is due to *conduction block*, most often caused by focal *demyelination*, but, when very short lived, presumably caused by focal ischemia. The axon is not injured at the lesion site. Compare with *axonotmesis* and *neurotmesis.*

neuromuscular transmission disorder Clinical disorder associated with pathology affecting the structure and function of the neuromuscular junction and interfering with synaptic transmission at that site. Specific diseases include *myasthenia gravis*, Lambert-Eaton myasthenic syndrome, and botulism.

neuromyopathy Clinical disorder associated with pathology affecting both nerve and muscle fibers.

neuromyotonia Clinical syndrome of continuous muscle fiber activity manifested as continuous muscle rippling and stiffness. It may be associated with delayed relaxation following voluntary muscle *contraction.* The accompanying electric activity may be intermittent or continuous. Terms used to describe related clinical syndromes are continuous muscle fiber activity syndrome, Isaac syndrome, Isaac-Merton syndrome, quantal squander syndrome, generalized

*The items with asterisks have an illustration in Section II.

myokymia, pseudomyotonia, normocalcemic *tetany* and neurotonia. Distinguish from *myotonia.*

*__neuromyotonic discharge__ Bursts of *motor unit action potentials* that fire at high rates (150 to 300 *Hz*) for a few seconds, often starting or stopping abruptly. The *amplitude* of the *waveforms* typically wanes. *Discharges* may occur spontaneously or be initiated by *needle electrode* movement, voluntary effort, ischemia, or percussion of a nerve. The activity originates in motor axons. Distinguish from *myotonic discharges* and *complex repetitive discharges.* One type of electrical activity recorded in patients who have clinical *neuromyotonia.*

neuropathic motor unit potential Abnormally high-*amplitude*, long-*duration*, polyphasic *motor unit action potential.* Use of term discouraged. Incorrectly implies a specific diagnostic significance of a motor unit action potential configuration. See *motor unit action potential.*

neuropathic recruitment A *recruitment* pattern characterized by a decreased number of *motor unit action potentials* firing at a rapid rate. Use of term discouraged. See preferred terms, *reduced interference pattern*, *discrete activity*, *single unit pattern.*

neuropathy Disorder of the peripheral nerves. May be classified by the anatomical structure of the nerve most affected by the disease: cell body (neuronopathy), the axon (axonopathy), or the myelin sheath (demyelinating neuropathy). May selectively affect *motor* or *sensory nerves* or both simultaneously. The etiology may be hereditary, metabolic, inflammatory, toxic, or unknown.

neurotmesis Partial or complete nerve severance including the axons, associated myelin sheaths, and supporting connective tissues, resulting in *axonal degeneration* distal to the injury site. Compare with *axonotmesis*, *neurapraxia.*

neurotonic discharges Repetitive *motor unit action potentials* recorded from intramuscular *electrodes* during *intraoperative monitoring.* Thought to arise from irritation or injury of nerves supplying the muscle from which the recording is made.

noise Electric activity not related to the signal of interest. In *electrodiagnostic medicine*, *waveforms* generated by *electrodes*, cables, amplifier, or storage media and unrelated to potentials of biologic origin. The term has also been used loosely to refer to one form of *end-plate activity.*

onset frequency The lowest stable *firing rate* for a single *motor unit action potential* that can be voluntarily maintained by a subject.

order of activation The sequence of appearance of different *motor unit action potentials* with increasing strength of voluntary *contraction.* See *recruitment.*

orthodromic Propagation of a nerve impulse in the same direction as physiologic conduction; e.g. conduction along *motor nerve* fibers towards the muscle and conduction along *sensory nerve* fibers towards the spinal cord. Contrast with *antidromic.*

paired stimuli Two consecutive stimuli delivered in a time-locked fashion. The time interval between the two stimuli and the intensity of each *stimulus* can be varied but should be specified. The first stimulus is called the *conditioning stimulus* and the second stimulus is the *test stimulus.* The conditioning stimulus may modify tissue *excitability*, which is then evaluated by the *response* to the test stimulus.

parasite potential See preferred term, *satellite potential.*

peak latency Interval between the onset of a *stimulus* and a specified peak of an evoked *waveform.*

peroneal neuropathy at the knee A *mononeuropathy* involving the common peroneal nerve as it passes around the head of the fibula. The presumed mechanism is compression of the nerve against the fibula. See also *crossed leg palsy.*

phase That portion of a *waveform* between the departure from, and the return to, the *baseline.*

plexopathy Axonal and/or demyelinating disorder affecting the nerve fibers exclusive

*The items with asterisks have an illustration in Section II.

to the cervical, brachial, lumbar, or sacral rearrangement of spinal nerve roots into peripheral nerves.

polarization The presence of an electric *potential* difference usually across an excitable cell membrane.

polyneuropathy Axonal and/or demyelinating disorder affecting nerve fibers, usually in a symmetrical fashion. The distal segments of the longer nerves in the lower extremities are usually the most severely affected. May be classified as sensory, motor, or sensorimotor depending on the function of nerve fibers affected.

polyphasic action potential An *action potential* with four or more *baseline* crossings, producing five or more *phases.* See *phase.* Contrast with *serrated action potential.*

polyradiculoneuropathy See *radiculopathy.*

*__positive sharp wave__ A biphasic, positive then negative *action potential* of a single muscle fiber. It is initiated by *needle electrode* movement (insertional or unsustained positive sharp wave) or occurs spontaneously. Typically *discharge* in a uniform, regular pattern at a rate of 1 to 50 *Hz;* the discharge *frequency* may decrease slightly just before cessation of discharge. The initial positive deflection is rapid (<1 ms), its *duration* is usually less than 5 ms, and the *amplitude* is up to 1 mV. The negative *phase* is of low amplitude, and its duration is 10 to 100 ms. A sequence of positive sharp waves is commonly referred to as a *train of positive sharp waves.* Assumed to be recorded from a damaged area of a muscle fiber. This configuration may result from the position of the needle electrode which is believed to be adjacent to the depolarized segment of a muscle fiber injured by the electrode. Note that the positive sharp *waveform* is not specific for muscle fiber damage. May occur in association with *fibrillation potentials* and are thought by some to be equivalent discharges. *Motor unit action potentials* and potentials in *myotonic discharges* may have the configuration of positive sharp waves.

positive wave Loosely defined, the term refers to a *positive sharp wave.* See preferred term, *positive sharp wave.*

postactivation The period following voluntary *activation* of a nerve or muscle. Contrast with *posttetanic.*

*__postactivation depression__ A reduction in the *amplitude* and area of the *M wave(s)* in response to a single *stimulus* or *train of stimuli* which occurs within a few minutes following a 10 to 60 second strong voluntary *contraction. Postactivation exhaustion* refers to the cellular mechanisms responsible for the observed phenomenon of postactivation depression. Also used to describe reduction of the M wave following a *tetanus*, which should more logically be termed *posttetanic depression.*

postactivation exhaustion A reduction in the safety factor (margin) of neuromuscular transmission after sustained *activation* at the neuromuscular junction. The changes in the configuration of the *M wave* due to postactivation exhaustion are referred to as *postactivation depression.*

postactivation facilitation See *facilitation.*

postactivation potentiation An increase in the force of *contraction* (mechanical *response*) after a strong voluntary contraction. Contrast *postactivation facilitation.*

posttetanic The period following *tetanus.* Contrast with *postactivation.*

posttetanic depression See *postactivation depression.*

posttetanic facilitation See *facilitation, potentiation.*

posttetanic potentiation 1) The incrementing mechanical *response* of muscle during and after *repetitive nerve stimulation.* 2) In central nervous system physiology, enhancement of *excitability* or *reflex* outflow of neuronal systems following a long period of high-*frequency* stimulation. See *facilitation, potentiation.*

potential 1) A difference in charges, measurable in volts, that exists between two points. Most biologically produced potentials arise from the difference in charge between two sides of a cell membrane. 2) A term for a physiologically recorded *waveform.*

*The items with asterisks have an illustration in Section II.

potentiation Physiologically, the enhancement of a *response.* The convention used in this glossary is to use the term *potentiation* to describe the incrementing mechanical response of muscle elicited by *repetitive nerve stimulation,* e.g., *posttetanic potentiation,* whereas the term *facilitation* is used to describe the incrementing electrical response elicited by repetitive nerve stimulation, e.g., postactivation facilitation.

prolonged insertion activity See *insertion activity.*

propagation velocity of a muscle fiber The speed of transmission of a *muscle fiber action potential.*

pseudodecrement An *artifact* produced by movement of the *stimulating* or *recording electrodes* during *repetitive nerve stimulation.* The *amplitude* and area of the *M wave* can vary in a way that resembles a *decrementing response*; however, the *responses* are generally irregular and not reproducible.

*__pseudofacilitation__ See *facilitation.*

pseudohypertrophy See *muscle hypertrophy.*

pseudomyotonic discharge Formerly used to describe *complex repetitive discharges.* Use of term discouraged.

pseudopolyphasic action potential Use of term discouraged. See preferred term, *serrated action potential.*

QEMG Abbreviation for *quantitative electromyography*.

QSART Abbreviation for *quantitative sudomotor axon reflex test*.

QST Abbreviation for *quantitative sensory testing*.

quantitative electromyography (QEMG) A systematic method for measuring the recordings made by an intramuscular *needle electrode.* Measurements include *motor unit action potential* characteristics such as *amplitude, duration,* and *phases,* or *interference pattern* characteristics. See *turns and amplitude analysis.*

quantitative sensory testing (QST) An instrumented method for measuring cutaneous sensation.

quantitative sudomotor axon reflex test (QSART) Test of post-ganglionic sympathetic sudomotor axons function by measuring sweat output following *activation* of axon terminals by local application of acetylcholine. *Antidromic* transmission of the impulse from the nerve terminals reaches a branch point, then travels *orthodromically* to release acetylcholine from the nerve terminals, inducing a sweating *response.* In small fiber *polyneuropathy,* the response may be reduced or absent. In painful *neuropathies,* and in *reflex* sympathetic dystrophy, the response may be excessive and persistent or reduced.

R1, R2 waves See *blink responses.*

radiculopathy Axonal and/or demyelinating disorder affecting the nerve fibers exclusive to one spinal nerve root or spinal nerve. May affect the anterior (motor) or posterior (sensory) spinal nerve roots, or both, at one spinal cord segment level. The resulting clinical syndrome may include pain, sensory loss, parethesia, weakness, *fasciculations,* and *muscle atrophy.* If more than one spinal root is involved, the term *polyradiculopathy* may be used as a descriptor.

raster A method for display of a free-running sweep in *electromyography.* Sweeps are off-set vertically so that each successive sweep is displayed below the one preceding it.

raw EMG Unprocessed *EMG* signal recorded with surface or intramuscular *electrodes.*

reciprocal inhibition Inhibition of a motor neuron pool secondary to the *activation* of the motor neuron pool of its antagonist. It is one of several important spinal mechanisms of motor control that help to make movements smoother and utilize less energy. There are multiple mechanisms for reciprocal inhibition, including one mediated by the Ia inhibitory interneuron that activates Ia afferents and disynaptically inhibits the muscle that is antagonist to the source of the Ia afferents.

recording electrode Device used to record electric *potential* difference. All electric recordings require two *electrodes.* The electrode close to the source of the activity to be recorded is called the *active* or *exploring electrode,* and the other recording electrode is

*The items with asterisks have an illustration in Section II.

called the *reference electrode.* Active electrode is synonymous with *input terminal 1,* or *E-1* (or older terms whose use is discouraged, *grid 1,* and *G1*). Reference electrode is synonymous with *input terminal 2,* or *E-2* (or older terms whose use is discouraged *grid 2,* and *G2).* In some recordings it is not certain which electrode is closer to the source of the biologic activity, e.g., recording with a *bifilar needle recording electrode,* or when attempting to define *far-field* potentials. In this situation, it is convenient to refer to one electrode as input electrode 1, or E-1, and the other as input electrode 2, or E-2. By present convention, a potential difference that is negative at the active electrode (input terminal 1, E-1) relative to the reference electrode (input terminal 2, E-2) causes an upward deflection on the display screen. The term "monopolar recording" is not recommended, because all recordings require two electrodes; however, it is commonly used to describe the use of one type of intramuscular *needle electrode.* A similar combination of needle electrodes has been used to record nerve activity and also has been referred to as "monopolar recording."

recruitment The successive *activation* of the same and additional *motor units* with increasing strength of voluntary muscle *contraction.* See *motor unit action potential.*

recruitment frequency *Firing rate* of a *motor unit action potential (MUAP)* when a different MUAP first appears during gradually increasing voluntary muscle *contraction.* This parameter is essential to assessment of *recruitment pattern.*

recruitment interval The *interdischarge interval* between two consecutive *discharges* of a *motor unit action potential (MUAP)* when a different MUAP first appears during gradually increasing voluntary muscle *contraction.* The reciprocal of the recruitment interval is the *recruitment frequency.* See also *interdischarge interval.*

* **recruitment pattern** A qualitative and/or quantitative description of the sequence of appearance of *motor unit action potentials* during increasing voluntary muscle *contraction.* The *recruitment frequency* and *recruitment interval* are two quantitative measures commonly used. See *interference pattern, early recruitment, reduced recruitment* for qualitative terms commonly used.

recurrent inhibition Decreased probability of firing of a motor neuron pool mediated by Renshaw cells. Renshaw cells are activated by recurrent collaterals from the axons of alpha-motoneurons. Such inhibition influences the same cells that originate the excitatory impulses and their neighbors.

reduced insertion activity See *insertion activity.*

reduced interference pattern See *interference pattern.*

reduced recruitment pattern A descriptive term for the *interference pattern* when the number of *motor units* available to generate a muscle *contraction* are reduced. One cause for a *reduced interference pattern.* See *interference pattern, recruitment pattern.*

reference electrode See *recording electrode.*

reflex A stereotyped *motor response* elicited by a sensory *stimulus.* Its anatomic pathway consists of an afferent, *sensory* input to the central nervous system, at least one synaptic connection, and an efferent output to an effector organ. The response is most commonly *motor,* but reflexes involving autonomic effector organs also occur. Examples include the *H reflex* and the sudomotor reflex. See *H wave, quantitative sudomotor axon reflex test.*

refractory period General term for the time following an *action potential* when an excitable membrane cannot be stimulated to produce another action potential. The *absolute refractory period* is the time following an action potential during which no *stimulus,* however strong, evokes a further *response.* The *relative refractory period* is the time following an action potential during which a stimulus must be abnormally large to evoke a second response. The *functional refractory period* is the time following an action potential during which a second action potential cannot yet excite the given region.

refractory period of transmission Interval following an *action potential* during which

*The items with asterisks have an illustration in Section II.

a nerve cannot conduct a second one. Distinguish from *refractory period*, as commonly used, which deals with the ability of a *stimulus* to produce an action potential.

regeneration motor unit potential Use of term discouraged. See *motor unit action potential.*

relative refractory period See *refractory period.*

*__repair of the decrement__ See *facilitation.*

repetitive discharge General term for the recurrence of an *action potential* with the same or nearly identical form. May refer to recurring potentials recorded in muscle at rest, during voluntary *contraction*, or in response to a single nerve *stimulus.* See *double discharge, triple discharge, multiple discharge, myokymic discharge, complex repetitive discharge, neuromyotonic discharge,* and *cramp discharge.*

*__repetitive nerve stimulation__ The technique of repeated *supramaximal stimulation* of a nerve while recording successive *M waves* from a muscle innervated by the nerve. Commonly used to assess the integrity of neuromuscular transmission. The number of *stimuli* and the *frequency* of stimulation should be specified. *Activation procedures* performed as a part of the test should be specified, e.g. sustained voluntary *contraction* or contraction induced by nerve stimulation. If the test includes an activation procedure, the time elapsed after its completion should also be specified. For a description of specific patterns of *responses*, see *incrementing response, decrementing response, facilitation,* and *postactivation depression.*

repolarization A return in membrane *potential* from a depolarized state toward the normal resting level.

residual latency The calculated time difference between the measured *distal latency* of a *motor nerve* and the expected latency, calculated by dividing the distance between the stimulating *cathode* and the active *recording electrode* by the maximum *conduction velocity* measured in a more proximal segment of the nerve. It is due in part to neuromuscular transmission time and to slowing of conduction velocity in terminal axons due to decreasing diameter and the presence of unmyelinated segments.

response An activity elicited by a *stimulus.*

resting membrane potential *Voltage* across the membrane of an excitable cell in the absence of a *stimulus.* See *polarization.*

rheobase See strength-duration curve.

rigidity A velocity independent increase in *muscle tone* and stiffness with full range of joint motion as interpreted by the clinical examiner from the physical examination. Often associated with simultaneous low-grade *contraction* of agonist and antagonist muscles. Like muscle *spasticity*, the involuntary *motor unit action potential* activity increases with activity or passive stretch. Does not seem to change with the velocity of stretch, and, on passive stretch, the increased tone has a "lead pipe" or constant quality. It is a cardinal feature of central nervous system disorders affecting the basal ganglia. Contrast with *spasticity.*

rise time The interval from the onset of a polarity change of a *potential* to its peak. The method of measurement should be specified.

*__satellite potential__ A small *action potential* separated from the main *motor unit action potential* by an isoelectric interval which fires in a time-locked relationship to the main action potential. It usually follows, but may precede, the main action potential. Less preferred terms include *late component, parasite potential, linked potential,* and *coupled discharge.*

scanning EMG A technique by which a *needle electrode* is advanced in defined steps through muscle while a separate *SFEMG* electrode is used to trigger both the display sweep and the advancement device. Provides temporal and spatial information about the *motor unit.* Distinct maxima in the recorded activity are considered to be generated by muscle fibers innervated by a common branch of an axon. These groups of fibers form a *motor unit fraction.*

sea shell sound (sea shell roar or noise) Use of term discouraged. See *end-plate activity, monophasic.*

sensory latency Interval between the onset of a *stimulus* and the onset of the negative

*The items with asterisks have an illustration in Section II.

deflection of the *compound sensory nerve action potential.* This term has been used loosely to refer to the *sensory peak latency.* May be qualified as proximal sensory latency or distal sensory latency, depending on the relative position of the stimulus.

sensory nerve A nerve containing only sensory fibers, composed mainly of axons innervating cutaneous receptors.

sensory nerve action potential (SNAP) See *compound sensory nerve action potential.*

sensory nerve conduction velocity The speed of propagation of *action potentials* along a *sensory nerve.*

sensory peak latency Interval between the onset of a *stimulus* and the peak of the negative *phase* of the *compound sensory nerve action potential.* Contrast with *sensory latency.*

sensory potential Synonym for the more precise term, *compound sensory nerve action potential.*

sensory response Synonym for the more precise term, *compound sensory nerve action potential.*

SEP Abbreviation for *somatosensory evoked potential*.

serrated action potential A *waveform* with several changes in direction *(turns)* which do not cross the *baseline.* Most often used to describe a *motor unit action potential.* The term is preferred to *complex motor unit action potential* and *pseudopolyphasic action potential.* See also *turn* and *polyphasic action potential.*

SFEMG Abbreviation for *single fiber electromyography*.

shock artifact See *artifact.*

short-latency reflex A *reflex* with one (monosynaptic) or few (oligosynaptic) synapses. Used in contrast to *long-latency reflex.*

*__short-latency somatosensory evoked potential (SSEP)__ That portion of the *waveforms* of a *somatosensory evoked potential* normally occurring within 25 ms after stimulation of the median nerve in the upper extremity at the wrist, 40 ms after stimulation of the common peroneal nerve in the lower extremity at the knee, and 50 ms after stimulation of the posterior tibial nerve at the ankle.

signal averager A digital device that improves the signal-to-*noise* ratio of an electrophysiological recording by adding successive time-locked recordings to preceding traces and computing the average value of each data point. A signal acquired by this method is described as an "averaged" *waveform.*

silent period A pause in the electric activity of a muscle that may be produced by many different *stimuli.* Stimuli used commonly in clinical neurophysiology include rapid unloading of a muscle, electrical stimulation of a peripheral nerve, or *transcranial magnetic stimulation.*

*__single fiber electromyography (SFEMG)__ The technique and conditions that permit recording of single *muscle fiber action potentials.* See *single fiber needle electrode, blocking,* and *jitter.*

single fiber EMG See *single fiber electromyography*.

single fiber needle electrode A *needle electrode* with a small recording surface (usually 25 μm in diameter) which permits the recording of single *muscle fiber action potentials* between the recording surface and the cannula. See *single fiber electromyo-graphy.*

single unit pattern See *interference pattern.*

SNAP Abbreviation for sensory nerve action potential. See compound sensory nerve action potential.

snap, crackle, and pop A benign type of *increased insertion activity* that follows, after a very brief period of electrical silence, the normal *insertion activity* generated by *needle electrode* movement. It consists of trains of *potentials* that vary in length, however, they can persist for a few seconds. Each train consists of a series of up to 10 or more potentials in which the individual components fire at irregular intervals. The potentials consistently vary in *amplitude, duration,* and configuration. Individual potentials may be mono-, bi-, tri-, or multiphasic in appearance; they often have a positive *waveform.* The variation on sequential

*The items with asterisks have an illustration in Section II.

firings produces a distinctive sound, hence the name. See most often in those with mesomorphic builds, especially young adult males. Found most often in lower extremity muscles, especially the medial gastrocnemius.

somatosensory evoked potential (SEP) Electric *waveforms* of biologic origin elicited by electric stimulation or physiologic *activation* of peripheral *sensory nerves* and recorded from peripheral and central nervous system structures. Normally is a complex *waveform* with several components which are specified by polarity and average *peak latency.* The polarity and latency of individual components depend upon 1) subject variables, such as age, gender, and body habitus, 2) *stimulus* characteristics, such as intensity and rate of stimulation, and 3) recording parameters, such as amplifier time constants, *electrode* placement, and electrode combinations. See *short-latency somatosensory evoked potentials.*

spasticity A velocity-dependent increase in *muscle tone* due to a disease process that interrupts the suprasegmental tracts to the alpha motor neurons, gamma motor neurons, or segmental spinal neurons. May be elicited and interpreted by the clinical examiner during the physical examination by brisk passive movement of a limb at the joint. Almost uniformly accompanied by hyperreflexia, a Babinski sign, and other signs of upper motor neuron pathology, including clonus and the clasp-knife phenomenon. The clasp-knife phenomenon is a rapid decrease of tone following a period of increased tone during passive rotation of the joint. The pathophysiology is not certain and may include more than dysfunction of the corticospinal tracts.

spike 1) A short-lived (1 to 3 ms), all-or-none *waveform* that arises when an excitable membrane reaches *threshold.* 2) The electric record of a nerve or muscle impulse.

spinal evoked potential Electric *waveforms* of biologic origin recorded over the spine in response to electric stimulation or physiologic *activation* of peripheral sensory fibers. See preferred term, *somatosensory evoked potential.*

spontaneous activity Electric activity recorded from muscle at rest after *insertion activity* has subsided and when there is not voluntary *contraction* or an external *stimulus.* Compare with *involuntary activity.*

SSEP Abbreviation for *short-latency somatosensory evoked potential*.

staircase phenomenon The progressive increase in muscle *contraction* force observed in response to continued low rates of muscle *activation.*

startle (reflex) A *response* produced by an unanticipated *stimulus* that leads to alerting and protective movements such as eye lid closure and flexion of the limbs. Auditory stimuli are typically most efficacious.

stiffman syndrome A disorder characterized by continuous muscle *contraction* giving rise to severe stiffness. Axial muscles are typically affected most severely. Patients have difficulty moving. Walking and voluntary movements are slow. Sensory stimulation often induces severe spasms. *Electromyography* demonstrates continuous activity of *motor unit action potentials* in a normal pattern that cannot be silenced by contraction of the antagonist muscle. It is often associated with circulating antibodies to glutamic acid decarboxylase (GAD), and the resulting deficiency of GABA may play a role in its pathophysiology. Since women are affected in equal or greater numbers than men, the term *stiff-person syndrome* may be preferable.

stiffperson syndrome Synonym for *stiffman syndrome.*

stigmatic electrode A term of historic interest. Used by Sherrington for *active* or *exploring electrode.*

stimulated SFEMG See preferred term *stimulation SFEMG.*

stimulating electrode Device used to deliver electric current. All electric stimulation requires two *electrodes;* the negative terminal is termed the *cathode,* and the positive terminal is the *anode.* By convention, the stimulating electrodes are called *bipolar* if

they are encased or attached together and are called *monopolar* if they are not. Electric stimulation for *nerve conduction studies* generally requires application of the cathode in the vicinity of the neural tissue to produce *depolarization.*

stimulation single fiber electromyography (stimulation SFEMG) Use of electrical stimulation instead of voluntary *activation* of *motor units* for the analysis of *single fiber electromyography.* The method is used in patients who are unable to produce a steady voluntary muscle *contraction.* The stimulation can be delivered to intramuscular axons, nerve trunks, or muscle fibers.

stimulus Any external agent, state or change that is capable of influencing the activity of a cell, tissue, or organism. In clinical *nerve conduction studies,* an electric stimulus is applied to a nerve. It may be described in absolute terms or with respect to the *evoked potential* of the nerve or muscle. In absolute terms, it is defined by a *duration* (ms), a *waveform* (square, exponential, linear, etc.), and a strength or intensity measured in *voltage* (V) or current (mA). With respect to the evoked potential, the stimulus may be graded as *subthreshold, threshold, submaximal, maximal,* or *supramaximal.* A threshold stimulus is one just sufficient to produce a detectable *response.* Stimuli less than the threshold stimulus are termed subthreshold. The maximal stimulus is the stimulus intensity after which a further increase in intensity causes no increase in the *amplitude* of the evoked potential. Stimuli of intensity below this level but above threshold are submaximal. Stimuli of intensity greater than the maximal stimulus are termed supramaximal. Ordinarily, supramaximal stimuli are used for nerve conduction studies. By convention, an electric stimulus of approximately 20% greater voltage/current than required for the maximal stimulus is used for supramaximal stimulation. The *frequency,* number and duration of a series of stimuli should be specified.

stimulus artifact See *artifact.*

strength-duration curve Graphic presentation of the relationship between the intensity (Y axis) and various *durations* (X axis) of the *threshold* electric *stimulus* of a nerve or muscle. The *rheobase* is the intensity of an electric current of infinite duration necessary to produce a minimal *action potential.* The *chronaxie* is the time required for an electric current twice the rheobase to elicit the first visible action potential. Measurement of the strength-duration curve is not a common practice in modern *electrodiagnostic medicine.*

stretch reflex A *reflex* produced by passive lengthening of a muscle. The principal sensory *stimuli* come from group la and group II muscle spindle afferents. It consists of several *phases.* The earliest component is monosynaptic and is also called the myotatic reflex, or tendon reflex. There are also long-*latency* stretch reflexes. See also *muscle stretch reflex, T wave.*

submaximal stimulus See *stimulus.*

subnormal period A time interval that immediately follows the *supernormal period* of nerve which is characterized by reduced *excitability* compared to the resting state. Its *duration* is variable and is related to the *refractory period.*

subthreshold stimulus See *stimulus.*

supernormal period A time interval that immediately follows the *refractory period* which corresponds to a very brief period of partial *depolarization.* It is characterized by increased nerve *excitability* and is followed by the *subnormal period.*

supraclavicular plexus That portion of the *brachial plexus* which is located superior to the clavicle.

supraclavicular stimulation Percutaneous nerve stimulation at the base of the neck which activates the upper, middle, and/or lower trunks of the *brachial plexus.* This term is preferred to *Erb's point stimulation.*

supramaximal stimulus See *stimulus.*

surface electrode Conducting device for stimulating or recording placed on the skin surface. The material (metal, fabric, etc.), configuration (disk, ring, etc.), size, and separation should be specified. See *electrode (ground, recording, stimulating).*

*sympathetic skin response** Electrical *potential* resulting from electrodermal activity in sweat glands in response to both direct and *reflex* peripheral or sympathetic trunk stimulation of autonomic activity.

synkinesis Involuntary movement made by muscles distant from those activated voluntarily. It is commonly seen during recovery after *facial neuropathy.* It is due to aberrant reinnervation and/or *ephaptic transmission.*

*T wave** A *compound muscle action potential* evoked from a muscle by rapid stretch of its tendon, as part of the *muscle stretch reflex.*

tardy ulnar palsy A type of *mononeuropathy* involving the ulnar nerve at the elbow. The nerve becomes compressed or entrapped due to deformity of the elbow from a previous injury. See also *cubital tunnel syndrome* and *ulnar neuropathy at the elbow.*

template matching An automated method used in *quantitative electromyography* for selecting *motor unit action potentials* for measurement by extracting only *potentials* which resemble an initially identified potential.

temporal dispersion Relative desynchronization of components of a *compound muscle action potential* due to different rates of conduction of each synchronously evoked component from the stimulation point to the *recording electrode.* It may be due to normal variability in individual axon *conduction velocities*, especially when assessed over a long nerve segment, or to disorders that affect myelination of nerve fibers.

terminal latency Synonymous with preferred term, *distal latency.* See *motor latency* and *sensory latency.*

TES Abbreviation for *transcranial electrical stimulation*.

test stimulus See *paired stimuli.*

tetanic contraction The *contraction* produced in a muscle through repetitive maximal direct or indirect stimulation at a sufficiently high *frequency* to produce a smooth summation of successive maximum twitches. The term may also be applied to maximum voluntary contractions in which the firing frequencies of most or all of the component *motor units* are sufficiently high that successive twitches of individual motor units fuse smoothly. Their combined tensions produce a steady, smooth, maximum contraction of the whole muscle.

tetanus 1) The continuous *contraction* of muscle caused by repetitive stimulation or *discharge* of nerve or muscle. Contrast with *tetany.* 2) A clinical disorder caused by circulating tetanus toxin. Signs and symptoms are caused by loss of inhibition in the central nervous system and are characterized by muscle spasms, hyperreflexia, seizures, respiratory spasms, and paralysis.

tetany A clinical syndrome manifested by muscle twitching, cramps, and carpal and pedal spasm. These clinical signs are manifestations of peripheral and central nervous system nerve irritability from several causes. In these conditions, *repetitive discharges* (*double discharge*, *triple discharge*, *multiple discharge*) occur frequently with voluntary *activation* of *motor unit action potentials* or may appear as *spontaneous activity.* This activity is enhanced by systemic alkalosis or local ischemia.

tetraphasic action potential *Action potential* with three *baseline* crossings, producing four *phases.*

thermography A technique for measuring infrared emission from portions of the body surface. The degree of emission depends upon the amount of heat produced by the region that is studied. Its use in the diagnosis of *radiculopathy*, peripheral nerve injury, and disorders of the autonomic nervous system is controversial.

thermoregulatory sweat test A technique for assessing the integrity of the central and peripheral efferent sympathetic pathways. It consists of measuring the sweat distribution using an indicator powder while applying a controlled heat *stimulus* to raise body temperature sufficient to induce sweating.

thoracic outlet syndrome An *entrapment neuropathy* caused by compression of the neurovascular bundle as it traverses the shoulder region. Compression arises from acquired or congenital anatomic variations

*The items with asterisks have an illustration in Section II.

in the shoulder region. Symptoms can be related to compression of vascular structures, portions of the *brachial plexus*, or both.

threshold The level at which a clear and abrupt transition occurs from one state to another. The term is generally used to refer to the *voltage* level at which an *action potential* is initiated in a single axon or muscle fiber or a group of axons or muscle fibers.

threshold stimulus See *stimulus.*

tic Clinical term used to describe a sudden, brief, stereotyped, repetitive movement. When associated with vocalizations, may be the primary manifestation of Tourette syndrome.

tilt table test A test of autonomic function that is performed by measuring blood pressure and heart rate before and a specified period of time after head up tilt. The *duration* of recording and amount of tilt should be specified.

TMS Abbreviation for *transcranial magnetic stimulation.*

tone The resistance to passive stretch of a joint. When the resistance is high, this is called *hypertonia*, and when the resistance is low, this is called *hypotonia.* Two types of hypertonia are *rigidity* and *spasticity.*

train of positive sharp waves See *positive sharp wave.*

train of stimuli A group of *stimuli.* The *duration* of the group or the number of stimuli as well as the stimulation *frequency* should be specified.

transcranial electrical stimulation (TES) Stimulation of the cortex of the brain through the intact skull and scalp by means of a brief, very high *voltage*, electrical *stimulus. Activation* is more likely under the *anode* rather than the *cathode.* Because it is painful, this technique has largely been replaced by *transcranial magnetic stimulation.*

transcranial magnetic stimulation (TMS) Stimulation of the cortex of the brain through the intact skull and scalp by means of a brief magnetic *stimulus.* In practice, a brief pulse of strong current is passed through a coil of wire in order to produce a time-varying magnetic field in the order of 1 to 2 Tesla. Contrast with *transcranial electrical stimulation.*

tremor Rhythmical, involuntary oscillatory movement of a body part.

triphasic action potential *Action potential* with two *baseline* crossings, producing three *phases.*

triple discharge Three *motor unit action potentials* of the same form and nearly the same *amplitude*, occurring consistently in the same relationship to one another and generated by the same axon. The interval between the second and third *action potentials* often exceeds that between the first two, and both are usually in the range of 2 to 20 ms. See also *double discharge*, *multiple discharge.*

triplet Synonym for the preferred term, *triple discharge.*

turn Point of change in polarity of a *waveform* and the magnitude of the *voltage* change following the turning point. It is not necessary that the voltage change pass through the *baseline.* The minimal excursion required to constitute a change should be specified.

turns and amplitude analysis See preferred term, *interference pattern analysis.* Refers to the interference pattern analysis developed by Robin Willison in the 1960s.

ulnar neuropathy at the elbow A *mononeuropathy* involving the ulnar nerve in the region of the elbow. At least two sites of *entrapment neuropathy* have been recognized. The nerve may be entrapped or compressed as it passes through the retrocondylar groove at the elbow. Alternatively, it may be entrapped just distal to the elbow as it passes through the cubital tunnel. Anatomic variations or deformities of the elbow may contribute to nerve injury. See also *cubital tunnel syndrome* and *tardy ulnar palsy.*

unipolar needle electrode See synonym, *monopolar needle recording electrode.*

upper motor neuron syndrome A clinical condition resulting from a pathological process affecting descending motor pathways including the corticospinal tract or its cells of origin. Signs and symptoms include weakness, *spasticity*, and slow and clumsy motor performance. On *electromyographic* examination of weak muscles, there is slow *motor unit action potential* firing at maximal effort.

utilization time See preferred term, *latency of activation.*

Valsalva maneuver A forcible exhalation against the closed glottis which creates an abrupt, transient elevation of intrathoracic and intra-abdominal pressure. This results in a characteristic pattern of heart rate and blood pressure changes that can be used to quantify autonomic function. See *Valsalva ratio.*

Valsalva ratio The ratio of the fastest heart rate occurring at the end of a forced exhalation against a closed glottis (*phase* II of the *Valsalva maneuver*), and the slowest heart rate within 30 seconds after the forced exhalation (phase IV). In patients with disorders of the autonomic nervous system, the ratio may be reduced.

VEP Abbreviation for *visual evoked potential.*

VER Abbreviation for *visual evoked response.* See *visual evoked potential.*

*__visual evoked potential (VEP)__ Electric *waveforms* of biologic origin recorded over the cerebrum and elicited in response to visual stimuli. They are classified by *stimulus* rate as transient or steady state, and they can be further divided by stimulus presentation mode. The normal transient VEP to checkerboard pattern reversal or shift has a major positive occipital peak at about 100 ms (P100), often preceded by a negative peak (N75). The precise range of normal values for the *latency* and *amplitude* of P100 depends on several factors: 1) subject variables, such as age, gender, and visual acuity, 2) stimulus characteristics, such as type of stimulator, full-field or half-field stimulation, check size, contrast and luminescence, and 3) recording parameters, such as placement and combination of *recording electrodes.*

visual evoked response (VER) Synonym for preferred term, *visual evoked potential.*

volitional activity Synonymous with *voluntary activity.*

voltage *Potential* difference between two recording sites usually expressed in volts (V) or millivolts (mV).

volume conduction Spread of current from a *potential* source through a conducting medium, such as body tissues.

voluntary activity In *electromyography*, the electric activity recorded from a muscle with consciously controlled *contraction.* The effort made to contract the muscle may be specified relative to that of a corresponding normal muscle, e.g., minimal, moderate, or maximal. If the recording remains isoelectric during the attempted contraction and equipment malfunction has been excluded, it can be concluded that there is no voluntary activity.

wake-up test A procedure used most commonly in spinal surgery. During critical portions of an operation in which the spinal cord is at risk for injury, the level of general anesthesia is allowed to decrease to the point where the patient can respond to commands. The patient is then asked to move hands and feet, and a movement in response to commands indicates the spinal cord is intact. This procedure is used routinely in some centers. *Somatosensory evoked potential* monitoring has supplanted its use in most centers, except sometimes in the situation where they indicate the possibility of spinal cord injury.

wallerian degeneration Degeneration of the segment of an axon distal to nerve injury that destroys its continuity.

waning discharge A *repetitive discharge* that gradually decreases in *frequency* or *amplitude* before cessation. Contrast with *myotonic discharge.*

wave A transient change in *voltage* represented as a line of differing directions over time.

waveform The shape of a *wave.* The term is often used synonymously with *wave.*

wire electrodes Thin wires that are insulated except for the tips, which are bared. The wire is inserted into muscle with a needle. After the needle is withdrawn, the wire remains in place. Wire electrodes are superior to *surface electrodes* for *kinesiologic EMG*, because they are less affected by *cross talk* from adjacent muscles. They also record selectively from the muscle into which they are inserted.

*The items with asterisks have an illustration in Section II.

SECTION II: **ILLUSTRATIONS OF SELECTED WAVEFORMS**

Each illustration is accompanied by a complete explanation that is, in most cases, the same as that given in the alphabetic section. The definitions have been repeated in full with the illustrations so that readers do not need to refer back and forth between the illustration and definition.

The illustrations have been modified and adapted from materials submitted by AAEM members. The illustrations of the short-latency somatosensory evoked potentials were reprinted from the *Journal of Clinical Neurophysiology* (1978; 1:41–53) with permission of the journal editor and the authors.

COMPOUND SENSORY NERVE ACTION POTENTIALS

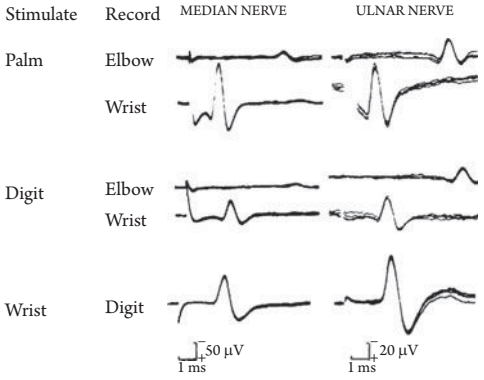

FIGURE 1 *Compound sensory nerve action potentials* recorded with surface *electrodes* in a normal subject. A *compound nerve action potential* is considered to have been evoked from afferent fibers if the recording electrodes detect activity only in a *sensory nerve* or in a sensory branch of a *mixed nerve*, or if the electric *stimulus* is applied to a sensory nerve or a dorsal nerve root, or an adequate stimulus is applied synchronously to sensory receptors. The *amplitude*, *latency*, *duration*, and configuration should be noted. Generally, the amplitude is measured as the maximum peak-to-peak *voltage* when there is an initial positive deflection or from *baseline*-to-peak when there is an intial negative deflection. The latency is measured as either the latency to the initial deflection or the peak latency to the negative peak, and the duration as the interval from the first deflection of the *waveform* from the baseline to its final return to the baseline. The compound sensory nerve action potential is also referred to by the less preferred terms *sensory response*, *sensory potential*, or *SNAP.*

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIAL (SSEP)

Median Nerve

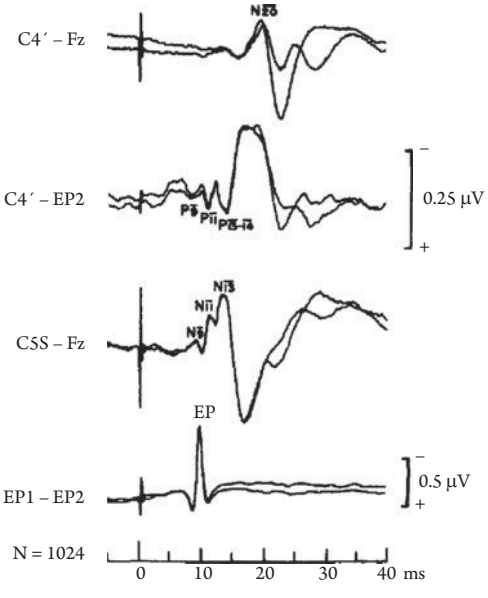

FIGURE 2 Short-latency somatosensory evoked potentials evoked by stimulation of the median nerve in a normal subject. Recordings were made from the scalp to a cephalic reference (C4′-Fz), the scalp to eontralateral Erb's point (C4′-EP2), cervical spine to a frontal reference (C5S-Fz), and ipsilateral Erb's point to the eontralateral Erb's point (EP1-EP2). Short-latency somatosensory evoked potentials elicited by electric stimulation of the median nerve at the wrist occur within 25 ms of the *stimulus* in normal subjects. Normal short-latency response components to median nerve stimulation are designated P9, P11, P13, P14, N20, and P23 in records taken between scalp and noncephalic *reference electrodes*, and N9, N11, N13, and N14 in cervical spine-scalp derivation. It should be emphasized that *potentials* having opposite polarity but similar *latency* in spine-scalp and scalp-noncephalic reference derivations do not necessarily have identical *generator* sources. The C4′ designation indicates that the recording scalp electrode was placed 2 cm posterior to the International 10–20 C4 electrode location.

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIAL (SSEP)

Common Peroneal Nerve

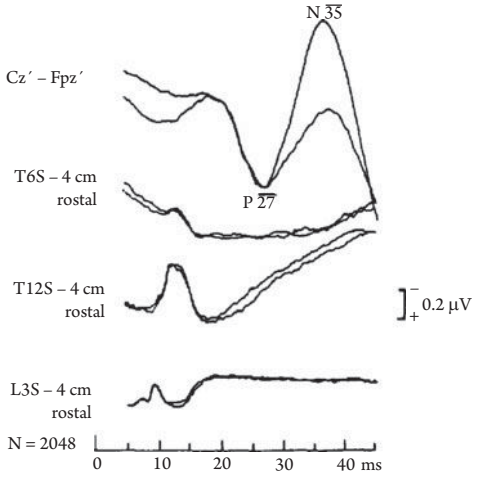

FIGURE 3 *Short-latency somatosensory evoked potentials* evoked by stimulation of the common peroneal nerve in a normal subject. Recordings were made from the scalp (Cz'-Fpz'), the mid-thoracic spine (T6S-4 cm rostral), the lower thoracic spine (T12S-4 cm rostral), and the lumbar spine (L3S-4 cm rostral). Short-latency somatosensory evoked potentials elicited by stimulation of the common peroneal nerve at the knee occur within 40 ms of the *stimulus* in normal subjects. It is suggested that individual response components be designated as follows: (1) Spine components: L3 and T12 spine potentials. (2) Scalp components: P27 and N35. The Cz' and Fpz' designations indicate that the recording scalp *electrode* was placed 2 cm posterior to the Intemationai 10–20 Cz and Fpz electrode locations.

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIAL (SSEP)

Posterior Tibial Nerve

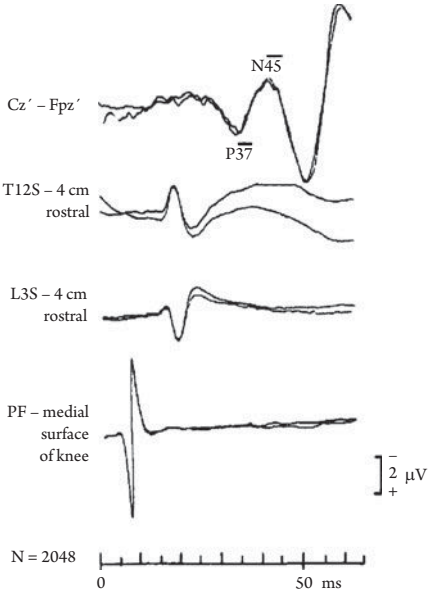

FIGURE 4 *Short-latency somatosensory evoked potentials* evoked by stimulation of the posterior libial nerve at the ankle. Recordings were made from the scalp (Cz'-Fpz'), The lower thoracic spine (T12S-4cm rostral), the lumbar spine (L3S-4cm rostral), and the popliteal fossa (PF-medial surface of knee). Short-latency somatosensory evoked potentials elicited by electric stimulation of the posterior tibial nerve at the ankle occur within 50 ms of the *stimulus* in normal subjects. It is suggested that individual response components be designated as follows: (1) Nerve trunk (tibial nerve) component in the popliteal fossa: PF potential. (2) Spine components: L3 and T12 potentials. (3) Scalp components: P37 and N45 waves. The Cz' and Fpz' designations indicate that the recording scalp *electrode* was placed 2 cm posterior to the *International 10–20 system* Cz and Fpz electrode locations.

VISUAL EVOKED POTENTIAL (VEP)

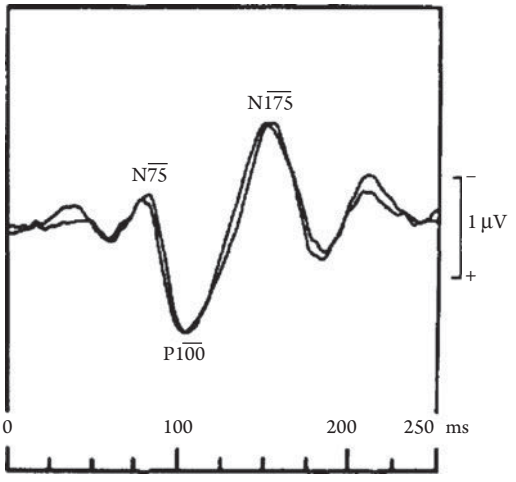

FIGURE 5 Normal occipital visual evoked potential to checker-board pattern reversal stimulation recorded between occipital (01) and vertex (Cz) electrodes showing N75, P100, and N175 peaks. Visual evoked potentials are electric waveforms of biologic origin recorded over the cerebrum and elicited by visual *stimuli.* VEPs are classified by stimulus rate as transient or steady state and can be further divided by stimulus presentation mode. The normal transient VEP to checkerboard pattern reversal or shift has a major positive occipital peak at about 100 ms (P100), often preceded by a negative peak (N75). The precise range of normal values for the *latency* and *amplitude* of P100 depends on several factors: (1) subject variables, such as age, gender, and visual acuity, (2) stimulus characteristics, such as type of stimulator, full-field or half-field stimulation, check size, contrast and luminescence, and (3) recording parameters, such as placement and combination of *recording electrodes.*

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP)

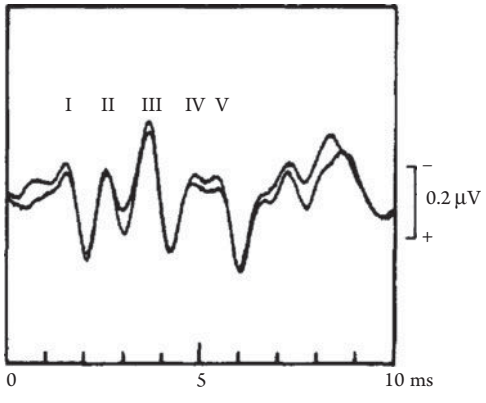

FIGURE 6 Normal brainstem auditory evoked potential to stimulation of the left ear, recorded between left ear (A1) and vertex (Cz) electrodes. Brainstem auditory evoked potentials are electric *waveforms* of biologic origin elicited in response to sound *stimuli.* The normal BAEP consists of a sequence of up to seven waves, designated I to VII, which occur during the first 10 ms after the onset of the stimulus and have positive polarity at the vertex of the head. In this recording, negativity in input terminal 1 or positivity in input terminal 2 causes an upward deflection.

M WAVE

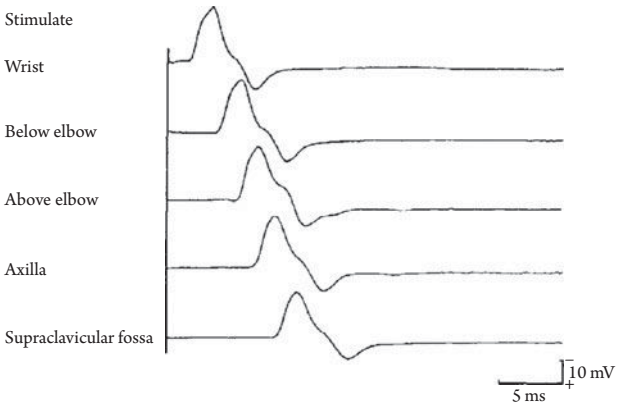

FIGURE 7 *M waves* recorded with surface *electrodes* over the abductor digiti quinti muscle elicited by electric stimulation of the ulnar nerve at several levels. The M wave is a *compound muscle action potential* evoked from a muscle by an electric *stimulus* to its *motor nerve.* By convention, the M wave elicited by a supramaximal stimulus is used for motor *nerve conduction studies.* Ideally, the *recording electrodes* should be placed so that the initial deflection of the *evoked potential* from the *baseline* is negative. The *latency*, commonly called the motor latency, is the time from stimulation (ms) to the onset of the first *phase* (positive or negative) of the M wave. The *amplitude* (mV) is the baseline-to-peak amplitude of the first negative phase, unless otherwise specified. The *duration* (ms) refers to the duration of the first negative phase, unless otherwise specified. Normally, the configuration of the M wave (usually biphasic) is quite stable with repeated stimuli at slow rates (1–5 *Hz*). See *repetitive nerve stimulation.*

F WAVE

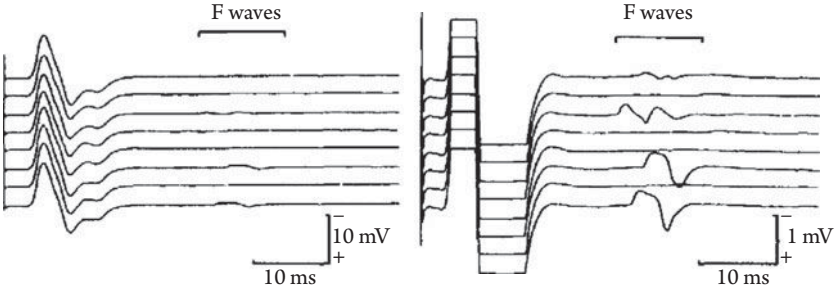

FIGURE 8 *F waves* recorded with *surface electrodes* over the abductor digiti quinti muscle elicited by electric stimulation of the ulnar nerve at the wrist with two different gain settings. The F wave is an *action potential* evoked intermittently from a muscle by a supramaximal *stimulus* to the nerve. Compared with the maximal *amplitude M wave* of the same muscle, the F wave has a smaller amplitude (1–5% of the M wave), variable configuration and a longer, more variable *latency.* The F wave can be found in many muscles of the upper and lower extremities, and the latency is longer with more distal sites of stimulation. The F wave is due to *antidromic activation* of motor neurons. It was named by Magladery and McDougal in 1950. Compare with the *H wave* and the *A wave.* One of the *late responses.*

H WAVE

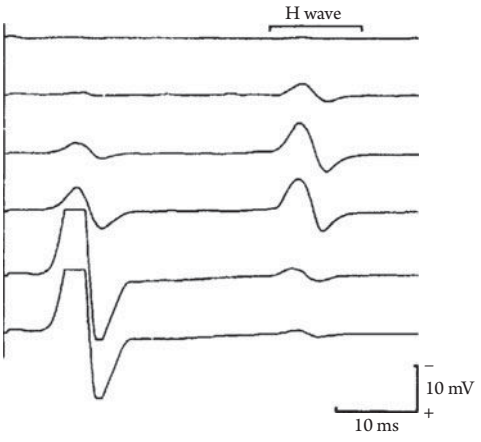

FIGURE 9 *H waves* recorded with *surface electrodes* over the soleus muscle elicited by electric stimulation of the posterior tibial nerve at the knee. The *stimulus* intensity was gradually increased (top tracing to bottom tracing). The H wave is a *compound muscle action potential* having a consistent *latency* evoked regularly, when present, from a muscle by an electric *stimulus* to the nerve. It is regularly found in adults only in a limited group of physiologic extensors, particularly the calf muscles. The H wave is most easily obtained with the *cathode* positioned proximal to the *anode.* Compared with the maximum *amplitude M wave* of the same muscle, the H wave has a smaller amplitude, a longer *latency*, and a lower optimal stimulus intensity. The latency is longer with more distal sites of stimulation. A stimulus intensity sufficient to elicit a maximal amplitude M wave reduces or abolishes the H wave. The H wave is thought to be due to a spinal *reflex*, the Hoffmann reflex, with electric stimulation of afferent fibers in the *mixed nerve* to the muscle and activation of motor neurons to the muscle mainly through a monosynaptic connection in the spinal cord. The reflex and wave are named in honor of Hoffmann's description in 1918. Compare with the *F wave.*

A WAVE

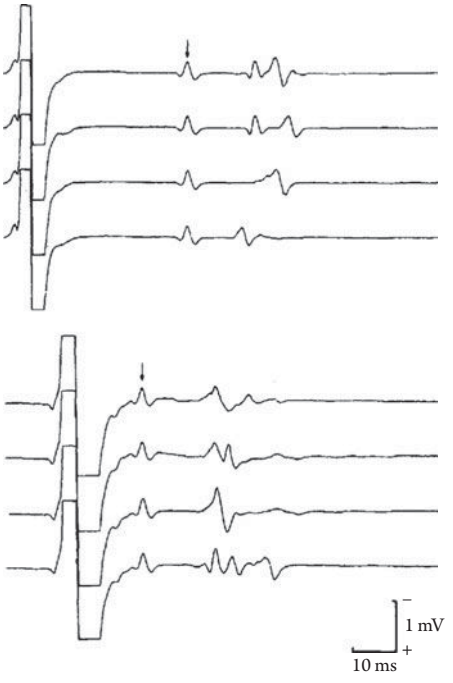

FIGURE 10 *A waves* (under arrow markers) recorded with surface *electrodes* over the abductor hallucis brevis elicited by electric stimulation of the posterior tibial nerve at the level of the ankle (top four traces) and at the level of the knee (bottom four traces). The A wave is a *compound muscle action potential* evoked consistently from a muscle by *submaximal stimuli* to the nerve and frequently abolished by *supramaximal stimuli.* The *amplitude* of the A wave is similar to that of the *F wave*, but the *latency* is more constant. The A wave usually occurs before the F wave, but it may occur afterwards. It is thought to be due to extra *discharges* in the nerve, *ephapses* between adjacent nerve fibers, or axonal branching. Compare with the *F wave.*

T WAVE

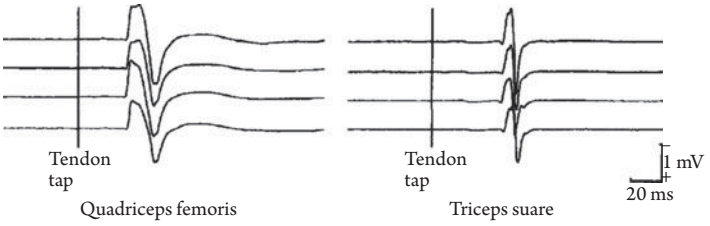

FIGURE 11 *T waves* produced by triggering a microswitch in the handle of a *reflex* hammer by striking the patellar tendon (quadriceps femoris) or the Achilles tendon (triceps surae). The T wave is a *compound muscle action potential* evoked by rapid stretch of a tendon, as part of the *muscle stretch reflex.*

BLINK RESPONSES

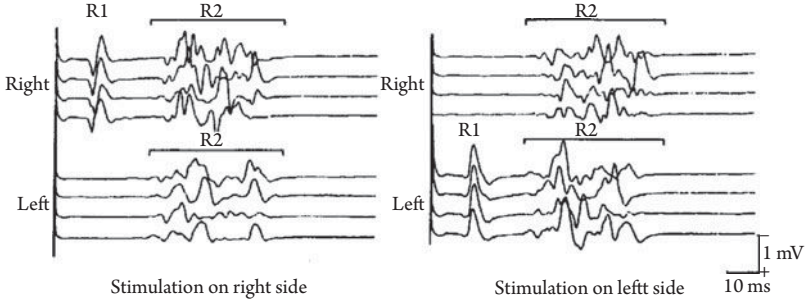

FIGURE 12 *Blink responses* recorded with surface *electrodes* over the right orbicularis oculi (upper tracings) and left orbicularis oculi (lower tracings) elicited by electric stimulation of the supraorbital nerve on the right (left tracings) and on the left (right tracings). The blink responses are *compound muscle action potentials* evoked from orbicularis oculi muscles as a result of brief electric or mechanical *stimuli* to the cutaneous area innervated by the supraorbital (or less commonly, the infraorbital) branch of the trigeminal nerve. Typically, there is an early compound muscle action potential (*R1 wave*) ipsilateral to the stimulation site with a *latency* of about 10 ms and a bilateral late compound muscle action potential (*R2 wave*) with a latency of approximately 30 ms. Generally, only the R2 wave is associated with a visible twitch of the orbicularis oculi. The configuration, *amplitude*, *duration*, and latency of the two components, along with the sites of recording and the sites of stimulation, should be specified. R1 and R2 waves are oligosynaptic and polysynaptic brainstem *reflexes*, respectively, together called the *blink reflex.* The afferent arc is provided by the sensory branches of the trigeminal nerve, and the efferent arc is provided by facial nerve motor fibers.

REPETITIVE NERVE STIMULATION
Normal Response

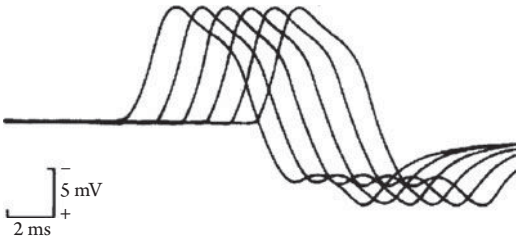

FIGURE 13 *Repetitive nerve stimulation* study in a normal subject. The successive *M waves* are displayed to the right. The M waves were recorded with *surface electrodes* over the hypothenar eminence (abductor digiti quinti) during ulnar nerve stimulation at a rate of 3 *Hz*. Note the configuration of the successive M waves is unchanged. Repetitive nerve stimulation is a technique of repeated *supramaximal stimulation* of a nerve while recording M waves from the muscle innervated by the nerve. It is commonly used to assess the integrity of neuromuscular transmission. The number of *stimuli* and the *frequency* of stimulation should be specified. *Activation procedures* performed prior to the test should be specified, e.g., sustained voluntary *contraction* or contraction induced by nerve stimulation. If the test was performed after an activation procedure, the time elapsed after it was completed should also be specified. The technique is commonly used to assess the integrity of neuromuscular transmission. For a description of specific patterns of responses, see *incrementing response*, *decrementing response*, *facilitation*, and *postactivation depression.*

REPETITIVE NERVE STIMULATION
Decrementing Response

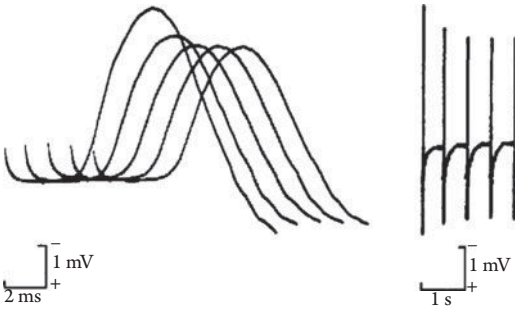

FIGURE 14 *Repetitive nerve stimulation* study in a patient with *myasthenia gravis*. Successive *M waves* were recorded with *surface electrodes* over the rested nasalis muscle during repetitive facial nerve stimulation at a rate of 2 *Hz*, with a display to permit measurement of the *amplitude* and *duration* of the negative *phase* (left) or peak-to-peak amplitude (right). A *decrementing response* is a reproducible decline in the amplitude and/or area of the M wave of successive responses to repetitive nerve stimulation. The rate of stimulation and the total number of *stimuli* should be specified. Decrementing responses with disorders of neuromuscular transmission are most reliably seen with slow rates (2 to 5 Hz) of nerve stimulation. A decrementing response with repetitive nerve stimulation commonly occurs in disorders of neuromuscular transmission, but can also be seen in some *polyneuropathies*, *myopathies*, and *motor neuron disease*. An *artifact* resembling a decrementing response can result from movement of the stimulating or *recording electrodes* during repetitive nerve stimulation (*pseudo-decrement*). Contrast with *incrementing response.*

REPETITIVE NERVE STIMULATION

Incrementing Response

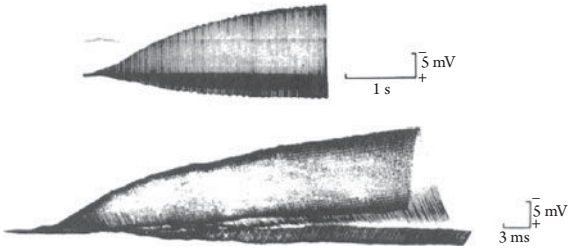

FIGURE 15 *Repetitive nerve stimulation* study in a patient with Lambert-Eaton myasthenic syndrome (LEMS). An *incrementing response* was recorded with *surface electrodes* over the hypothenar eminence (abductor digiti quinti) during repetitive ulnar nerve stimulation at a rate of 50 *Hz* with a display to permit measurement of the peak-to-peak *amplitude* (top) or amplitude and *duration* of the negative *phase* (bottom). An incrementing response is a reproducible increase in amplitude and/or area of successive responses (*M waves*) to repetitive nerve stimulation. The rate of stimulation and the number of *stimuli* should be specified. An incrementing response is commonly seen in two situations. First, in normal subjects the configuration of the M wave may change with repetitive nerve stimulation so that the amplitude progressively increases as the duration decreases, but the area of the M wave remains the same. This phenomenon is termed *pseudofacilitation.* Second, in disorders of neuromuscular transmission, the configuration of the M wave may change with repetitive nerve stimulation so that the amplitude progressively increases as the duration remains the same or increases, and the area of the M wave increases. This phenomenon is termed *facilitation.* Contrast with *decrementing response.*

REPETITIVE NERVE STIMULATION

Normal (N), Myasthenia Gravis (MG), Lambert-Eaton Myasthenic Syndrome (LEMS)

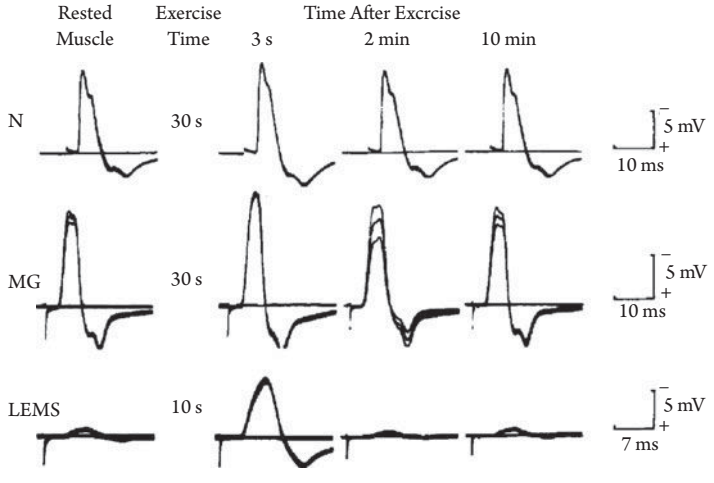

FIGURE 16 *Repetitive nerve stimulation* studies in a normal subject (N) and patients with *myasthenia gravis* (MG) and Lambert-Eaton myasthenic syndrome (LEMS). Three successive *M waves* were elicited by repetitive nerve stimulation at a rate of 2 *Hz*. The three *responses* were superimposed. This method of display emphasizes a change in the configuration of successive responses but does not permit identification of their order. In each superimposed display of three responses where the configuration did change, the highest amplitude response was the first, and the lowest amplitude response was the third. After testing the rested muscle, the muscle was maximally contracted for 10 to 30 seconds (exercise time). Repetitive nerve stimulation was carried out again 3 s, 2 min, and 10 min after the exercise ended. The results illustrate *facilitation* and *postactivation depression.*

REPETITIVE NERVE STIMULATION

Pseudofacilitation

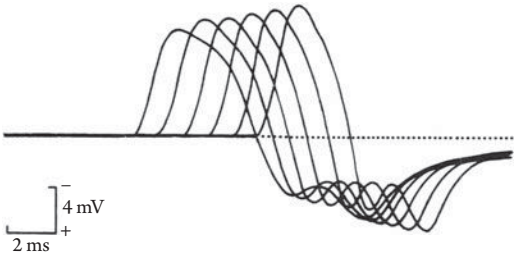

FIGURE 17 *Repetitive nerve stimulation* study in a normal subject. The successive M waves were recorded with *surface electrodes* over the hypothenar eminence (abductor digiti quinti) during ulnar nerve stimulation at a rate of 30 *Hz*. *Pseudofacilitation* may occur in normal subjects with repetitive nerve stimulation at high (20–50 Hz) rates or after strong volitional *contraction*, and probably reflects a reduction in the *temporal dispersion* of the summation of a constant number of *muscle fiber action potentials* due to increases in the propagation velocity of muscle cell *action potentials* with repeated activation. Pseudofacilitation should be distinguished from *facilitation*. The recording shows an *incrementing response* characterized by an increase in the *amplitude* of the successive M waves with a corresponding decrease in the *duration*, resulting in no change in the area of the negative *phase* of successive M waves.

INSERTION ACTIVITY

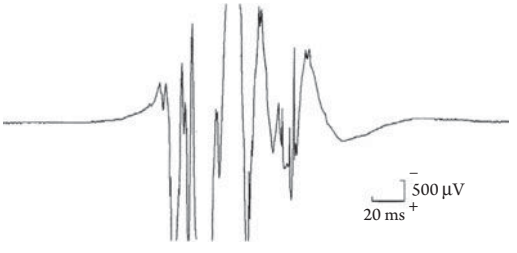

FIGURE 18 *Insertion activity* recorded by an intramuscular *needle electrode* in a normal subject. Insertion activity is the electric activity caused by insertion or movement of a needle electrode within a muscle. The amount of the activity may be described as normal, reduced, or increased (prolonged), with a description of the *waveform* and repetitive rate.

END-PLATE ACTIVITY

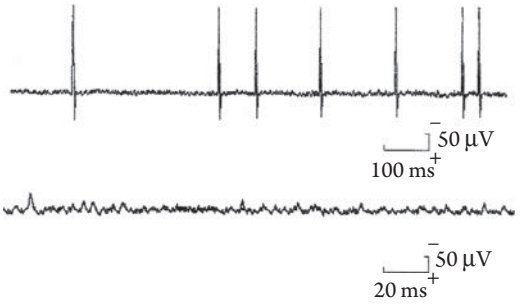

FIGURE 19 *Spontaneous activity* recorded by an intramuscular *needle electrode* close to muscle end-plates. May be either of two forms:

1. *Monophasic end-plate activity* (upper and lower traces): Low *amplitude* (10 to 20 μV), short-duration (0.5 to 1 ms), monophasic (negative) *potentials* that occur in a dense, steady pattern and are restricted to a localized area of the muscle. Because of the multitude of different potentials occurring, the exact *frequency*, although appearing to be high, cannot be defined. These nonpropagated potentials are probably *miniature end-plate potentials* recorded extracellularly. This form of end-plate activity has been referred to as *end-plate noise* or *sea shell sound (sea shell noise or roar).*
2. *Biphasic end-plate activity* (upper trace): Moderate amplitude (100 to 300 μV), short-duration (2 to 4 ms), biphasic (negative-positive) *spike* potentials that occur irregularly in short bursts with a high frequency (50 to 100 *Hz*), restricted to a localized area within the muscle. These propagated potentials are generated by muscle fibers excited by activity in nerve terminals. These potentials have been referred to as *end-plate spikes*, and, incorrectly, *nerve potentials.*

FIBRILLATION POTENTIAL

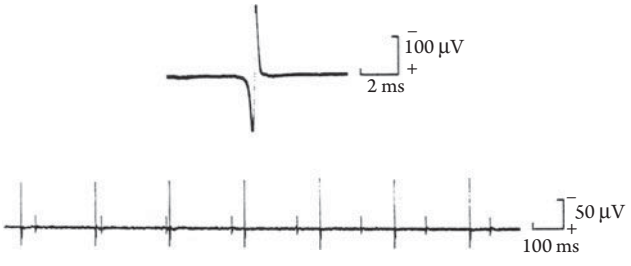

FIGURE 20 *Fibrillation potentials* recorded by an intramuscular *needle electrode.* The top trace shows the *waveform* of a single fibrillation potential. The bottom trace shows the pattern of discharge of two other fibrillation potentials which differ with respect to *amplitude* and discharge *frequency.* A fibrillation potential is the electric activity associated with a spontaneously contracting (fibrillating) muscle fiber. It is the *action potential* of a single muscle fiber. The action potentials may occur spontaneously or after movement of the needle electrode. They usually fire at a constant rate, although a small proportion fire irregularly. Classically, the potentials are biphasic *spikes* of short *duration* (usually less than 5 ms) with an initial positive phase and a peak-to-peak amplitude of less than 1 mV. When recorded with concentric or *monopolar needle electrodes*, the firing rate has a wide range (1 to 50 Hz) and often decreases just before cessation of an individual discharge. A high-pitched regular sound is associated with the discharge of fibrillation potentials and has been described in the older literature as "rain on a tin roof." In addition to this classic form of fibrillation potentials, *positive sharp waves* may also be recorded from fibrillating muscle fibers when the action potentials arise from an area immediately adjacent to the needle electrode.

POSITIVE SHARP WAVE

TRAIN OF POSITIVE SHARP WAVES

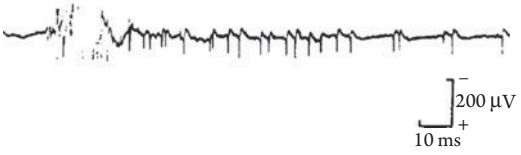

FIGURE 21 *Positive sharp waves* recorded by an intramuscular *needle electrode.* The top trace shows a single positive sharp wave. The bottom trace shows the pattern of initial *discharge* of a number of different positive sharp waves after movement of the needle electrode in a denervated muscle. A positive sharp wave is a biphasic, positive-negative *action potential* initiated by needle movement and recurring in a uniform, regular pattern at a rate of 1 to 50 *Hz.* The discharge *frequency* may decrease slightly just before cessation. The initial positive deflection is rapid (<1 ms), its *duration* is usually less than 5 ms, and the *amplitude* is up to 1 mV. The negative *phase* is of low amplitude, with a duration of 10 to 100 ms. A sequence of positive sharp waves is commonly referred to as a *train of positive sharp waves.* Positive sharp waves can be recorded from the damaged area of fibrillating muscle fibers. Their configuration may result from the position of the needle electrode which is believed to be adjacent to the depolarized segment of a muscle fiber injured by the electrode. Note that the positive sharp *waveform* is not specific for muscle fiber damage. *Motor unit action potentials* and potentials in *myotonic discharges* may have the configuration of positive sharp waves.

MYOTONIC DISCHARGE

FIGURE 22 *Myotonic discharge* recorded by an intramuscular needle electrode. A myotonic discharge is a *repetitive discharge* which fires at rates of 20 to 80 *Hz.* There are two types: (1) biphasic (positive-negative) *spike potentials* less than 5 ms in *duration* resembling *fibrillation potentials*, and (2) *positive waves* of 5 to 20 ms duration resembling *positive sharp waves.* Both potential forms are recorded after *needle electrode* insertion, voluntary muscle *contraction* or muscle percussion, and are due to independent, repetitive discharges of single muscle fibers. The *amplitude* and *frequency* of the potentials must both wax and wane to be identified as a myotonic discharge. This change produces a characteristic musical sound in the audio display of the *electromyograph* due to the corresponding change in pitch, which has been likened to the sound of a "dive bomber." Contrast with *waning discharge.*

COMPLEX REPETITIVE DISCHARGE

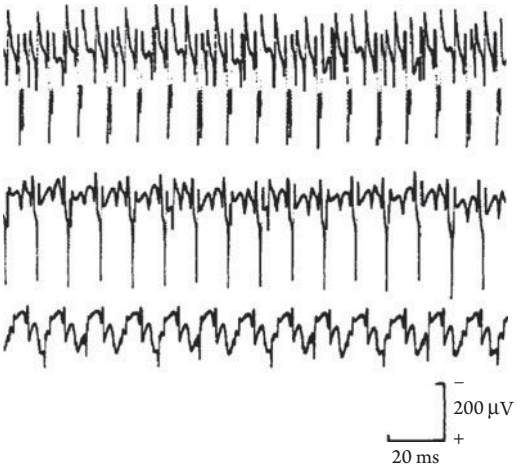

FIGURE 23 *Complex repetitive discharges* recorded by an intramuscular *needle electrode.* A complex repetitive discharge is a polyphasic or serrated *action potential* that may begin spontaneously or after needle movement. The *discharges* have a uniform *frequency*, shape, and *amplitude*, with abrupt onset, cessation, or change in configuration. Amplitudes range from 100 μV to 1 mV and the frequency of discharge from 5 to 100 Hz. This term is preferred to *bizarre high frequency discharge*, *bizarre repetitive discharge*, *bizarre repetitive potential*, or *pseudomyotonic discharge.*

FASCICULATION POTENTIAL

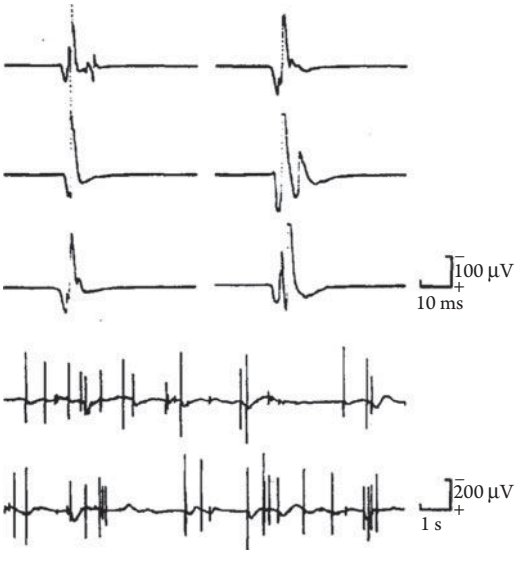

FIGURE 24 *Fasciculation potentials* recorded by an intramuscular *needle electrode.* Six different fasciculation potentials are displayed in the top traces, on a time scale which permits characterization of the individual *waveforms.* The bottom two traces display fasciculation potentials on a time scale which demonstrates the random discharge pattern. A fasciculation potential is an *action potential* which is often associated with a visible *fasciculation.* It has the configuration of a *motor unit action potential* but occurs spontaneously. Most commonly these potentials occur sporadically and are termed "single fasciculation potentials." Occasionally, the potentials occur as a *grouped discharge* and are termed a "brief *repetitive discharge."* The repetitive firing of adjacent fasciculation potentials, when numerous, may produce an undulating movement of muscle (see *myokymia*). Use of the terms *benign fasciculation* and *malignant fasciculation* is discouraged. Instead, the configuration of the potentials, peak-to-peak *amplitude*, *duration*, number of *phases*, and stability of configuration, in addition to the *frequency* of occurrence, should be specified.

MYOKYMIC DISCHARGE

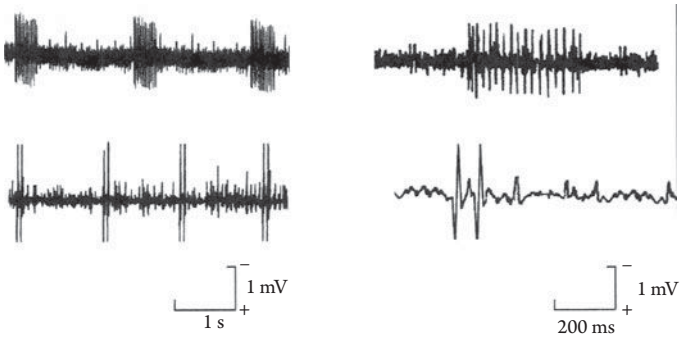

FIGURE 25 Tracings of two different *myokymic discharges* recorded with an intramuscular *needle electrode* are displayed on a time scale (left) which illustrates the firing pattern and with a different time scale (right) which illustrates that the individual *potentials* have the configuration of a *motor unit action potential.* A myokymic discharge is a group of motor unit action potentials that fire repetitively and may be associated with clinical *myokymia.* Two firing patterns have been described. (1) Commonly, the discharge is a brief, repetitive firing of single motor unit action potentials for a short period (up to a few seconds) at a uniform rate (2 to 60 *Hz*) followed by a short period (up to a few seconds) of silence, with repetition of the same sequence for a particular *potential.* (2) Rarely, the potential recurs continuously at a fairly uniform firing rate (1 to 5 Hz). Myokymic discharges are a subclass of *grouped discharges* and *repetitive discharges.*

NEUROMYOTONIC DISCHARGE

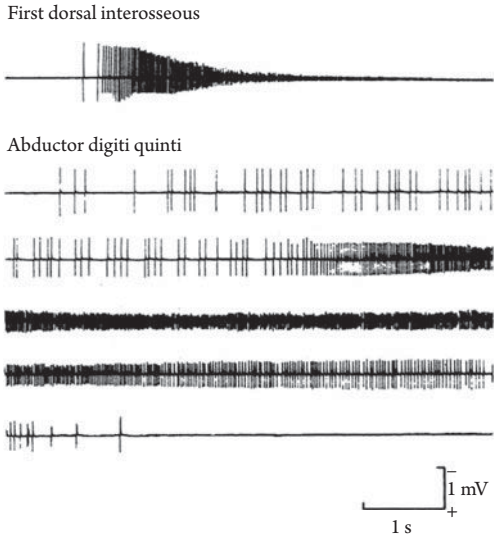

FIGURE 26 *Neuromyotonic discharges* recorded by an intramuscular *needle electrode* are shown on a time scale which illustrates the characteristic firing pattern. A neuromyotonic discharge is a burst of *motor unit action potentials* which originates in motor axons firing at high rates (150 to 300 *Hz*) for a few seconds. They often start and stop abruptly. The *amplitude* of the *waveforms* typically wanes. *Discharges* may occur spontaneously or be initiated by *needle electrode* movement, voluntary effort, ischemia, or percussion of a nerve. These discharges should be distinguished from *myotonic discharges* and *complex repetitive discharges.* They are one type of electrical activity that may be recorded in patients who have clinical *neuromyotonia.*

CRAMP DISCHARGE

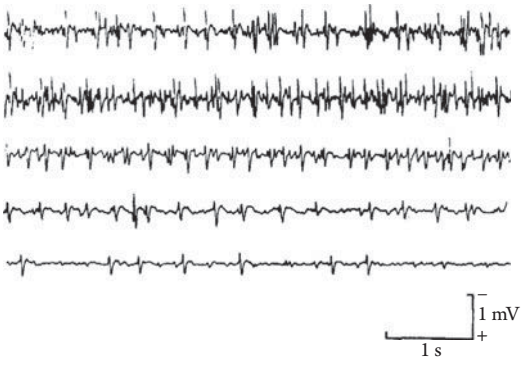

FIGURE 27 *Cramp discharges* recorded by an intramuscular *needle electrode.* A cramp discharge arises from the involuntary repetitive firing of *motor unit action potentials* at a high *frequency* (up to 150 *Hz*) in a large area of muscle, usually associated with painful muscle *contraction.* Both the *discharge frequency* and the number of motor unit action potentials firing increase gradually during development, and both subside gradually with cessation. See *muscle cramp.*

MOTOR UNIT ACTION POTENTIALS

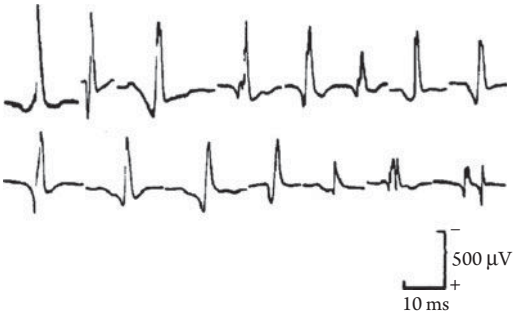

FIGURE 28 A selection of different *motor unit action potentials* recorded with an intramuscular *needle electrode.* A motor unit action potential is a *potential* which reflects the electrical activity of a single *motor unit.* It is the *compound action potential* of those muscle fibers within the recording range of an *electrode.* When it is produced by voluntary muscle contraction, the potential is characterized by its consistent appearance and relationship to the force of contraction. The following parameters may be specified, quantitatively if possible, after the *recording electrode* is placed randomly within the muscle.

1. Configuration
   a. *Amplitude*, peak-to-peak (µV or mV).
   b. *Duration*, total (ms).
   c. Number of *phases* (*monophasic*, *biphasic*, *triphasic*, *tetraphasic*, *polyphasic*).
   d. Sign of each *phase* (negative, positive).
   e. Number of *turns.*
   f. Variation of shape (*jiggle*), if any, of consecutive *discharges.*
   g. Presence of *satellite* (*linked potentials*), if any.
   h. *Spike* duration, the duration of the spike including satellites.
2. *Recruitment* characteristics
   a. *Threshold* of activation (first recruited, low threshold, high threshold).
   b. *Onset frequency*
   c. *Recruitment frequency* (*Hz*) or *recruitment interval* (ms) of individual potentials.

Descriptive terms implying diagnostic significance are not recommended, e.g., myopathic, neuropathic, regeneration, nascent, giant, BSAP and BSAPP. See *polyphasic action potential*, *serrated action potential.*

SATELLITE POTENTIAL

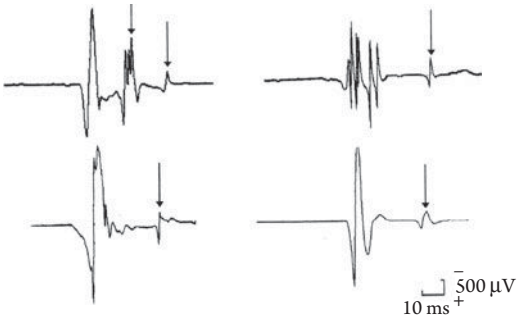

FIGURE 29 Four discharges of the same *motor unit action potential* with *satellite potentials* are indicated by the arrows. A satellite potential is a small *action potential* separated from the main motor unit action potential by an isoelectric interval which fires in a time-locked relationship to the main action potential. These *potentials* usually follow, but may precede, the main action potential. Less preferred terms include *late component, parasite potential, linked potential,* and *coupled discharge.*

RECRUITMENT PATTERN/INTERFERENCE PATTERN

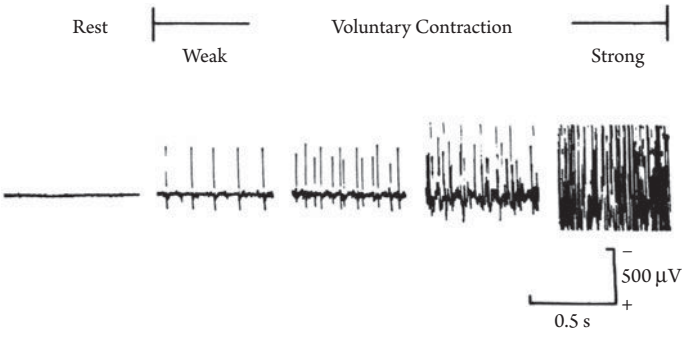

FIGURE 30 Recordings made with an intramuscular *needle electrode* at five different levels of force of voluntary *contraction. Recruitment* refers to the successive *activation* of the same and new *motor units* with increasing strength of voluntary muscle contraction. The recruitment pattern is a qualitative and/or quantitative description of the sequence of appearance of *motor unit action potentials* during increasing voluntary muscle contraction. The *recruitment frequency* and *recruitment interval* are two quantitative measures commonly used. The *interference pattern* is the electric activity recorded from a muscle with a *needle electrode* during maximal voluntary effort. A full interference pattern implies that no individual motor unit action potentials can be clearly identified (see tracing on far right). A reduced interference pattern (intermediate interference pattern) is one in which some of the individual motor unit action potentials may be identified while others cannot due to superimposition of *waveforms.* The term "discrete activity" is used to describe the electric activity recorded when each of several different motor unit action potentials can be identified due to limited superimposition of waveforms. The term "single unit pattern" is used to describe a single motor unit action potential, firing at a rapid rate (should be specified) during maximum voluntary effort. The force of contraction associated with the interference pattern should be specified.

SINGLE FIBER ELECTROMYOGRAPHY

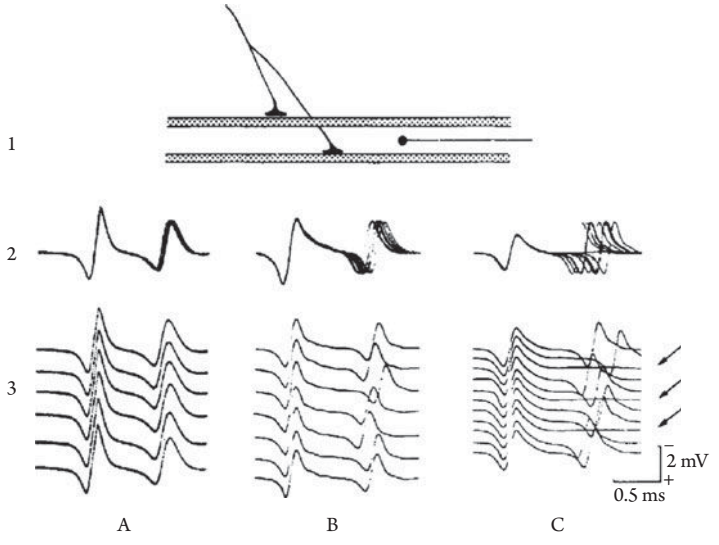

FIGURE 31 Schematic representation of the location of the recording surface of a *single fiber needle electrode* recording from two muscle fibers innervated by the same motor neuron (row 1). Consecutive *discharges* of a *potential* pair are shown in a superimposed display (row 2) and in a *raster* display (row 3). The potential pairs were recorded from the extensor digitorum communis of a patient with *myasthenia gravis.* They show normal jitter (column A), increased *jitter* (column B), and increased jitter and *impulse blocking* (column C, arrows). Jitter is synonymous with "single fiber electromyographic jitter." It is the variability of the *interpotential interval* between two *muscle fiber action potentials* belonging to the same *motor unit* on consecutive discharges. It is usually expressed quantitatively as the mean value of the difference between the interpotential intervals of successive discharges (the *mean consecutive difference, MCD*). Under certain conditions, jitter is expressed as the mean value of the difference between interpotential intervals arranged in the order of decreasing interdischarge intervals (the *mean sorted difference, MSD*).

MACROELECTROMYOGRAPHY (MACRO-EMG)

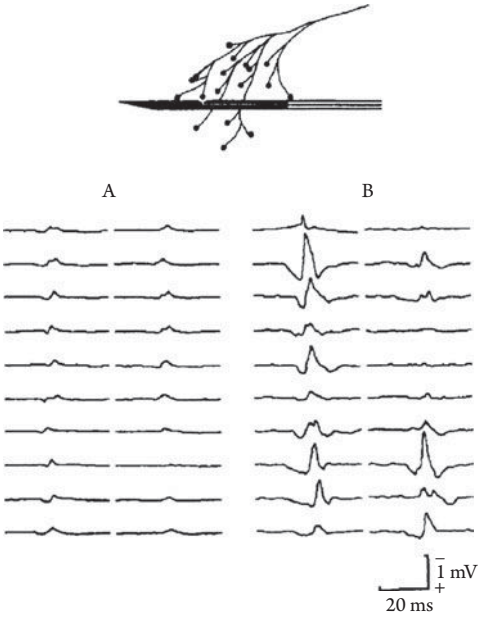

FIGURE 32 Schematic representation of the location of the recording surface of the *macro-EMG needle electrode* recording from all the muscle fibers innervated by the same motor neuron (upper diagram). *Macro motor unit potentials* recorded by the technique of *macroelectromyography* (lower traces) from a healthy subject (column A) and from a patient with amyotrophic lateral sclerosis (column B). "Macroelectromyography" is a general term referring to the technique and conditions that approximate recording of all *muscle fiber action potentials* arising from the same *motor unit.*

NEEDLE ELECTRODES

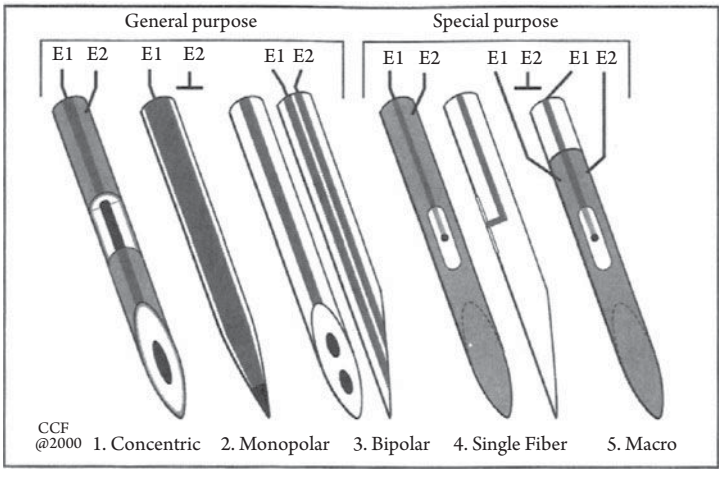

FIGURE 33 Schematic representation of five different types of needle electrodes. (1) The *concentric needle electrode* consists of a hollow, stainless steel cannula (light gray) containing a centrally located wire (black) from which it is insulated. The latter serves as the *active electrode (E1)*, while the entire barrel of the needle serves as the *reference electrode (E2).* (2) The *monopolar needle electrode* consists of a solid stainless steel needle coated with insulation except for its distal tip, which serves as the cone-shaped recording surface (E1). The reference electrode (E2) consists of either another monopolar needle electrode or a *surface electrode.* (3) The *bipolar needle electrode* consists of a stainless steel hollow cannula which contains two wires, insulated from each other and from the cannula itself. The exposed distal tips of these wires on the bevel surface serve as the active (E1) and reference (E2) electrodes. (4) *Single fiber needle electrode.* Similar to the concentric needle electrode, the proximal portion of this electrode consists of a hollow cannula, which contains a central wire from which it is insulated. This wire, instead of ending on the bevel tip, is exposed through a side port in the cannula opposite the bevel tip. The bared area serves as the active electrode (E1) while the surface of the cannula serves as the reference electrode (E2). (5) The *macro-EMG needle electrode* consists mainly of a modified single fiber needle electrode. Two different *potentials* are recorded. The first is recorded from the single fiber EMG needle electrode. The recording surface opposite the bevel of the needle serves as the active electrode (E1), and the uninsulated portion of the cannula (light gray) serves as the reference electrode (E2). The potential recorded from this electrode is used to trigger the sweep for recording the *macro motor unit potential* from the second electrode. The second electrode consists of the uninsulated portion of the cannula, which serves as the active electrode (E1). A surface electrode serves as the reference electrode (E2).

FULL WAVE RECTIFIED EMG

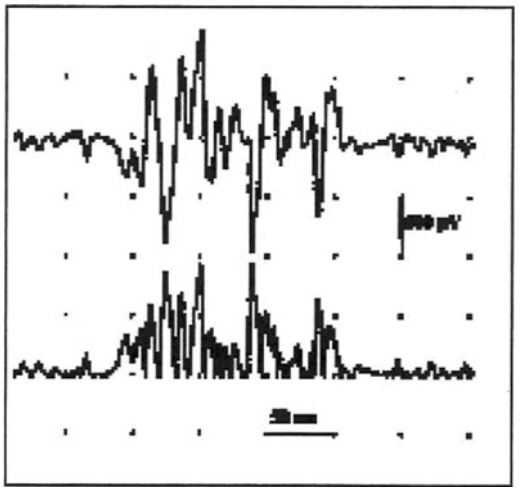

FIGURE 34 *Motor unit action potentials* recorded normally (top sweep) and simultaneously as a *full wave rectified EMG* signal (bottom sweep). A full wave rectified EMG signal is the absolute value of the raw EMG signal. Full wave rectification involves inverting all the *waveforms* below the *isopotential line* and displaying them with opposite polarity above the line. A technique used to analyze *kinesiologic EMG* signals.

SYMPATHETIC SKIN RESPONSE

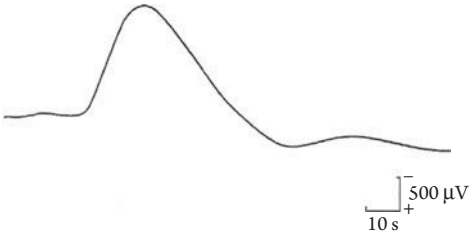

FIGURE 4–35 *Sympathetic skin response* recorded from the palm following stimulation of the contralateral median nerve. The sympathetic skin response is an electric *potential* resulting from electrodermal activity in sweat glands in response to both direct and peripheral or sympathetic trunk stimulation of autonomic activity.

SECTION III:
ABBREVIATIONS

The Glossary follows the recommendations of the Council of Biology Editors Style Manual (6th edition)[1] for abbreviations of units of measurement. The abbreviations are as follows:

meter	m	millivolt	mV
centimeter	cm	microvolt	μV
millimeter	mm	ampere	A
hour	h	milliampere	mA
minute	min	microampere	μA
second	s	ohm	Ω
millisecond	ms	hertz	Hz
microsecond	μs	cycles per second	cps or c/s
volt	V		

1. CBE Style Manual Committee. *Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers.* 6th ed. Council of Biology Editors, 1994.

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